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Clinical Observation of Concurrent Radio-Chemotherapy Combined with Adjuvant Chemotherapy in Treating Locoregionally Advanced Nasopharyngeal Carcinoma

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OBJECTIVE To investigate the efficacy and side effects of concurrent radiochemotherapy using the TP regimen (paclitaxel and cisplatin) combined with adjuvant treatment in treating patients with locoregionally advanced nasopharyngeal carcinoma (NPC).

METHODS A total of 82 patients with a confirmed diagnosis of locoregionally advanced stage-III and IVa NPC were randomly divided into 2 groups: the treatment group (TG) with concurrent radiochemotherapy combined with adjuvant chemotherapy (n = 44) and the control group (CG) with simple radiotherapy (RT) (n = 38). A total dose of 68 - 74 Gy of conformal radiation (X-ray, 4 MV or 8 MV) was given to patients in both groups. In the TG, a regimen of paxlitaxel and cisplatin was given via intravenous infusion in the 1st and 6th week concurrently with RT. After a 2-week intermission following RT, these patients received 2 cycles of the same chemotherapeutic regimen triweekly.

RESULTS The effective rates of the treatment were, respectively, 71.1% and 76.3% in the CG, and 88.6% and 95.5% in the TG, at the end of treatment and 3 months thereafter. The differences in the therapeutic efficacy between the 2 groups were statistically significant ($P < 0.05$). The 1- and 2-year survival rates were 81.1% and 73%, and 95.2% and 90.5%, respectively in the CG and the TG, and the differences between the 2 groups were statistically significant ($P < 0.05$). The grade I-II reactions in the gastrointestinal tract, skin and oral mucosa were higher in patients receiving concurrent radiochemotherapy combined with adjuvant chemotherapy than in patients receiving simple radiotherapy ($P < 0.05$). The differences in the occurrence of grade III-IV side effects including gastrointestinal, dermal and oral mucosal discomfort, other side effects, and late radioactive damage between the 2 groups were not statistically significant.

CONCLUSION Concurrent radiochemotherapy combined with adjuvant chemotherapy in treating patients with locoregionally advanced NPC can further improve short-term therapeutic effects and the overall survival. However, there is an increased trend in toxicity secondary to treatment.

KEY WORDS: nasopharyngeal carcinoma, locoregionally advanced, paclitaxel, cisplatin, concurrent radiochemotherapy, adjuvant chemotherapy.

Introduction

Nasopharyngeal carcinoma (NPC) is a common malignant tumor, and radiation therapy (RT) is the primary modality for treatment of the disease. Before the 1980s, a simple RT regimen was the first choice for patients with NPC in all stages. The 5-year overall survival rate of NPC patients ranged from 47% to 52%, among which the rate for stage-III patients was 40.64% to 50%, and that for stage-IV patients was only 22% to 24%[1,2]. The major reasons for treatment failure included regional relapse and distant metastasis, which resulted in the discovery of a combined therapy to improve therapeutic effect. Concurrent radiochemotherapy, as a new mode of treatment, has been widely utilized in the treatment of cancer and has been accepted by oncologists because of its favorable treatment outcome. In our hospital, from October 2004 to October 2006, concurrent radiochemotherapy combined with adjuvant chemotherapy using a regimen of paclitaxel and cisplatin via intravenous infusion was used in 82 locoregionally advanced NPC patients, while simple RT was used as control. Our study as well as our findings are described and detailed in the following.

Patients and Methods

Patients

All 82 patients with locoregionally advanced NPC (stage III or stage IV_a, based on the Chinese 1992 staging system) treated in our hospital were enrolled in our study. The Karnofsky scores of the 82 patients were ≥ 80. Forty-four of the 82 patients were selected randomly for the treatment group (TG), in which concurrent radiochemotherapy combined with adjuvant chemotherapy was given to the subjects. The other 38 were selected randomly for the control group (CG), in which simple RT was given to the patients. The diagnosis of the patients in the 2 groups was confirmed after pathologic examination. The results of routine examinations on blood, hepatorenal, and cardiac function were all normal, indicating that there were no contraindications for radiotherapy and chemotherapy in these patients. There were no statistical differences in the age, gender, and staging between the patients in the 2 groups (Table 1).

