

RESEARCH ARTICLE

Selective Radiotherapy after Distant Metastasis of Nasopharyngeal Carcinoma Treated with Dose-Dense Cisplatin plus Fluorouracil

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Abstract

Purpose: To investigate the efficacy and safety of selective radiotherapy after distant metastasis of nasopharyngeal carcinoma (NPC) treated with dose-dense cisplatin plus fluorouracil. **Materials and Methods:** Eligible patients were randomly assigned to a study group treated with dose-dense cisplatin plus fluorouracil following selective radiotherapy and a control group receiving traditional cisplatin plus fluorouracil following selective radiotherapy according to a 1:1 distribution using a digital random table method. The primary endpoint was overall survival (OS). Secondary endpoints were progression-free survival (PFS), objective response rate, relapse or progression rate in the radiation field and treatment toxicity. **Results:** Of 52 patients in the study group, 20 cases underwent radiotherapy, while in the control group of 51 patients, 16 underwent radiotherapy. The median PFS, median OS, survival rates in 1, 2 and 3 years in study and control group were 20.9 vs 12.7 months, 28.3 vs 18.8 months, 85.2% vs 65.9%, 62.2% vs 18.3%, and 36.6% vs 5.2% (*p* values of 0.00, 0.00, 0.04, 0.00 and 0.00, respectively). Subgroup analysis showed that the median OS and survival rates of 1, 2, 3 years for patients undergoing radiotherapy in the study group better than that in control group (43.2 vs 24.1 months, 94.1% vs 86.7%, 82.4% vs 43.3%, 64.7% vs 17.3%, (*p*=0.00, 0.57, 0.04 and 0.01, respectively). The complete response rate, objective response rate after chemotherapy and three months after radiotherapy, relapse or progression rate in radiation field in study group and in control group were 19.2% vs 3.9%, 86.5% vs 56.9%, 85% vs 50%, 95% vs 81.3% and 41.3% vs 66.7% (*p*=0.03, 0.00, 0.03, 0.30, 0.01 respectively). The grade 3-4 acute adverse reactions in the study group were significantly higher than in the control group (53.8% vs 9.8%, *p*=0.00). **Conclusions:** The survival of patients benefits from selective radiotherapy after distant metastasis of NPC treated with dose-dense cisplatin plus fluorouracil.

Keywords: Nasopharyngeal carcinoma - distant metastases - dose dense chemotherapy - radiotherapy

Asian Pac J Cancer Prev, 16 (14), 6011-6017

Introduction

The incidence of NPC is high in China and Southeast Asian countries, especially Pearl River Basin of Guangxi and Guangdong. The annual incidence rate is as high as 20/100,000 (Jemal et al., 2011). The local area is one of the high incidence areas in China. The progress of radiotherapy technology increased the local control rate by 75-95% (Ng et al., 2010; Xiao et al., 2011; Abbasi et al., 2013). There were about 40% of patients with unsuccessful local therapy combined with distant metastasis; The distant metastasis still appeared on 18.5% of patients with local control (Kong et al., 2014); In addition, about 95% of NPC was undifferentiated non-keratinizing carcinoma. Its biological characteristics are highly invasive and distant metastasis easily occurs (Lee et al., 2012). The distant metastasis occurred on about 20% of newly diagnosed

patients (Xiao et al., 2011). Chemotherapy is the main method for treating distant metastasis of NPC and various kinds of cytotoxic drugs have anticancer activity to NPC. Although there are many drugs in recent years, cisplatin is the most effective drug treatment for NPC now (Kua, et al., 2013). The response rate and progression-free survival time of cisplatin in combination with docetaxel or gemcitabine scheme was not superior to those of cisplatin in combination with fluorouracil (Kertmen et al., 2015). Therefore, cisplatin in combination with fluorouracil remains the standard chemotherapy scheme of NPC. Its objective response rate was about 60% (Wang et al., 1991). But the progression-free survival and overall survival were still low. The progression-free survival was from 5.6 to 10.6 months and the overall survival was from 7.6 to 19.6 months.

