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Original Article

Randomized study of sinusoidal chronomodulated versus flat intermittent induction chemotherapy with cisplatin and 5-fluorouracil followed by traditional radiotherapy for locoregionally advanced nasopharyngeal carcinoma

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Abstract

Neoadjuvant chemotherapy plus radiotherapy is the most common treatment regimen for advanced nasopharyngeal carcinoma (NPC). Whether chronomodulated infusion of chemotherapy can reduce its toxicity is unclear. This study aimed to evaluate the toxic and therapeutic effects of sinusoidal chronomodulated infusion versus flat intermittent infusion of cisplatin (DDP) and 5-fluorouracil (5-FU) followed by radiotherapy in patients with locoregionally advanced NPC. Patients with biopsy-diagnosed untreated stages III and IV NPC (according to the 2002 UICC staging system) were randomized to undergo 2 cycles of sinusoidal chronomodulated infusion (Arm A) or flat intermittent constant rate infusion (Arm B) of DDP and 5-FU followed by radical radiotherapy. Using a "MELODIE" multi-channel programmed pump, the patients were given 12-hour continuous infusions of DDP (20 mg/m^2) and 5-FU (750 mg/m^2) for 5 days, repeated every 3 weeks for 2 cycles. DDP was administered from 10:00 am to 10:00 pm, and 5-FU was administered from 10:00 pm to 10:00 am each day. Chronomodulated infusion was performed in Arm A, with the peak deliveries of 5-FU at 4:00 am and DDP at 4:00 pm. The patients in Arm B underwent a constant rate of infusion. Radiotherapy was initiated in the fifth week, and both arms were treated with the same radiotherapy techniques and dose fractions. Between June 2004 and June 2006, 125 patients were registered, and 124 were eligible for analysis of response and toxicity. The major toxicity observed during neoadjuvant chemotherapy was neutropenia. The incidence of acute toxicity was similar in both arms. During radiotherapy, the incidence of stomatitis was significantly lower in Arm A than in Arm B (38.1% vs. 59.0%, P = 0.020). No significant differences were observed for other toxicities. The 1-, 3-, and 5-year overall survival rates were 88.9%, 82.4%, and 74.8% for Arm A and 91.8%, 90.2%, and 82.1% for Arm B. The 1-, 3-, and 5-year progression-free survival rates were 91.7%, 88.1%, and 85.2% for Arm A and 100%, 94.5%, and 86.9% for Arm B. The 1-, 3-, and 5-year distant metastasis-free survival rates were 82.5%, 79.1%, and 79.1% for Arm A and 90.2%, 85.2%, and 81.7% for Arm B. Chronochemotherapy significantly reduced stomatitis but was not superior to standard chemotherapy in terms of hematologic toxicities and therapeutic response.

Key words Chronochemotherapy, cisplatin, 5-fluorouracil, nasopharyngeal carcinoma, radiotherapy

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Nasopharyngeal carcinoma (NPC) is a common malignancy in southern China, especially in Guangdong province. Approximately 70% of patients with newly diagnosed NPC present with locally advanced non-metastatic stage III or IV disease. Although NPC is a radiosensitive tumor, the results of conventional radiotherapy and fractionation techniques are unsatisfactory for patients with locoregionally advanced disease. The benefits of induction chemotherapy have been widely investigated since the 1980s. Induction chemotherapy can deliver drugs to an untreated tumor via

the native vasculature, which optimizes the likelihood of reducing tumor bulk and ultimately leads to better local control. The use of induction chemotherapy in NPC has been investigated in 4 major randomized clinical trials, which demonstrated that induction chemotherapy improves the local control rate but does not alter the overall survival (OS) rate due to the high incidence of late distant metastasis in this disease[1-5]. These studies highlight the need for intensive systemic therapy to eradicate micrometastatic disease, i.e., when the metastases are undetectable and in the most curable state.

The standard treatment for advanced NPC is concurrent chemoradiotherapy with or without adjuvant chemotherapy. However, the tolerance to chemotherapy after radiotherapy is usually very poor, and only 55% of patients finished the scheduled 3 cycles of chemotherapy in the Intergroup 0099 trial[6]. Adjuvant chemotherapy has failed to show any benefits in NPC patients in other trials[7-9].

Induction chemotherapy combining cisplatin (DDP) and 5-fluorouracil (5-FU) followed by radiotherapy was the standard protocol for locally advanced NPC at Sun Yat-sen University Cancer Center when the study was designed in 2003. However, whether chronomodulated infusion of chemotherapy could reduce the toxicity of this treatment for NPC patients is not clear.

