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ORIGINAL ARTICLE

Efficacy of induction chemotherapy combined with chrono-chemotherapy and intensity-modulated radiotherapy on locally advanced nasopharyngeal carcinoma

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Summary

Purpose: *The purpose of this study was to compare the efficacy and safety of induction chemotherapy combined with chrono-chemotherapy or conventional chemotherapy and intensity-modulated radiotherapy (IMRT) in locally advanced nasopharyngeal carcinoma.*

Methods: *150 patients with locally advanced nasopharyngeal carcinoma were divided into two groups: chrono-chemotherapy group (n=75, receiving induction chemotherapy combined with chrono-chemotherapy and IMRT, and control group (n=75, receiving induction chemotherapy combined with conventional chemotherapy and IMRT. Besides, the levels of T lymphocyte subsets in peripheral blood before and after treatment were compared, and the long-term survival and disease progression were followed up and recorded.*

Results: *After treatment, the short-term efficacy of patients was evaluated. The overall response rate was 94.7% (71/75) in chrono-chemotherapy group and 96.0% (72/75) in control group. Moreover, the levels of cluster of differentiation (CD)3$^+$, CD4$^+$, CD8$^+$, CD4$^+$/CD8$^+$, CD16$^+$CD56$^+$ and CD19$^+$ T cells in peripheral blood of patients at 6 months after treatment were significantly lower than those before treatment. The level of posttreatment CD16$^+$CD56$^+$ T cells in chrono-chemotherapy group was significantly higher than that in control group. Furthermore, the follow-up results showed that the 3-year overall survival (OS) was 73.3% and 69.3%, and the 3-year progression-free survival (PFS) was 60.0% and 62.7% in chrono-chemotherapy group and control group, respectively. Finally, Log-rank test showed no significant differences in OS and PFS between the two groups of patients.*

Conclusions: *As a new treatment mode, chrono-chemotherapy combined with induction chemotherapy and IMRT can reduce the incidence rate and severity of treatment-related adverse reactions and improve immunosuppression without reducing clinical efficacy, which is worthy of clinical promotion and application.*

Key words: *induction chemotherapy, chrono-chemotherapy, intensity-modulated radiotherapy, nasopharyngeal carcinoma, efficacy*

Introduction

Nasopharyngeal carcinoma is a common malignant tumor of the head and neck in China. Most patients are in advanced stage at diagnosis owing to its hidden lesion site and difficulty in the detection of early symptoms [1]. The induction chemotherapy combined with chemoradiotherapy has been taken as the recommended research mode for locally advanced nasopharyngeal carcinoma and docetaxel + cisplatin + 5-fluorouracil (5-FU) (TPF) as the recommended mode for induction chemotherapy in the

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National Comprehensive Cancer Network (NCCN) guideline [2,3]. In clinical practice, due to the adverse reactions of patients, it is often necessary to reduce the dosage of chemotherapy drugs or terminate treatment [4].

Chrono-chemotherapy is also known as time-regulated chemotherapy, in which the appropriate time of administration was selected according to the changes of biological rhythms, so as to improve the efficacy, reduce the side effects of chemotherapy drugs and improve the patient quality of life [5,6]. In recent years, encouraging achievements have been made in the field intensity-modulated radiotherapy (IMRT) among high-precision radiotherapy methods. Compared with patients receiving traditional two-dimensional radiotherapy, those undergoing IMRT have an increased 5-year overall survival (OS) from 67.1% to over 80% and a raised local recurrence-free survival (LRFS) from 83.8% to 90.5%. The survival analysis of several studies also indicates that the 5-year local control rate (LC) was >90% [7-9]. In this study, the efficacy and safety of induction chemotherapy combined with chrono-chemotherapy or conventional chemotherapy and IMRT in the treatment of locally advanced nasopharyngeal carcinoma patients were compared, in order to provide a strong basis for the treatment of such patients.