Table 1. Clinical data of the patients in the 2 groups.

Characteristics	TG	CG
No. of cases (Male / Female)	44 (30/14)	38 (29/9)
Mean age (years)	55.3	59.5
Staging		
Stage III	29	24
Stage IVa	15	14
Pathologic type		
Squamous cell carcinoma	8	5
Non-keratinizing carcinoma	36	33

Treatment methods

Radiotherapy

4 MV and 8 MV X-ray extracorporeal irradiation were used, with isocentric lead shield plus facial mask fixation. The irradiation field was configured according to the extent of tumor invasion based on clinical examination and CT scan, which included the nasopharynx, cranial base, and neck. First, combined irradiation at the faciocervical and bilateral supraclavicular tangential fields was given, with conventional fractionated exposure at 2 Gy/d, 5 times a week. Then split field irradiation at the facial and cervical fields was performed as the dose in the nasopharyngeal target area reached 36 Gy. The accumulated dose was at 68-74 Gy in the nasopharynx, and the prophylactic dose was at 50 Gy in the neck; a dose of 66 - 70 Gy was given when lymphatic metastasis had occurred.

Chemotherapy

The chemotherapeutic TP regimen was given on the same day as radiation therapy. Concurrent radiochemotherapy combined with adjuvant chemotherapy was administered, including 135 mg/m^2 of paclitaxel on Day 1 and 25 mg/m^2 of cisplatin on Day 1 to Day 3. A 10 mg dose of dexamethasone was given orally 12 h and 6 h, respectively, before the administration of paclitaxel. Diphenhydramine and cimetidine pretreatment was given 30 min before therapy. The chemotherapeutic regimen was repeated on the 6th week of treatment. There was a 2-week discontinuation after completion of radiotherapy, and another 2 cycles of chemotherapy was given using the same regimen, 21 days for 1 cycle, and 4 cycles of chemotherapy in total.

Evaluation criterion

Routine blood examination was repeated on each patient once a week during treatment. Hepatic function and renal function were evaluated and an electrocardiogram was repeated during a 2-week interval. Examination of the nasopharynx and CT scan of bilateral cervical areas were performed again at the end of the month and 3 months after treatment. Evaluation of the curative effect was based on the accepted WHO standards, which includes complete regression (CR), partial regression (PR), stable disease (SD) and progression of disease (PD). The total effective rate was CP plus PR. The evaluation of side effects was carried out in accordance with the WHO and RTOG grading criterion for side effects.

Follow-up

Follow up of the study subjects continued until December 2008, and the follow-up period ranged from 6 months to 26 months. During this period, 3 patients were lost to follow-up, 2 from the TG, and 1 from the CG; therefore, the follow-up rate reached 96%.

Statistical analysis

SPSS10.0 statistical soft ware was used, including the Kaplan-Meier curve method for calculating the survival rate, the log-rank method for testing and analyzing the significance of the differences in groups, and the Chi-square test for comparing the survival rates. The value of $P < 0.05$ was regarded as statistically significant for the differences between the groups.

Results

Therapeutic effect

Treatment was completed in all 82 cases according to the outlined treatment plan, with an achievement rate of 100%. At the end of treatment and 3 months thereafter, the effective rates were 88.6% and 95.5%, respectively, in the TG, and 71.1% and 76.3%, respectively, in the CG. The differences in effective rates between the 2 groups were statistically significant ($P < 0.05$). In the 79 evaluable cases, with the exclusion of the 3 patients who were lost to follow up, the 1- and 2-year survival rates were 95.2% and 90.5%, respectively, in the TG, and 81.1% and 73%, respectively, in the CG. The differences in 1- and 2-year survival rates between the 2 groups were also statistically significant ($P < 0.05$, Table 2).