Chronotherapy aims to administer cytotoxic agents at the time when they will exhibit the lowest toxicity. Randomized phase III trials with platinum and 5-FU as the main agents have confirmed that the delivery of cytotoxic agents using chronotherapy can reduce toxicity-related adverse events in colorectal cancer[10]. Our preclinical studies using a mouse xenograft model of human NPC indicated a 10-hour time difference in the circadian rhythm of DNA synthesis in tumor tissues and normal tissues[11]. Additionally, circadian rhythms in dihydropyrimidine dehydrogenase (DPD), the initial enzyme for catabolism of 5-FU, and glutathione (GSH), which protects cell membranes and proteins, metabolizes endogenous compounds, and transports amino acids, were linked to reduced 5-FU and platinum toxicities in 20 NPC patients. The concentration of DPD peaked in the morning, and the concentration of GSH peaked in the early afternoon [12]. Based on these experimental findings, we designed a chronomodulated infusion regimen for advanced NPC.

In a phase II trial conducted by our groups, the chronomodulated infusion of 5-FU alone or in combination with leucovorin (LV) and DDP could be administered at high doses without an increase in toxicity[13]. Therefore, we initiated the present randomized clinical trial to test whether chronomodulated chemotherapy could reduce toxicity in NPC treatment.

Patients and Methods

Patient enrollment

Approximately 60 patients in each group were needed to detect a 5% decrease in chemotherapy-induced toxicity.

Between June 2004 and June 2006, patients with advanced NPC were enrolled in this study. Written informed consent was obtained from every patient before registration. The protocol was approved by the Institutional Ethics Committee and was conducted in accordance with the principles of the Declaration of Helsinki.

Eligibility criteria

The eligibility criteria included biopsy-diagnosed non-keratinizing or undifferentiated carcinoma of the nasopharynx, as defined by the WHO classification[14]; stage III or IVA and IVB disease, as defined by the International Union Against Cancer staging system (2002 UICC 6th edition), with no gross evidence of distant metastasis[15]; 18 to 60 years old; adequate hematologic function with a total leukocyte count (WBC) $\geqslant$4,000 cells/mL and platelet count $\geqslant$100,000 platelets/mL; adequate hepatic and renal functions with normal serum bilirubin, alanine aminotransferase (ALT), and alkaline phosphatase (ALP) levels of less than two times the upper limit of normal, and a 24-hour creatinine clearance (CrCl) $\geqslant$ 60 mL/min; and satisfactory performance status ($\leqslant$ 2) as defined by the Eastern Cooperative Oncology Group system[16]. The exclusion criteria included keratinizing squamous cell carcinoma or adenocarcinoma; pregnancy or lactation; history of previous radiotherapy; and history of cardiac, hepatic, or renal disease.

Pretreatment evaluation and randomization

The pretreatment evaluation included a medical history and physical examination, baseline hematologic and biochemical profiles, and electrocardiography. All patients underwent fiberoptic endoscopy and biopsy of the nasopharynx and a magnetic resonance imaging (MRI) scan of the nasopharynx, base of the skull, and neck. The metastatic workup included a chest radiograph, liver ultrasound, and bone scintigraphy. All patients were referred for dental examination before radiotherapy.

The eligible patients were randomized to undergo 2 cycles of sinusoidal chronomodulated infusion (Arm A) or intermittent constant rate infusion (Arm B) of DDP and 5-FU, followed by radical radiotherapy. Randomization was performed using a computer-generated coding system. The trial profile is shown in **Figure 1**.

Chemotherapy

The chemotherapy regimen consisted of 12-hour continuous infusions of DDP (20 mg/m^2) or 5-FU (750 mg/m^2) for 5 days, repeated every 3 weeks for 2 cycles. On each treatment day, 5-FU was given from 10:00 am to 10:00 pm, and DDP was given from 10:00 pm to 10:00 am. For Arm A, sinusoidal chronomodulated infusion was administered with the peak delivery of 5-FU at 4:00 am and peak delivery of DDP at 4:00 pm (**Figure 2A**). For Arm B, intermittent constant rate infusion was administered (**Figure 2B**). If a toxicity of $\geqslant$ grade II was observed after the first cycle of chemotherapy and the patient did not recover within 2 weeks, then the second cycle was canceled.