Methods

Research subjects

A total of 150 patients with locally advanced nasopharyngeal carcinoma were selected. According to different treatment regimens, the patients were divided into two groups, namely, chrono-chemotherapy group [n=75, receiving induction chemotherapy combined with chrono-chemotherapy and IMRT and control group (n=75, receiving induction chemotherapy combined with conventional chemotherapy and IMRT]. Inclusion criteria were set as follows: 1) patients definitely diagnosed with stage III, IVa, IVb nasopharyngeal carcinoma by pathology (according to UICC 2010 staging standards) and undergoing treatment for the first time, 2) those aged >18 years old, 3) those with good physical condition and Karnofsky score ≥70 points, and 4) those whose estimated survival time was >3 months. Exclusion criteria are shown below: 1) patients with contraindications to radiotherapy or chemotherapy, 2) those complicated with other tumors, 3) those with serious dysfunction of important organs such as heart, liver and kidney, 4) those with serious uncontrolled medical diseases or acute infections, 5) those with serious coagulation disorder or bleeding tendency, or 6) those with definite neurological or mental disorders in the past. Among the 150 patients, there were 106 males and 44 females aged 18-72 years old, with an average age of 54.60±9.59 years. There were no statistically significant differences in baseline data between the two groups of patients, and the data were comparable (Table 1, p>0.05). This study complied with

Table 1. Baseline demographic and clinical characteristics of the studied patients

Parameters	*Chrono-chemotherapy group (n=75)* *n (%)*	*Control group (n=75)* *n (%)*	*p*
Age, years	53.86±9.23	55.04±9.44	0.440
Gender (Male/ Female)	51/24	55/20	0.591
Pathologic type			0.651
Nonkeratinized differentiated carcinoma	9 (12.0)	12 (16.0)	
Nonkeratinized undifferentiated carcinoma	61 (81.3)	59 (78.7)	
Keratinizing squamous cell carcinoma	5 (6.7)	4 (5.3)	
T stage			0.384
T1-T2	8 (10.7)	5 (6.7)	
T3-T4	67 (89.3)	70 (93.3)	
N stage			0.282
N0-N1	19 (25.3)	25 (33.3)	
N2-N3	56 (74.7)	50 (66.7)	
TNM stage			0.519
III	16 (21.3)	13 (17.3)	
IVa	49 (65.3)	53 (70.7)	
IVb	11 (14.7)	9 (12.0)	
KPS score			0.245
80-90	41 (54.7)	48 (64.0)	
70-80	34 (45.3)	27 (36.0)	

TNM: tumor, lymph node, metastasis; KPS: Karnofsky performance status.

Helsinki Declaration and was reviewed by the Ethics Committee of the hospital, and the patients signed the informed consent.

Treatment methods

All patients received induction chemotherapy using TPF regimen: patients underwent intravenous drips of docetaxel (75 mg/m^2) and cisplatin (75 mg/m^2) on the first day and were continuously pumped with 5-FU (750 mg/m^2/d) intravenously for 1-5 d (120 h) for a total of 2 cycles (21 days a cycle).

Three-dimensional conformal IMRT was conducted for all patients once a day for 5 times a week after induction chemotherapy. Specifically, IMRT was applied in the whole target area (the primary lesion and lymphatic drainage area were covered in one intensity-modulated target area), and the target area was outlined with reference to MRI images of patients. The radiation dose of target areas are set as follows: GTVnx (nasopharyngeal tumor and invasion area shown in imaging examination): 69.96-73.92 Gy/33f, planning target volume of the nasopharynx (PTVnx) (OTVnx + 3 mm): 69.96 Gy/33f, clinical volume 1 (CTV1) (PTVnx + high surrounding area + upper neck lymph node drainage area): 60.06 Gy/33 f and CTV2 (1-2 neck areas beyond lymph node metastasis): 50.96 Gy/28 f.

Chrono-chemotherapy was carried out during radiotherapy, and patients in experimental groups were administered using the French "Melodie" multi-channel programming infusion pump computer. The patients in chrono-chemotherapy group were given 100 mg/m^2 cisplatin at 10:00-22:00 (peaked at 16:00) on the 1st d in the form of a sinusoid. In the meantime, the patients in control group received conventional intravenous instilling of 100 mg/m^2 cisplatin on the 1st d. In both groups, the administration was conducted for a total of 2-3 cycles, with 21 d as a cycle.