In 1979, the probability of drug resistance was

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calculated by Goldie and Coldman from cell proliferation dynamics perspective. The tumor cells had a certain probability of mutation in cell proliferation process, leading to the production of drug-resistant cells. The more the doubling times were, the more the drug-resistant cells produced. Shortening the interval of chemotherapy could reduce the production of drug-resistant cells. This viewpoint was being confirmed by more and more clinical practice. For example, doxorubicin, cyclophosphamide and paclitaxel sequential treatment scheme was modified into dose dense in the treatment of high-risk postoperative breast cancer patients. The patient's disease-free survival rate and total survival rate were improved (Hudis et al., 2015). The dose-dense chemotherapy also improved overall survival rate in lymphoma (Aoki et al., 2013), ovarian cancer (Kumar et al., 2015).

Dose-dense chemotherapy is one of the major progresses in chemotherapy achieved in recent years (Hudis et al., 2015). The patients with NPC of the distant metastasis whose lesion was not disseminated and the objective response was better after dose-dense cisplatin combined with fluorouracil chemotherapy, was selected to treat by radiotherapy. The overall survival was significantly increased. The similar report was not retrieved. The results were summarized as follows.

Materials and Methods

Inclusion criteria of patients

All enrolled patients were admitted in the hospital and met the following conditions at the same time from April 1st 2010 to July 30th 2014. (1)The pathological diagnosis was NPC. CT/ECT/MRI/ B ultrasound showed metastatic carcinoma; (2)There was at least one measurable lesion by imaging examination; (3)The age was 18-70 years old; (4)The patients or clients signed the informed consent which was agreed by hospital medical ethics committee and were willing to accept follow-up; (5) The expectancy of life was greater than 3 months and ECOG performance

status score was 0-2; (6)No chronic pulmonary or heart disease. The heart and lung function was normal; (7) Blood test and chemistry profile: Hb > 100 g/L, neutrophil > $1.5 \times 10^9/L$, platelet > $100 \times 10^9/L$, serum creatinine < the upper limit of normal value, serum total bilirubin < the upper limit of normal value, alanine aminotransferase < 2 times of the upper limit of normal value; (8) The patients who received radiotherapy should meet additionally 2 conditions: Firstly, the lesion was not disseminated and disappeared or reduced after 4-6 cycles of chemotherapy. Secondly, accepting and completing radiotherapy.

Exclusion criteria of patients

One of the following cases should be excluded: (1) NPC in combination with brain metastasis; (2) Receiving chemotherapy within 6 months; (3) Being allergic to cisplatin and fluorouracil; (4) With a hepatitis or nephritis history; (5) The pregnant or lactating patients.

Randomization

Of 123 patients involved in the qualification evaluation, 20 patients did not meet the qualification, and 103 patients were eligible. The patients were randomly divided into two groups, and 52 patients in study group receiving radiotherapy after dose-dense chemotherapy, while the other 51 patients in control group receiving radiotherapy after traditional chemotherapy according to 1:1 using digital random table method. The baseline features of patients in two groups meeting statistical analysis requirements are listed in Table 1.

Chemotherapy schedule

Patients were treated with cisplatin in combination with fluorouracil chemotherapy. Routine hydration and antiemetic were performed for 6 cycles or until progression of disease, intolerable side effects or death. Control group: Cisplatin 80 mg/m² was intravenously injected on day1 of a 4-week cycle; fluorouracil 4000 mg/m² continuous infusion for 96 hours of a 4-week

Table 1. Patients Baseline Characteristics n(%)

Characteristics of patients	Study group n=52	Control group n=51	p value
Average age(range)	46.8(27~70)	44.2(34~69)	0.07
Sex(male/ female)	41/11	39/12	0.82
Pathological types WHOII/III	2/50	4/47	0.44
Nasopharyngeal lesions with/without	30/22	28/23	0.84
Single/multiple organ metastasis	11/41	15/36	0.37
Metastatic site			0.78
Bone metastasis	30(57.7)	33(64.7)	
Hepatic metastasis	19(36.5)	15(29.4)	
Pulmonary metastasis	10 (19.2)	13(25.5)	
Abdominal lymph node metastasis	6 (11.5)	5(9.8)	
Primary treatment	28(53.8)	25(49.0)	0.89
Radiotherapy history	24(46.2)	26(51.0)	
Chemotherapy history	18(34.6)	18(35.3)	
Chemotherapy drugs			0.79
Platinum	18(34.6)	18(35.3)	
Paclitaxel	12(23)	10(19.6)	
Gemcitabine	6(11.5)	8(15.7)	
ECOG performance status score(0/1/2)	8/28/16	10/30/11	0.55