Radiotherapy

Radiotherapy was initiated within 1 week of the completion of

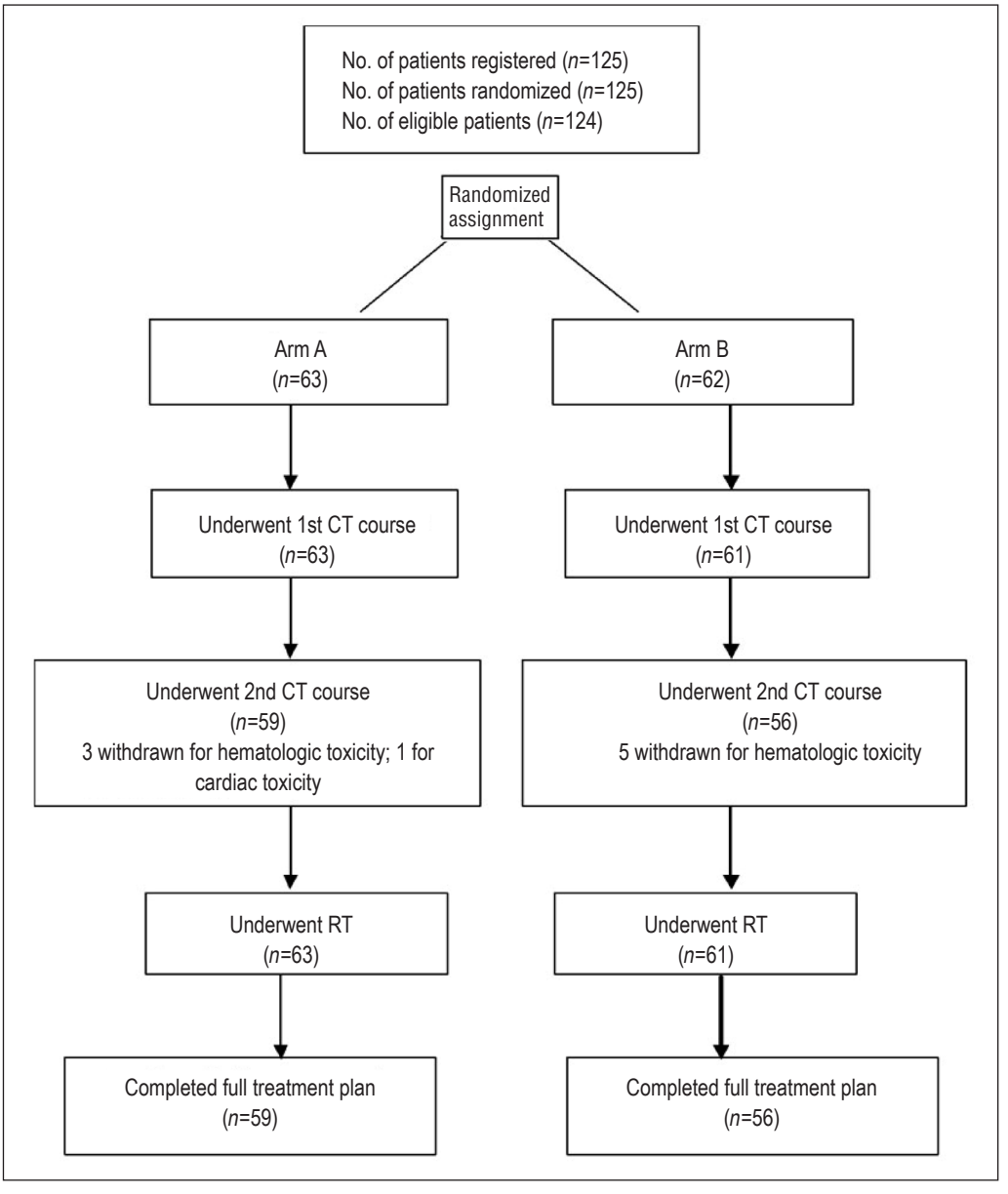

Figure 1. **Trial profile of patients with locoregionally advanced nasopharyngeal carcinoma (NPC) treated by sinusoidal chronomodulated or flat intermittent induction chemotherapy with cisplatin (DDP) and 5-fluorouracil (5-FU) followed by traditional radiotherapy.** Arm A, sinusoidal chronomodulated infusion; Arm B, intermittent constant rate infusion; CT, chemotherapy; RT, radiotherapy.

the second cycle of chemotherapy. Megavoltage photons (6–8 MV or cobalt-60) were used to treat the primary tumor and neck lymph nodes. The patients were administered conventional fractionation radiotherapy (2 Gy/day, five times a week). The irradiation fields were chosen according to the extent of the tumor. The target volume, defined as the entire tumor with a 2-cm margin in each direction, received at least 90% of the mid-depth central axis dose. The primary tumor was treated with 36 Gy at two lateral opposing faciocervical fields, followed by the shrinking-field technique (two laterally opposed-facial fields) to a total dose of 68–72 Gy. An anterior field was used to treat the lower neck using a laryngeal block. The accumulated dose was 60–66 Gy to the involved areas of the neck and 50 Gy to the uninvolved areas. The treatment and evaluation scheme is listed in **Figure 3**.