Observational indexes

After treatment, the clinical efficacy of patients was evaluated according to the WHO criteria for evaluating the efficacy of solid tumors as follows: complete remission (CR): the tumor disappears completely for ≥1 month, partial remission (PR): the product of the maximum diameter and the maximum vertical diameter of the tumor is reduced by ≥50%, and the duration is ≥1 month, stable disease (SD): the product of two diameters of lesions is decreased by <50%, or increased by <25%, and the duration is ≥1 month, and progressive disease (PD): the lesion is increased by ≥25%, or new lesions appear. Overall response rate (ORR) = (CR + PR)/total cases × 100%. The incidence rates of treatment-related adverse reactions, including oral mucositis, gastrointestinal reactions, bone marrow suppression and liver function damage, were recorded. All adverse reactions were evaluated by Common Terminology Criteria for Adverse Events (CTCAE 3. 0).

The levels of peripheral blood immune cells, including T lymphocyte subsets [cluster of differentiation (CD)3$^+$, CD4$^+$, CD8$^+$, CD4$^+$/CD8$^+$, CD16$^+$CD56$^+$], were measured by flow cytometry before treatment and at 6 months after treatment.

After treatment, the patients were reexamined every 1-2 months in the first year, every 3 months in the second year and every 3-6 months after the third year. Patients' survival and disease progression were recorded during follow-up, and the deadline for follow-up was May 2020.

Statistics

SPSS 22.0 (IBM, Armonk, NY, USA) was adopted for statistical analyses. Measurement data were expressed as mean ± standard deviation, and the comparison between two groups was conducted using the t-test. Count data were expressed by percentage (%) and compared via x^2 test or Fisher's exact test. The t-test was applied for intergroup comparison, while the two-way analysis of variance was utilized for intragroup comparison. Survival curves were plotted using Kaplan-Meier method, and Log-rank test was carried out. P<0.05 indicated statistically significant difference.

Results

Response of patients

According to the short-term efficacy evaluation, there were 9 cases (12.0%) of CR, 62 cases (82.7%) of PR, 4 cases (5.3%) of SD, and 0 cases of PD, with an ORR of 94.7% (71/75). In control group, there were 11 cases (14.7%) of CR, 61 cases (81.3%) of PR, 3 cases (4.0%) of SD, and 0 cases of PD, with an ORR of 96.0% (72/75). No statistically significant difference was detected in the short-term clinical ORR between the two groups (p=0.598) (Table 2).

Table 2. Comparison of short-term efficacy between the two groups of patients

Indicators	*Chrono-chemotherapy group (n=75)* *n (%)*	*Control group (n=75)* *n (%)*	*p*
Complete response (CR)	9 (12.0)	11 (14.7)	
Partial response (PR)	62 (82.7)	61 (81.3)	
Stable disease (SD)	4 (5.3)	3 (4.0)	
Progressive disease (PD)	0 (0)	0 (0)	
ORR (CR + PR)	71 (94.7)	72 (96.0)	0.598

ORR: Overall response rate.

Incidence of adverse reactions of patients

Treatment-related adverse reactions of the two groups of patients mainly included leukopenia, neutropenia, anemia, thrombocytopenia, gastrointestinal reactions, oral mucositis and liver function damage, most of which were grade I-II and could be obviously alleviated after symptomatic treatment. Among patients with grade III-IV adverse reactions, there were 15 cases (20.0%) and 17 cases (22.7%) of leukopenia, 8 cases (10.7%) and 9 cases (12.0%) of neutropenia, 0 cases and 2 cases (2.7%) of anemia, 0 cases and 2 cases (2.7%) of thrombocytopenia, 0 cases and 5 cases (6.7%) of gastrointestinal reactions, and 1 case (1.3%) and 5 cases (6.7%) of oral mucositis in chrono-chemotherapy group and control group, respectively. The incidence rates of gastrointestinal reactions and oral mucositis in chrono-chemotherapy group were significantly lower than those in control group (p=0.032, p=0.044), showing statistically significant differences, but there were no statistically significant differences in other adverse reactions (p>0.05) (Table 3).