Abbreviations: ECOG, Eastern Cooperative Oncology Group; WHO, World Health Organization

cycle. Study group: Cisplatin 80mg/m² was intravenously injected on day1 of a 2-week cycle; fluorouracil 4000 mg/m² continuous infusion for 96 hours of a 2-week cycle; 300ug recombinant human granulocyte colony stimulating factor was subcutaneously injected, days6-10. Those patients receiving radiotherapy were intravenously injected with 30 mg/m² cisplatin weekly during the period of radiotherapy

Radiotherapy scheme

The enrolled patients underwent three dimensional conformal radiotherapy at 3~4 weeks after chemotherapy by using Elekta 6MV X-ray. The patients were immobilized in the supine position with a thermoplastic mask and vacuum bag. CT scan thickness: head and neck 3mm, chest, abdomen and limbs 5mm. The workstation was Elekta Precise Plan R2.15 three-dimensional treatment planning system. The delineation of target and organ at risk referred to the definition ICRU No. 83 report. Gross tumor volume (GTV) was residual tumor showed by CT and MRI after chemotherapy; clinic tumor volume (CTV) was gross tumor extended to 3~10 mm showed by MRI/CT before chemotherapy. Special circumstances that if vertebral metastasis CTV included the entire vertebral body, neck lymph nodes metastasis included the drainage area of the lymph node, and lesion had bone barrier, it was generally extended to 3mm; planning target volume (PTV) had a great difference between the different parts according to respiratory motion size and posture repeatability. Generally, the head and neck extended to 3~5mm, chest, abdomen and limbs extended to 8~15mm. Nasopharyngeal or neck radiotherapy dose: if the local and distant lesion disappeared, primary tumor bed for a total

dose 60 Gy. Nevertheless, if the local residual and distal lesion disappeared, local for total dose 70 Gy. Supposing the local and distant had lesion residue, for its total dose 50 Gy; The normal organ tolerance dose was taken as the reference principle of RTOG (Radiation Therapy Oncology Group) for rest radiation doses. The target region dose should be increased. Meanwhile it did not exceed the limited dose of organ at risk. The fractionated dose and segmentation method was 2Gy each time, once a day, 5 times every week.

Efficacy and toxicity evaluation

What's more, medical history and physical examination, blood test, chemistry profile, bone scanning, chest X-ray or chest CT, abdominal/ pelvic B ultrasound or CT, nasopharynx and neck MRI and other discomfort symptom parts were checked correspondingly. From the beginning of chemotherapy to 4 weeks after the end of chemotherapy, blood test was taken for 2-3 times every a week, chemistry profile and physical condition assessment had been tested once. Lesion was reviewed every 4 weeks. One month later, chemistry profile and lesion were tested every 2-3 months. Two years later, chemistry profile and lesion were tested every 4-6 months. If new symptoms appeared on patients, the corresponding examinations were performed at any time. The primary endpoint was overall survival (OS). The second endpoints were progression-free survival (PFS), objective response rate, relapse or progression rate in radiation field and toxicity. The objective response rate was evaluated by RECIST1.1 version. The toxicity of chemotherapy was evaluated once every cycle by NCI-CTC version 3. The acute or chronic radiotherapy injury was evaluated by RTOG radiation toxicity criteria.

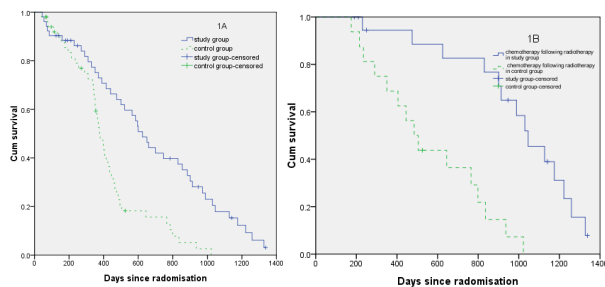


Figure 1. Kaplan-Meier Curve of Progression-Free Survival (PFS) 1A Comparisons between Study and Control Group, 1B Comparisons between Chemotherapy Following Radiotherapy in Study and Control Group

Statistical analysis

Statistical analysis was performed by using SPSS 17.0 software. PFS and OS evaluations were analyzed by Kaplan-Meier analysis. The log-rank test was compared between PFS and OS in two groups. The objective response rate, relapse or progression rate in radiation field, toxicity and other counting data were tested using Fisher's exact test in descriptive statistics analysis. The measurement data such as average age was tested by T test. $p < 0.05$ was considered statistically significant.