Patient assessment

The primary endpoints of the study were acute toxicity and response. The secondary endpoints were OS and progression-free survival (PFS). Acute toxicity was evaluated according to version 3.0 of the National Cancer Institute of Canada-Common Toxicity Criteria (NCIC CTC). OS was defined as the time from registration to death from any cause. PFS was defined as the time from registration to the first observation of disease progression or death from any cause. Patient response was evaluated according to the WHO criteria. Complete response (CR) was defined as the absence of clinical or radiographic evidence of residual disease; partial response (PR) was defined as tumor shrinkage $\geqslant$ 50% of the sum of the longest diameters of all measurable lesions with no progression of

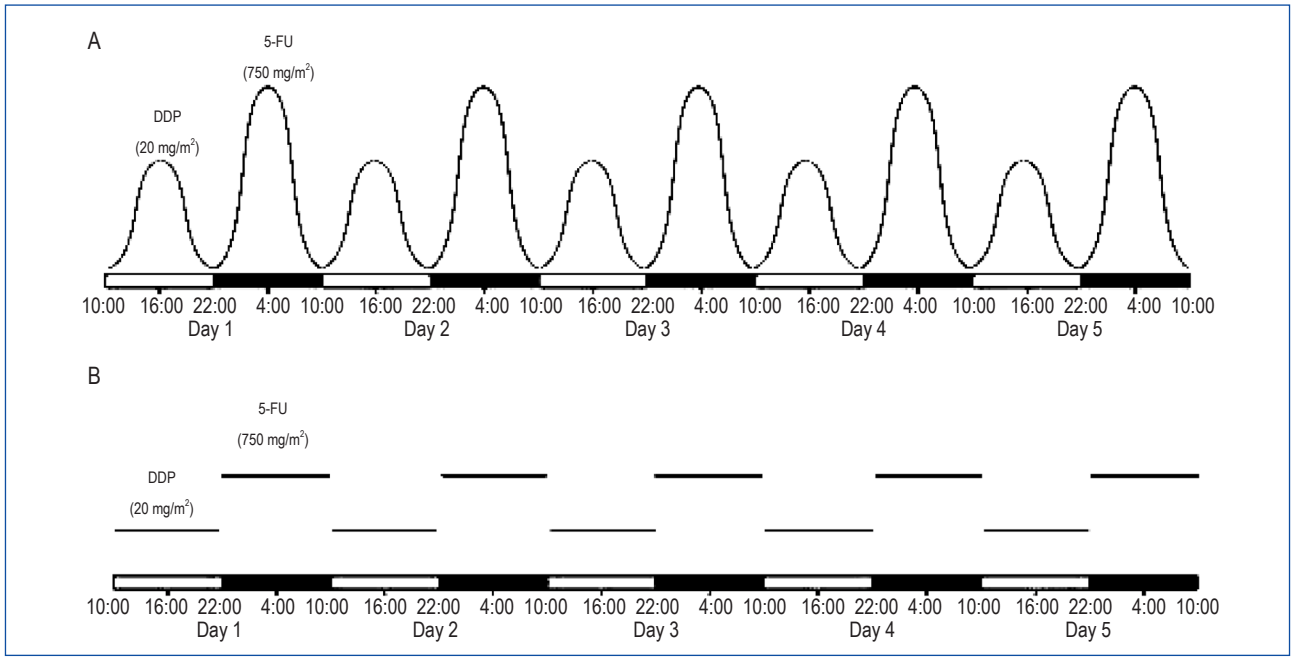

Figure 2. **Chemotherapy regimen combining DDP and 5-FU for NPC patients.** Patients in Arm A underwent sinusoidal chronomodulated infusion over 5 days, and those in Arm B underwent flat intermittent constant rate infusion over 5 days.