Level of immune cells in peripheral blood of patients before and after treatment

Before treatment, there were no statistically significant differences in the levels of $CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$, $CD16^+CD56^+$ and $CD19^+$ T cells between the two groups (p>0.05). At 6 months after treatment, the levels of $CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$, $CD16^+CD56^+$ and $CD19^+$ T cells in peripheral blood of patients were significantly lower than those before treatment (p<0.05). Moreover,

Table 3. Comparison of adverse reactions between the two groups of patients

Parameters	*Chrono-chemotherapy group (n=75)*		*Control group (n=75)*		*p*
	Grade I-II *n (%)*	*Grade III-IV* *n (%)*	*Grade I-II* *n (%)*	*Grade III-IV* *n (%)*	
Leukopenia	42 (56.0)	15 (20.0)	46 (61.3)	17 (22.7)	0.221
Neutropenia	35 (46.7)	8 (10.7)	39 (52.0)	9 (12.0)	0.403
Anemia	43 (57.3)	0 (0)	48 (64.0)	2 (2.7)	0.414
Thrombocytopenia	11 (14.7)	0 (0)	13 (17.3)	2 (2.7)	0.388
Gastrointestinal reaction	53 (70.7)	0 (0)	57 (76.0)	5 (6.7)	0.032
Oral mucositis	56 (74.6)	1 (1.3)	61 (81.3)	5 (6.7)	0.044
Liver function damage	10 (13.3)	0 (0)	12 (16.0)	0 (0)	0.544

Table 4. Comparison of T lymphocyte subsets levels between the two groups of patients

	Chrono-chemotherapy group (n=75)	*Control group (n=75)*	*p*
$CD3^+$ T cell (%)			
Pretreatment	66.17±10.48	65.08±9.94	0.514
Posttreatment	62.31±10.73	60.62±10.44	0.330
$CD3^+CD4^+$ T cell (%)			
Pretreatment	37.31±7.65	35.28±7.08	0.084
Posttreatment	30.51±9.58	28.76±5.25	0.113
$CD3^+CD8^+$ T cell (%)			
Pretreatment	36.13±6.76	34.85±7.69	0.148
Posttreatment	29.23±5.11	27.88±9.77	0.387
$CD4^+/CD8^+$ ratio			
Pretreatment	1.35±0.39	1.23±0.36	0.172
Posttreatment	1.12±0.43	1.07±0.40	0.129
$CD16^+CD56^+$ T cell (%)			
Pretreatment	25.23±9.51	24.62±10.40	0.708
Posttreatment	21.71±9.59	18.34±10.17	0.034
$CD19^+$ T cell (%)			
Pretreatment	10.57±5.51	11.03±5.10	0.597
Posttreatment	7.82±3.79	7.41±3.56	0.396