Follow up

The last follow-up time was March 27th 2015. Median

Table 2. Best Response According to RECIST n (%)

	after chemotherapy			three months after radiotherapy		
	study group (n=52)	control group (n=51)	p value	study group (n=20)	control group (n=16)	p value
CR	10(19.2)	2(3.9)	0.03	17(85)	8(50)	0.03
PR	35(67.3)	27(53.0)	0.16	2(10)	5(31.3)	0.20
SD	3(5.8)	17(33.3)	0.00	3(18.7)	0.08	
PD	4 (7.7)	5(9.8)	1(5)	0.00	1.00	
OR	45(86.5)	29(56.9)	0.00	19(95)	13(81.3)	0.30
DC	48(92.3)	46(90.2)	0.74	19(95)	16(100)	1.00

Abbreviations: CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, OR: objective response, DC: disease control

follow-up was 30 months. 40 patients (77%) died of tumor progression and 12 survived in study group. Among them, 3 patients survived for more than 3 years. 44 patients (86.3%) died of tumor progression and 7 survived in control group. Among them, 1 patient survived for about 3 years.

Results

Evaluation for best response

The number of patients in study group who completed 6 cycles was significantly higher than that of control group (90.4% vs 74.5%, $p=0.04$). Of 20 patients in study group underwent radiotherapy, whose 2-5 parts received radiotherapy, such as nasopharynx and neck, liver, lung, humerus and lumbar. There were a total of 63 parts and the average was 3.15 parts. 16 patients in control group underwent radiotherapy, whose 2-4 parts received radiotherapy in each patient and a total of 48 parts and the average was 3 parts. Local and distant lesion residual rates in control group were high after chemotherapy. So the cases and average radiotherapy doses of lesion in study group and control group respectively are: nasopharynx and neck: 20 (58Gy) vs 16 (52.5Gy); liver: 15 (35.7Gy) vs 9 (40.9Gy); lung: 6 (49Gy) vs 5 (50.4Gy); para-aortic lymph node: 3 (48Gy) vs 1 (48Gy); thoracic vertebra: 6 (40Gy) vs 5 (40Gy); lumbar vertebra: 10 (40Gy) vs 7 (40Gy); pelvis: 4 (40Gy) vs 3 (40Gy); humerus: 1 (40Gy) vs 0 and femur 1 (40Gy) vs 2 (40Gy).

The objective response rate was assessed by RECIST 1.1 version after chemotherapy or radiotherapy. The complete response rate and the objective response rate in study group were higher for 15.3% and 29.6% than those of control group, which had statistical significance. The primary tumor bed of complete response or residual lesions was assessed after radiotherapy for 3 months. The complete response rate was also higher than those of control group (Table 2). In addition, in-field recurrence or progression of 26 parts appeared during follow-up period

in 63 radiotherapy parts in study group (41.3%). While in-field recurrence or progression of 32 parts appeared in 48 radiation parts in control group (66.7%). There was statistically significant in-field recurrence or progression rate between two groups, $P=0.01$.