Side effects

During treatment, the acute side effects mainly included reaction of the digestive tract (RDT), bone marrow depression, skin reaction (SR), oral mucosal reaction (OMR), weight loss, and impairment of hepatorenal function, among which the severity of the RDT, SR and OMR was higher in the TG than in the CG. The differences in the side effects between the 2 groups were statistically significant ($P < 0.05$). Nevertheless, most side effects were grade I and grade II. The incidence rates of the side effects in patients with grade III and grade IV disease were similar in the 2 groups, without statistical significance ($P > 0.05$). In the CG, the duration of therapy was extended for 5 additional days because of grade III oral mucositis in 2 cases and grade III SR in one. In the TG, the duration of therapy was extended for 4 to 7 days or so because of grade III and grade IV oral mucositis in 5 cases and grade III skin reaction in 4. The incidence rates for side effects were similar in the 2 groups, which was not statistically significant (Table 3). Late radioactive damage mainly included skin reactions, mucosal lesions and dry mouth. The incidence rates of these events were similar in the 2 groups, which was not statistically significant ($P > 0.05$). Toxic injury secondary to drug treatment and occurring later was not seen (Table 4).

Table 2. Results of the evaluation of therapeutic effect in the patients in the 2 groups.

Groups	At the end of the treatment (*n*)					3 months after the treatment (*n*)					1-year survival rate (%)	2-year survival rate (%)
	CR	PR	SD	PD	Effective rate (%)	CR	PR	SD	PD	Effective rate (%)		
TG	30	9	5	0	88.6	40	2	2	0	95.5	95.2	90.5
CG	20	7	10	1	71.1	22	7	8	1	76.3	81.1	73

Table 3. Acute side effects in patients in the 2 groups, evaluated based on the WHO grading standard.

	TG (*n*)					CG (*n*)				
	Grade 0	I	II	III	IV	Grade 0	I	II	III	IV
Nausea and Vomiting		10	29	4	1	2	23*	12*	1	
Leukopenia	2	25	11	6		8	27	3		
Thrombocytopenia	26	15	3			26	11	1		
Anemia	24	16	4			28	10			
SR		4	36	4			15*	22*	1	
OMR			39	4	1		8*	28*	2	
Weight loss		8	32	4		4	10	22	2	
Hepatic dysfunction	35	6	3			35	3			
Renal dysfunction	40	4				38				

*$P < 0.05$

Table 4. Advanced-stage radiation damage in patients in the 2 groups (RTOG grading standard).

	TG (*n*)				CG (*n*)			
	Grade 0	I	II	III	Grade 0	I	II	III
Skin	22	15	5		21	14	2	
Subcutaneous tissue	20	21	1		18	19		
Mucosa	9	29	4		7	24	6	
Salivary gland (dry mouth)	6	28	8		11	19	7	

Discussion

The early diagnosis of nasopharyngeal carcinoma (NPC) is difficult, since the site of invasion in this malignancy is occult and the early symptoms inconspicuous. Based on related reports[3-5], in NPC patients who visited the hospital for the first time, locoregionally advanced patients accounted for approximately 50%-70% of the total.

The long-term effects on patients who underwent simple radiotherapy remained unsatisfactory, in spite of continuing improvements in imaging diagnostics and the constantly evolving radiotherapy equipment and facilities over the past few years. The 5-year survival rate was only 50%-60%.