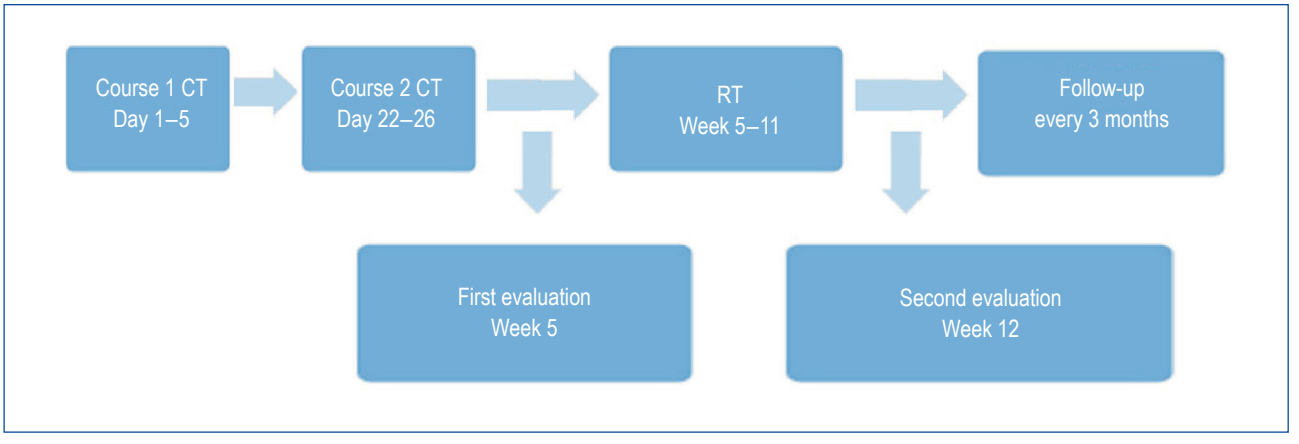

Figure 3. **Treatment and evaluation scheme for the NPC patients.**

assessable disease and no new lesions; stable disease (SD) was defined as a change in tumor volume of no more than 25% of the sum of the longest diameters of all measurable lesions with no new lesions; progressive disease (PD) was defined as an increase of more than 50% in tumor volume or the appearance of new lesions.

During treatment, a physical examination, blood cell counting, and biochemical profiling were performed every week. Toxicity was analyzed each week during treatment. Treatment response was evaluated with both MRI and flexible endoscopic nasopharyngoscopy after induction chemotherapy (week 5), at the end of radiotherapy (week 12), and every 3 months after treatment. The patients were followed up until August 2012. The follow-up duration was calculated from the day of randomization to either the day of death or the day of last examination.

Statistical methods

Response and toxicity were analyzed using the chi-square test. RFS and OS rates were calculated according to the life-table product limit method. The significance of differences in the survival curves was calculated using the log-rank test. *P* values of 0.05 or less were considered significant.

Results

General patient information

A total of 125 patients were registered between June 2004 and June 2006 (63 in Arm A and 62 in Arm B). All patients were diagnosed with non-keratinizing differentiated or undifferentiated NPC (WHO type II and III). In total, 124 patients were eligible for the toxicity and response analyses. One patient in Arm B was excluded based on a pathology review (lymphoma). The overall clinicopathologic features were similar in the two groups **(Table 1)**. The median patient age was 42 years (range, 20 to 63), and 79.2% of the patients were male; 95 (76.6%) patients had T3 or T4 primary tumors. Most patients had a nodal status of either N1 (32.8%) or N2 (47.2%); however, N3 disease was more frequent in Arm A. The baseline biological characteristics (hemoglobin, neutrophils, platelets, liver and renal test results) of both groups were comparable.

Toxicity

The treatment toxicities are listed in **Table 2**. No fatal toxicity related to the planned treatment occurred in either group. No serious non-hematologic toxicities were observed after the first cycle of chemotherapy. Four patients in Arm A did not undergo the second cycle of chemotherapy due to grade 4 neutropenia in 3 patients and angina pectoris in 1 patient. Five patients in Arm B did not undergo the second cycle of chemotherapy due to grade 4 neutropenia in 4 patients and grade 2 thrombocytopenia in 1 patient. Additionally, 4 patients in Arm A and 2 in Arm B had the second cycle delayed for 1 week because of grade 2 leucopenia. Grade 1/2 anemia was more common in Arm B than in Arm A (P = 0.05). After the second cycle of chemotherapy, radiotherapy was delayed for 1 week in 15 patients in Arm A and 12 in Arm B and for more than 2 weeks in 1 patient in Arm A and 2 in Arm B due to severe hematologic toxicities.