Evaluation of PFS

The median PFS in study and control group was 20.9

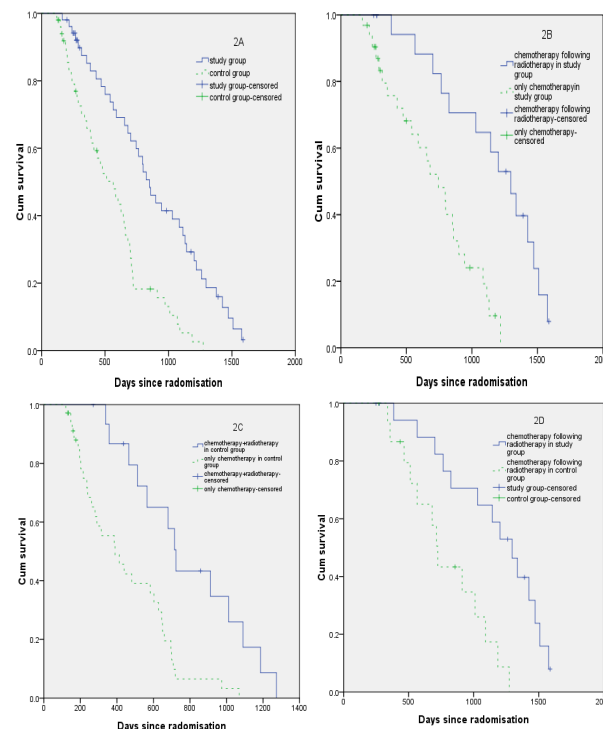


Figure 2. Kaplan-Meier Cure of Overall Survival, 2A Comparisons between study and Control Group, 2B Comparisons between Chemotherapy Following Radiotherapy and Only Chemotherapy in Study Group, 2C Comparisons between Chemotherapy Following Radiotherapy and Only Chemotherapy in Control Group, 2D comparisons between Chemotherapy Following Radiotherapy in Study and Control Group

Table 3. The Commonly Acute Treatment-Related Adverse Reactions n(%)

	All adverse reactions			Grade3-4 adverse reactions		
	Study group	Control group	p Value	Study group	Control group	p Value
	n=52	n=51		n=52	n=51	
Anemia	50 (96.2)	43 (84.3)	0.05	5 (9.6)	0.00	0.06
Granulopenia	30 (57.7)	26 (51.0)	0.56	4 (7.7)	0.00	0.12
Thrombocytopenia	50 (96.2)	21 (42.2)	0.00	7 (13.5)	0.00	0.01
Oral mucositis	51 (98.1)	21 (41.2)	0.00	27 (51.9)	12.00	0.00
Vomit	39 (75.0)	35 (68.6)	0.52	3 (5.8)	1 (2.0)	0.62
Nausea	51 (98.1)	47 (92.2)	0.21	2 (3.8)	0.00	0.50
Loss of appetite	50 (96.2)	35 (68.6)	0.00	6 (11.5)	0.00	0.03
Fatigue	38 (73.1)	16 (31.4)	0.00	11 (21.9)	2 (4.0)	0.02
Diarrhea	5 (9.6)	3 (5.9)	0.72	0.00	0.00	
Increased aminopherase	18 (34.6)	15 (29.4)	0.67	2 (3.8)	0.00	0.50
Increased bilirubin	6 (11.5)	2 (3.9)	0.27	1 (1.9)	0.00	1.00
Increased serum creatinine	5 (9.6)	3 (5.9)	0.72	0.00	0.00	
Neurotoxicity	5 (9.6)	3 (5.9)	0.72	0.00	0.00	
Ototoxicity	3 (5.8)	1 (2.0)	0.62	0.00	0.00	
Skin damage	20 (38.5)	9 (17.6)	0.03	4 (7.7)	2 (3.9)	0.68
Total cases	52 (100)	45 (94.0)	0.01	28 (53.8)	5 (9.8)	0.00

months [95%CI 17.5-24.1] vs 12.7 months [95%CI 11.2-14.1], which was significantly improved for 8.2 months in study group ($p=0.00$ Figure 1A). Compared with PFS in selective radiotherapy after chemotherapy, the median PFS in study and control group was 34.9 months [95%CI 29.1-40.6] and 16.2 months [95%CI 12.2-20.1]. The former median PFS was significantly prolonged for 18.7 months ($p=0.00$ Figure 1B)

Evaluation for OS

The median OS, the survival rates in 1, 2 and 3 years in study and control group were 28.3 months [95%CI 23.9-32.8] vs 18.8 months [95%CI 13.0-24.6], 85.2% vs 65.9%, 62.2% vs 18.3% and 36.6% vs 5.2%. The improvement in study group were statistically significant ($p=0.00, 0.04, 0.00, 0.00$ respectively (Figure 2A).

Subgroup analysis showed that the median OS, the survival rates in 1, 2 and 3 years compared

chemotherapy following radiotherapy with only chemotherapy in study group were 43.2 months [95%CI 35.0-51.3] vs 24.8 months [95%CI 17.3-32.3], 94.1% vs 75.7%, 82.4% vs 52.1%, 64.7% vs 19.2% ($p=0.00, 0.53, 0.05, 0.00$, respectively, Figure 2B). The median OS, the survival rates in 1, 2 and 3 years compared chemotherapy following radiotherapy with only chemotherapy in control group were 24.1 months [95%CI 21.5-26.7] vs 13.0 months [95%CI 7.4-18.6], 86.7% vs 55.4%, 43.3% vs 6.5%, 17.3% vs 0% ($p=0.00, 0.03, 0.00, 0.03$, respectively, Figure 2C). The chemotherapy following radiotherapy in study group was compared with that of control group, the median OS, the survival rates in 1, 2 and 3 years were 43.2 months [95%CI 35.0-51.3] vs 24.1 months [95%CI 21.5-26.7], 94.1% vs 86.7%, 82.4% vs 43.3%, 64.7% vs 17.3% ($p=0.00, 0.57, 0.04, 0.01$ respectively, Figure 2D).