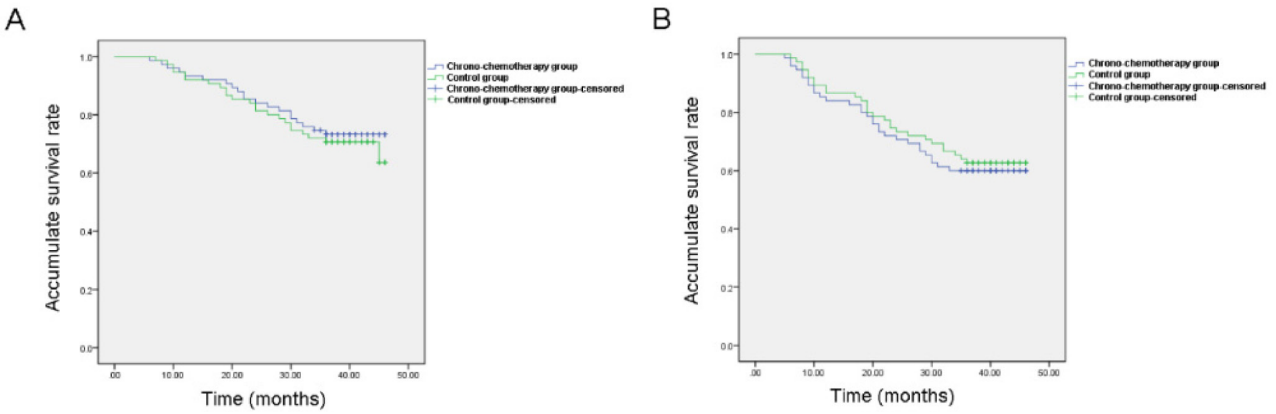

Figure 1. Kaplan-Meier survival curves of patients in Chrono-chemotherapy group and Control group. **A:** The difference in the overall survival rate of patients between Chrono-chemotherapy group and Control group had no statistical significance (p=0.518). **B:** The difference in the progression-free survival rate of patients between Chrono-chemotherapy group and Control group had no statistical significance (p=0.657).

after treatment, no statistically significant differences were detected in the levels of $CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ and $CD19^+$ T cells between the two groups (p>0.05), but the level of $CD16^+CD56^+$ T cells in chrono-chemotherapy group was significantly higher than that in control group (p=0.034) (Table 4).

Recurrence and survival of patients

The follow-up ended in May 2020, and the median follow-up time was 36.5 months. In chrono-chemotherapy group and control group, the one-year OS was 93.3% (70/75) and 92.0% (69/75), the 2-year OS was 84.0% (63/75) and 81.3% (61/75), and the 3-year OS was 73.3% (55/75) and 69.3% (52/75), respectively. Besides, the one-year PFS was 84.0% (63/75) and 86.7% (65/75), the 2-year PFS was 70.7% (53/75) and 73.3% (55/75), and the 3-year PFS was 60.0% (45/75) and 62.7% (47/75), respectively. As shown in Figure 1, the OS and PFS curves were plotted using Kaplan-Meier method and log-rank test showed no statistically significant differences in OS and PFS between the two groups of patients (p=0.518, p=0.657).

Discussion

Cisplatin + 5-FU (PF) is the commonly used chemotherapy regimen for nasopharyngeal carcinoma. In multiple clinical trials, locally advanced or advanced nasopharyngeal carcinoma are treated with docetaxel combined with cisplatin-based chemotherapy, followed by concurrent chemoradiotherapy. This regimen shows high efficacy, and its adverse reactions are tolerable [10]. TPF regimen is superior to PF regimen in LC, OS and PFS [11,12]. In some studies, patients with locally advanced nasopharyngeal carcinoma have been randomly researched, and it has been discovered that the short-term efficacy of TPF-induced chemotherapy combined with chemoradiotherapy group is good, with effective rate of 100%, and that TPF-induced chemotherapy is superior to PF regimen [13].

During concurrent chemoradiotherapy, chemotherapy drugs can improve the sensitivity of tumor cells to radiation, and radiotherapy can enhance their cytotoxicity. The combined application of the two methods can notably improve the killing effect on local tumor cells [14]. The theoretical basis of concurrent chemoradiotherapy for locally advanced nasopharyngeal carcinoma is that the cytotoxic effect of chemotherapy drugs can reduce the tumor volume and improve the blood supply and tumor hypoxia. Chemotherapy drugs suppress or interfere with the repair of sublethal injury and potentially fatal injury after radiotherapy, and combined radiotherapy can play a synergistic role [15]. Studies have shown that the 3-cycle concurrent chemoradiotherapy with a large dose of cisplatin (100 mg/m^2) has a high LC for nasopharyngeal carcinoma. Chan et al conducted a randomized study on patients with advanced nasopharyngeal carcinoma using chemotherapy with cisplatin, and discovered that concurrent chemoradiotherapy increased the 5-year survival rate of patients compared with radiotherapy alone [16]. Nevertheless, toxicity was increased remarkably while the tumor control rate was raised during concurrent chemoradiotherapy [17]. Many phase III clinical studies of concurrent chemotherapy showed that the acute reaction in cisplatin group was evidently increased [18,19]. Therefore, the way to take effective measures to

reduce the side effects of chemotherapy drugs is vital for improving the efficacy and the quality of life of patients.