During radiotherapy, the most frequent serious hematologic toxicities were neutropenia (15.9% in Arm A and 13.1% in Arm B, P = 0.896), leucopenia (11.1% in Arm A and 8.2% in Arm B, P = 0.481), thrombocytopenia (9.5% in Arm A and 4.9% in Arm B, P = 0.289), and anemia (4.8% in Arm A and 1.6% in Arm B, P = 0.508). The severe non-hematologic toxicities observed were grade 3 stomatitis (38.1% in Arm A and 59.0% in Arm B, P = 0.020), vomiting (15.9% in Arm A and 9.8% in Arm B, P = 0.316), diarrhea (1.6% in Arm A and 4.9% in Arm B, P = 0.583), anorexia (1.6% in Arm A and 6.6% in Arm B, P = 0.446), weight loss (9.5% in Arm A and 16.4% in Arm B, P = 0.313), and skin (irradiation field) toxicity (14.3% in Arm A and 26.2% in Arm B, P = 0.097). No severe renal or hepatic toxicity was observed in either group. None of the toxicities were significantly different between the two arms, except for stomatitis which was significantly reduced in Arm A.

Table 1. Baseline clinicopathologic characteristics of the 125 patients with nasopharyngeal carcinoma (NPC)

Parameter	Arm A (n=63)	Arm B (n=62)	Total (n=125)	P
Age (years)				
Median	42	41	42	
Range	20–61	23–63	20–63	
Sex [cases (%)]				0.627
Male	51 (80.9)	48 (77.4)	99 (79.2)	
Female	12 (19.1)	14 (22.6)	26 (20.8)	
ECOG PS [cases (%)]				0.778
0–1	55 (87.3%)	56 (90.3)	111 (88.8)	
2	8 (12.7)	6 (9.7)	14 (11.2)	
UICC T category [cases (%)]				0.859
T1	0 (0)	1 (1.6)	1 (0.8)	
T2	15 (23.8)	14 (22.6)	29 (23.2)	
T3	27 (42.9)	29 (46.8)	56 (44.8)	
T4	21 (33.3)	18 (29.0)	39 (31.2)	
UICC N category [cases (%)]				0.117
N0	7 (11.1)	3 (4.8)	10 (8.0)	
N1	18 (28.6)	23 (37.1)	41 (32.8)	
N2	27 (42.9)	32 (51.6)	59 (47.2)	
N3	11 (17.4)	4 (6.5)	15 (12.0)	
UICC clinical stage [cases (%)]				0.311
III	34 (53.9)	39 (62.9)	73 (58.4)	
IV	29 (46.1)	23 (37.1)	52 (41.6)	

Arm A, sinusoidal chronomodulated infusion; Arm B, intermittent constant rate infusion. ECOG, Eastern Cooperative Oncology Group; PS, performance status; UICC, Union for International Cancer Control.

Table 2. Toxicities after the first and second cycles of chemotherapy and during radiotherapy

Toxicity	First chemotherapy cycle			Second chemotherapy cycle			During radiotherapy		
	Arm A (*n*=63)	Arm B (*n*=61)	*P*	Arm A (*n*=63)	Arm B (*n*=61)	*P*	Arm A (*n*=63)	Arm B (*n*=61)	*P*
Hematologic toxicity									
Anemia			0.050			0.459			0.508
Grade 0	47	36		26	31		22	26	
Grade 1	11	18		25	20		29	26	
Grade 2	2	6		4	2		9	8	
Grade 3	3	1		3	2		1	1	
Grade 4	0	0		1	1		2	0	
Leucopenia			0.595			0.099			0.481
Grade 0	37	36		18	8		12	17	
Grade 1	20	19		15	25		20	19	
Grade 2	4	3		23	19		24	20	
Grade 3	2	3		3	4		7	4	
Grade 4	0	0		0	0		0	1	
Neutropenia			0.867			0.162			0.896
Grade 0	43	39		22	17		28	29	
Grade 1	11	11		10	13		16	16	
Grade 2	6	7		13	12		9	8	
Grade 3	0	0		14	13		6	7	
Grade 4	3	4		0	1		4	1	
Thrombocytopenia			0.887			1.000			0.289
Grade 0	56	54		37	35		39	46	
Grade 1	4	3		12	14		9	5	
Grade 2	2	4		8	6		9	7	
Grade 3	1	0		2	1		5	2	
Grade 4	0	0		0	0		1	1	
Renal toxicity									
Cr elevation			0.148			0.283			0.608
Grade 0	51	42		47	39		47	43	
Grade 1	11	19		9	16		13	17	
Grade 2	1	0		3	1		3	1	
Grade 3	0	0		0	0		0	0	
Grade 4	0	0		0	0		0	0	
Hepatic toxicity									
ALT elevation			0.825			0.449			0.301
Grade 0	51	48		48	42		50	45	
Grade 1	11	12		11	13		10	13	
Grade 2	1	1		0	1		3	3	
Grade 3	0	0		0	0		0	0	
Grade 4	0	0		0	0		0	0	
AST elevation			0.436			1.000			0.458
Grade 0	61	57		55	52		60	55	
Grade 1	2	4		4	4		3	6	
Grade 2	0	0		0	0		0	0	
Grade 3	0	0		0	0		0	0	
Grade 4	0	0		0	0		0	0	