Acute and late toxicities

The treatment related death that did not occur on all patients in the course of treatment. The total and grade 3-4 acute adverse reaction rates were 100% and 53.8% in study group, which was 6% and 44% higher than those of control group. The difference was statistically significant. The total adverse reactions including thrombocytopenia, oral mucositis, loss of appetite, fatigue, skin damage, 3-4 level adverse reactions including thrombocytopenia, oral mucositis, loss of appetite, fatigue were increased (Table 3). But the difference of chronic toxicity of radiotherapy had no statistically significant between study and control groups such as grade 1-2 xerostomia 40% vs 44%, grade 1-2 radiation related pneumonia 50% vs 40% (all $p>0.05$).

Discussion

To the best of our knowledge, this is the first clinical study on patients with distant metastases of NPC for dose-dense chemotherapy of cisplatin plus fluorouracil following selection radiotherapy to show an improvement in efficacy outcomes. Dose-dense chemotherapy refers to shorten the inter-treatment interval to minimize the regrowth of tumor cells, thus allowing for more effective cell killing (Hudis et al., 2015). The higher complete response

rate was obtained in study group by using dose-dense cisplatin combined with fluorouracil chemotherapy, so more complete response patients received radiotherapy that relapse or progression rate in radiation field, median PFS, median OS, survival rate in 2 and 3 years of whole or patients undergoing radiotherapy in study group were significantly better than those of control group. The possible mechanisms to improve the effect included: A. Dose-dense chemotherapy reduced the production of secondary drug resistant tumor cells, which is the main reason for the failure of chemotherapy. During the period of cell proliferation drug resistant cells can be generated, which are positively related with doubling times, therefore shortening chemotherapy interval can reduce the production of drug resistance cells, which can make drug eliminate cancer cells more thoroughly. B. To reduce tumor proliferation time. Tumor cell re-proliferation appears during chemotherapy interval. The longer the time is, the more the proliferation is. The chemotherapy cycle was shortened from 28 days to 14 days. In case of the doubling time of stem cell was 24 hours. Dose-dense chemotherapy could reduce the production of a tumor stem cell from 2^{28} to 2^{14} cells (reduce 16384 times). Although this pure theory value, which does not take the loss of tumor cells and stem cells which has turned to G0 or non proliferation cells into account, was higher than the actual situation. The complete response rate of dose-dense chemotherapy 19.2% was significantly higher than 3.9% in control group whose chemotherapy cycles were 28 days. This could explain the effect of reducing tumor proliferation time on size of tumor. C. Dose-dense chemotherapy residual tumor proliferation time was reduced. The tumor volume was smaller, but the growth proportion was increased. The cell cycle specific cytotoxic drugs such as cisplatin play a great role in the treatment. D. The tumor volume was decreased, which increased patients' confidence and compliance. The chemotherapy plan was easy to be completed. 90.4% of dose-dense chemotherapy patients completed 6 cycles of chemotherapy, but only 74.5% of patients completed chemotherapy in control group. Fandi (2000) advocates 6 cycles of chemotherapy for NPC patients with distant metastases because less cycles would affect treatment effect. E. Dose-dense chemotherapy could kill potential dispersed subclinical lesions more effectively. Therefore, the median OS in study group and patients who received dose-dense chemotherapy following radiotherapy in this group was prolonged for 9.5 and 19.1 months than that of control group. F. Dose-dense chemotherapy obtained higher complete response rate and objective response rate. The more cytoreduction cells were, the less residual tumor cells were. At the same time chemotherapy had little effect on blood vessel supplying tumor so hypoxia tumor cells obtained more oxygen led them more sensitive to radiotherapy that significantly reduced the recurrent or progressive rate in radiation field, and increased the overall survival rate in 2 and 3 years.