The secretion of various hormones and the activity of enzymes in the human body all show rhythmic changes, and the biological rhythm of the body causes circadian changes in the blood concentration, bioavailability and metabolism of drugs. The growth, proliferation, DNA synthesis and drug metabolism of normal cells and tumor cells have a biological rhythm in human body. During chrono-chemotherapy, the appropriate time of administration was selected based on the biological rhythm of human body, so as to improve the efficacy of drugs, reduce the adverse reactions of drugs and improve the tolerance of patients [20]. Currently, this medication has been recognized by a majority of European and American countries, and has been widely applied in clinical practice.

Phase I-II clinical trials by Focan et al manifested that the anti-tumor effect can be increased twice, the adverse reactions of mucosa can be reduced by 1/5, and the adverse reactions of peripheral nervous system can be decreased by 50% through chrono-chemotherapy, which has been confirmed by the European Institute for Cancer Therapy [21]. Cisplatin is a chemotherapy drug with a high risk of vomiting. The digestive symptoms of cisplatin usually depend on the concentration of free platinum in patients' plasma and the circadian secretion rhythm of reduced glutathione (GSH). Some studies have pointed out that the highest binding rate between free platinum in plasma and plasma protein appears at 16: 00, and GSH secretion also peaks in the afternoon. During this period, the adverse reactions caused by cisplatin are lighter [22]. The occurrence of oral mucositis has a close association with the administration of 5-FU, and the metabolism of 5-FU also changes periodically in normal cells. Dihydropyrimidine dehydrogenase (DPD) is the crucial enzyme limiting rates in this metabolic process. It has been pointed out in some studies that the activity of DPD also has an obvious circadian rhythm, and its adverse reactions can be markedly reduced by chrono-chemotherapy. In the observation of hematological adverse reactions in this study, it was discovered that the hematological adverse reactions were milder and the incidence rate of grade III or above adverse events was lower in chrono-chemotherapy group than those in control group, displaying no statistically significant differences, which was considered to be associated with the attenuation effect of chronochemotherapy. Moreover, the incidence rates and severity of vomiting and oral mucositis in chrono-chemotherapy group were also evidently lower than those in control group, which was basically consistent with the literature report [23]. Besides, short-term efficacy evaluation and follow-up results revealed that the two groups of patients had similar efficacy and prognosis.

The results of a study on the influence of different doses of everolimus on lymphocyte subsets in patients illustrated that immunosuppression is related to the poor prognosis of renal cancer patients, indicating that the change of lymphocyte subsets in malignant tumor patients is probably a potential prognostic factor [24]. In the current study, the count of each lymphocyte subset in both chrono-chemotherapy group and control group declined after induction therapy combined with chemoradiotherapy compared with that before treatment, suggesting that chemoradiotherapy leads to immunosuppression. However, chrono-chemotherapy group exhibited a remarkably higher absolute count of $CD16^+CD56^+$ lymphocytes than control group, and the difference was statistically significant, implying that the nonspecific immune function protection in chrono-chemotherapy group is better than that in control group. A retrospective study by Zhou et al demonstrated that the $CD16^+CD56^+$ lymphocyte count is correlated with the OS of patients with mantle cell lymphoma [25]. $CD16^+CD56^+$ lymphocytes, as a type of immune cells without MHC restriction, exert a direct killing effect on tumors, and the decrease of their absolute value count indicates the damage of non-specific immune function. Some studies suggest that $CD16^+$ $CD56^+$ lymphocytes are able to enhance the specific immune response of $CD8^+$ lymphocytes, presenting a better prognosis [26].

This study was retrospective with a limited number of patients enrolled, short follow-up period, and not comprehensive follow-up content. In the future, more rigorous multi-center prospective randomized studies with large sample size should be designed to confirm the research conclusions.

Conclusion

As a new treatment mode, chrono-chemotherapy combined with induction chemotherapy and IMRT can reduce the incidence rate and severity of treatment-related adverse reactions and improve immunosuppression without reducing clinical efficacy, which is worthy of clinical promotion and application.

Conflict of interests

The authors declare no conflict of interests.

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