(to be continued)

Table 2. Toxicities after the first and second cycles of chemotherapy and during radiotherapy *(continued)*

Toxicity	First chemotherapy cycle			Second chemotherapy cycle			During radiotherapy		
	Arm A (n=63)	Arm B (*n*=61)	*P*	Arm A (*n*=63)	Arm B (*n*=61)	*P*	Arm A (*n*=63)	Arm B (*n*=61)	*P*
Gastrointestinal toxicity									
Anorexia			0.827			0.407			0.446
Grade 0	26	24		20	15		7	6	
Grade 1	27	29		32	34		55	51	
Grade 2	10	8		7	7		0	0	
Grade 3	0	0		0	0		1	4	
Grade 4	0	0		0	0		0	0	
Diarrhea			0.373			0.365			0.583
Grade 0	56	57		48	49		45	41	
Grade 1	7	2		10	5		17	17	
Grade 2	0	2		1	2		0	0	
Grade 3	0	0		0	0		1	3	
Grade 4	0	0		0	0		0	0	
Vomiting			0.446			0.708			0.316
Grade 0	34	31		28	27		28	35	
Grade 1	22	22		21	16		25	20	
Grade 2	6	4		7	8		0	0	
Grade 3	1	4		3	5		10	6	
Grade 4	0	0		0	0		0	0	
Stomatitis			0.375			0.334			0.020
Grade 0	44	38		33	25		0	0	
Grade 1	19	23		17	16		39	25	
Grade 2	0	0		4	6		0	0	
Grade 3	0	0		5	9		24	36	
Grade 4	0	0		0	0		0	0	
Weight loss									0.313
Grade 0	-	-		-	-		15	18	
Grade 1	-	-		-	-		42	33	
Grade 2	-	-		-	-		0	0	
Grade 3	-	-		-	-		6	10	
Grade 4	-	-		-	-		0	0	
Skin damage (RT field)									0.097
Grade 0	-	-		-	-		0	0	
Grade 1	-	-		-	-		54	45	
Grade 2	-	-		-	-		0	0	
Grade 3	-	-		-	-		9	16	
Grade 4	-	-		-	-		0	0	

-, not applicable.

Treatment response

The patient responses are listed in **Table 3**. No patients achieved CR after induction chemotherapy. The PR rate was similar in Arm A and Arm B (84.7% and 87.5%, *P* = 0.838). Upon the completion of radiotherapy, all patients achieved either CR or PR, resulting in a RR of 92.7% for the entire patient cohort.

Survival and patterns of failure

The follow-up rates were 100.0%, 98.4%, and 96.0% at 1, 3, and 5 years after treatment, respectively. The median follow-up time was 70.9 months (range, 26 to 83 months). Locoregional recurrence occurred in 16 (12.1%) patients: 9 (14.3%) in Arm A and 7 (11.5%) in Arm B (*P* = 0.539). Distant metastasis represented the major failure

pattern and occurred in 27 (21.8%) patients: 16 (25.4%) in Arm A and 11 (18.0%) in Arm B (P = 0.597) (**Table 4**). No significant differences were found in OS, PFS, and distant metastasis-free survival (DMFS) rates between the two arms (**Table 5**).