First of all, a number of clinical literatures in recent years show that some patients with non dissemination distant metastasis achieved long-term survival after radiotherapy. (Lutz et al., 2014; Nagamata et al., 2014;

Guenne et al., 2014; Hingorani et al., 2015). Secondly, neoadjuvant chemotherapy based on cisplatin could improve local control and survival rate in radiotherapy of locally advanced NPC (Xu et al., 2012; Du et al., 2013; Kong et al., 2014). The radiotherapy of nasopharynx, neck and/ or bone metastases to treat the NPC patients with distant metastases could prolong complete response time and increase the survival rate after systematic chemotherapy (Chen et al., 2013; Agnese et al., 2014). Thirdly, NPC was sensitive to chemotherapy. The objective response rate of standard first-line schedule cisplatin combination with fluorouracil in the treatment of distant metastasis of NPC was 66-78% (Bensouda et al., 2011). The primary/ secondary drug resistance led to unsatisfactory total survival time. While the NPC cells were more sensitive to radiotherapy than chemotherapy, and radiotherapy remained valid on chemotherapy resistant patients (Pandey et al., 2013); Thus a corollary could be drawn: if subclinical lesions with diffuse metastasis was eliminated on distant metastasis of NPC patients by chemotherapy, then the radiotherapy effect on tumor bed would be further increased OS and even some patients obtained long-term survival. To eliminate the subclinical lesions with diffuse metastasis, intensive chemotherapy was the most commonly used methods. The intensive chemotherapy included dose-intensity and shortened chemotherapy dose-density (Peto et al., 2012). Dose-intensity chemotherapy in head and neck carcinoma failed to apply because of a randomized trial comparing 60 mg/m² vs 120 mg/m² of cisplatin failed to demonstrate a significant improvement in response and survival (Veronesi et al., 1985) and another trial that evaluated very high doses of cisplatin up to 200 mg/m² failed to complicate by severe toxicities. (Havlin et al., 1989). Otherwise dose-density chemotherapy has made a significant contribution to the adjuvant treatment of breast cancer (Hudis et al., 2015). NPC was also sensitive to chemotherapy, whether dose-dense chemotherapy could bring the same clinical benefit as patients with breast cancer? Our study showed that the CR rate was 19.2% after dose-dense chemotherapy, which was higher than 15% reported by Jamshed (2014), and was significantly higher than that (3.9%) of traditional chemotherapy. The rate of CR (3.9%) and PR (53.0%) in control group was similar with 4.3% and 51.7% reported by Zeng (2014). The CR rate 85% of patients following radiotherapy was higher than 50.0% in control group and 64.3% reported in the literature (Kang et al. 2013) after dose-dense chemotherapy. And the median OS, survival rate in 2 and 3 year were increased for 19.1 months, 39.1% and 47.4% than control group. These results suggested that dose-dense chemotherapy following selection radiotherapy was beneficial on the patients with distal metastasis of NPC.

The acute adverse reaction was increased obviously after dose-dense chemotherapy. The grade 3-4 adverse reaction reached as high as 53.8%, especially thrombocytopenia, oral mucositis, loss of appetite and fatigue, but patients could tolerate it. The other adverse reactions were non significantly difference between study and control group such as the transaminase was increased by 34.6% and bilirubin was increased by 11.5% after liver

radiotherapy, which was similar with Yin (2014).

The risk of neutropenia would increase significantly on patients after dose-dense chemotherapy. Serious neutropenia will cause chemotherapy delay, chemotherapy reduction or chemotherapy related infection was also increased (Aapro et al., 2011). But the severe neutropenia did not appear in our research. This was because of preventive use of recombinant human granulocyte colony stimulating factor (Crawford et al; 2010) from day6 to day10. Although the acute adverse reaction was increased obviously in study group, late radiotherapy toxicity did not increase. For example, the grade 1-2 xerostomia was 40%, which was similar with Li (2014).

Limitations: Firstly, chemotherapy was phase III clinical trial, but it was a single-center study and the number of samples was small. Secondly, the patients were randomly divided by using digital random table, but they were not stratified by metastatic site, primary treatment and history of chemotherapy drugs, dose of radiotherapy and performance status. This method would led to bias. Thirdly, the number of patients undergoing radiotherapy was less, radiotherapy position was not completely consistent with dose; Fourthly, radiotherapy was compared with only chemotherapy after intragroup chemotherapy, the former OS was significantly prolonged, but radiotherapy patients were those with good response to chemotherapy and the lesions were not dissemination.

Acknowledgements

This research was supported by Science and Technology Bureau of Guigang City, China (0807004).

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