Previous reports have shown[6,7] that aside from the effect of local control rate, the survival rate of NPC patients was influenced by the distant metastasis. Palazzi et al.[8] concluded that, after analyzing the data of the 171 NPC patients who underwent simple radiotherapy, N-staging was the major factor affecting the therapeutic effect and prognosis. The later the N-stage is, the worse the treatment outcome and prognosis, and the higher the rate of distant metastasis. Since T-staging only served as a minor correlation factor, no significant differences were found in addition to the statistical differences between the 5-year overall survival rates in T3 and T4 cases. This shows that radiochemotherapy in locoregionally advanced NPC patients with various N-stages may play an active role in reducing relapse and distant metastasis. The key breakthrough of combined radiochemotherapy in locoregionally advanced NPC patients could be attributed to an early report, no. 0099, the research project by Al-Sarraf et al.[9], which showed that the overall survival rate of NPC patients was elevated in all clinical trials evaluating concurrent radiochemotherapy. In the data from 2687 patients with locoregionally advanced NPC reported by Lee et al.[10], sequential or concurrent chemoradiotherapy was administered in only 23% of patients, and the survival rates for these patients without regional relapse and distant metastasis were 79% and 74%, respectively. These rates were much higher than those of patients who underwent conventional simple radiotherapy.

At present, concurrent radiochemotherapy has become the standard treatment for locoregionally advanced NPC[11-13]. In addition, therapeutic alliance with cisplatin drugs as the first-line treatment has been frequently used[14]. The increased treatment-related toxicity induced by synchronous radiochemotherapy has been existent, though treatment outcome has been proven. Owing to increased acute side effects, the implementation of concurrent radiochemotherapy has been hampered[15]. This has resulted in an unplanned discontinuation of radiotherapy and has affected therapeutic efficacy. At the same time, increased drug toxicity has also affected patients' quality of life. In the No. 0099 research project, the patients who could complete cisplatin-based chemotherapy plus radiotherapy accounted for 63% of the total, while those who completed concurrent radiochemotherapy combined with adjuvant chemotherapy only accounted for 55%[9], indicating the very poor tolerance and compliance of these patients. Therefore, an important goal of clinical research on NPC patients receiving radiochemotherapy is to minimize the side effects so that the full treatment plan can be implemented.

Paclitaxel, an antitumor drug, can repress cancer cells, which are most radiosensitive in the phase G_2 and M, by promoting the polymerization of microtubulin and preventing the depolymerization of microtubulin, thus impeding cell division and proliferation. Drugs can also strengthen the stability of the binding between cisplatin and DNA by forming a cytidine analogue, which can have a synergistic effect, inhibiting the reparation of the DNA damaged by the cisplatin drugs. Thus, concurrent radiochemotherapy (TP regimen) combined with adjuvant chemotherapy which was carried out in our study for treating locoregionally advanced NPC patients showed the expected treatment outcome and higher 1- and 2-year survival rates compared with those of patients who underwent only simple radiotherapy ($P < 0.05$).

In our study, in order to improve the tolerance and compliance of NPC patients, the treatment time of the 2nd-cycle chemotherapy was extended for patients undergoing concurrent radiochemotherapy, and it was given in the 6th week of treatment, so as to avoid acute toxic reactions. Treatment was discontinued when very severe toxic reactions occurred. After 2 weeks of discontinuation, concurrent radiochemotherapy (TP regimen) with adjuvant chemotherapy was resumed for 2 cycles. So, patients could complete treatment in accordance with the treatment plan. Although this therapeutic method resulted in more severe reactions, including grade I and II RDT, skin reactions, and OMR, in the TG than in the CG ($P < 0.05$), it was tolerated by the patients. The severe reactions did not impact synchronous radiotherapy. The incidence of other side effects and long-term radiation damage were similar in the 2 groups ($P > 0.05$).

In general, the concurrent radiochemotherapy (TP regimen) combined with adjuvant chemotherapy in the treatment of patients with locoregionally advanced NPC can improve the treatment outcome and extend the overall survival time, despite the increased side effects. Patients could tolerate the treatment plan after aggressive symptomatic treatment of side effects. Data from a large number of cases is needed to determine the optimal dose, the time and order of the administration of chemotherapeutic drugs, as well as the best mode of combined therapy in radiotherapy.

Conflict of interest statement

No potential conflicts of interest were disclosed.

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