Discussion

In this study, stomatitis during radiotherapy was significantly reduced in Arm A (the sinusoidal chronomodulated infusion group) compared with Arm B (the intermittent constant rate infusion group). Stomatitis was likely reduced during radiotherapy but not during neoadjuvant chemotherapy because the chemotherapy may not have achieved the maximum dose; thus, patients did not develop considerable adverse events after the first cycle of chemotherapy. However, we began radiotherapy just 1 or 2 days after the second cycle of chemotherapy. The early initiation of radiotherapy may have contributed to stomatitis and caused the difference between the two arms. These results were consistent with those of the

Table 3. Responses to induction chemotherapy and responses after the completion of radiotherapy

Response to induction chemotherapy	Arm A (n=59)	Arm B (n=56)	Total (n=115)
CR (cases)	0	0	0
PR (cases)	50	49	99
SD (cases)	9	7	16
PD (cases)	0	0	0
RR (%)	84.7	87.5	86.0
Response after completion of radiotherapy	**Arm A (n=63)**	**Arm B (n=61)**	**Total (n=124)**
CR (cases)	60	55	115
PR (cases)	3	6	9
SD (cases)	0	0	0
PD (cases)	0	0	0
RR (%)	95.2	90.1	92.7

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; RR, response rate covering both CR and PR. Four patients in Arm A and 5 patients in Arm B did not undergo a second cycle of chemotherapy (not evaluable for response after induction chemotherapy).

Table 4. Distribution of failure sites in the two treatment arms

Failure site	Arm A (n=63)	Arm B (n=61)	Total (n=124)
Locoregional only [cases(%)]	6 (9.5)	4 (6.6)	10 (8.1)
Distant only [cases(%)]	13 (20.6)	8 (13.1)	21 (16.9)
Locoregional and distant [cases(%)]	3 (4.8)	3 (4.9)	6 (4.8)

Table 5. The overall survival (OS), progression-free survival (PFS), and distant metastasis–free survival (DMFS) rates of patients in the two treatment arms

Group	OS rate (%)				PFS rate (%)				DMFS rate (%)			
	1-year	3-year	5-year	P	1-year	3-year	5-year	P	1-year	3-year	5-year	P
Arm A	88.9	82.4	74.8	0.374	91.7	88.2	85.2	0.539	82.5	79.1	79.1	0.597
Arm B	91.8	90.2	82.1		100.0	94.5	86.9		90.2	85.2	81.7	
Total	90.3	86.2	78.4		95.8	91.2	86.0		86.3	82.1	80.3	

EORTC chronotherapy study[10]. However, other adverse events were not significantly reduced by chronomodulated chemotherapy. It is possible that the absence of other significant differences in toxicities may be related to the relatively small sizes of the two arms. Alternatively, the chemotherapy doses may not have approached the maximum tolerated dose in these patients, or the design of the chronomodulated regimen may not have been optimal.

The chemotherapy regimen used in this study was effective. Although the 86.0% response rate to chemotherapy is superior to that of other reported cisplatin-based regimens[1,2], no patient achieved CR after induction chemotherapy in this study. The reported CR rate after induction chemotherapy for NPC varies (14% to 38%)[2,3]. Two cycles of induction chemotherapy were administered in this study; whereas other trials have used 3 cycles of induction chemotherapy, resulting in higher CR rates. Previously, Chua *et al*.[2] have reported that induction chemotherapy combined with radiotherapy for NPC led to a significantly higher CR rate (94%) than radiotherapy alone (87%). High CR rates were achieved after radiotherapy in both arms of our study (95.2% in Arm A and 90.1% in Arm B), which is not surprising given the sensitivity of NPC to chemotherapy and radiotherapy. Currently, sequential induction-concurrent schedules have been widely explored in several phase II trials with favorable outcomes in NPC[17-19], and phase III trials are ongoing.

A pooled data analysis of two randomized trials have shown that induction chemotherapy reduces the incidence of recurrence and improves DFS without improving OS in patients with advanced NPC[20]. In this report, the 5-year RFS rate was 66.9% and the DMFS rate was 74% in the induction chemotherapy group. In our study, the 5-year PFS rate was 86%, and the DMFS rate was 80%. The improvement of PFS in our study may be due to the use of a more modern imaging system (MRI rather than CT), the use of a different staging system (UICC 2002 rather than Hong Kong Ho's and Chinese 92), and improvements in radiotherapy technology. The main treatment failure event in our study was distant metastasis, which accounted for two-thirds of all failures.

In conclusion, chronomodulated infusion of DDP and 5-FU is an effective regimen for advanced NPC. Chronochemotherapy significantly reduces stomatitis in NPC patients during radiotherapy; however, no significant reduction in hematologic toxicity was achieved. Further research should be conducted to determine the optimal chronotherapy schedule for NPC.

Acknowledgments

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