INTERVENTION CHEMOTHERAPY IN COMPREHENSIVE TREATMENT OF ADVANCED NASOPHARYNGEAL CARCINOMA

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ABSTRACT

Objective: To study the use of interventional chemotherapy in comprehensive treatment for advanced nasopharyngeal carcinoma. Methods: Interventional chemotherapy with multi-drugs including cisplatin (DDP) 100 mg, 5-fluorouracil (5-FU) 1000 mg and bleomycin (BLM) 16 mg was used to treat 30 cases with advanced nasopharyngeal carcinoma before radiotherapy. 50 cases that received radiotherapy alone were used as a control group. The methods, time and dose schedule of radiotherapy were similar in the two groups. Results: The primary lesions in 16 cases and the cervical lymph nodes in 12 cases were reduced in size after interventional chemotherapy. Radiation doses of those in complete response in their primary lesion and cervical lymph nodes were lower than that of the control group ($P<0.05$). The complete response rate of study group was 83.3% and that of control group was 72.0% ($P<0.05$). Conclusion: Interventional chemotherapy plus radiotherapy is a valuable treatment method in advanced nasopharyngeal carcinoma.

Key words: Nasopharyngeal carcinoma, Interventional chemotherapy, Comprehensive treatment.

At present, the leading treatment for nasopharyngeal carcinoma (NPC) both at home and abroad is radiotherapy. Its 5-year survival rate, however, is only 50%, and that of advanced ones is only 20–30%.[1] We used intervention chemotherapy combined with regular radiotherapy to treat 30 cases of advanced NPC patients, so as to find out the value of intervention chemotherapy in comprehensive treatment of advanced NPC and provide a new therapy with a better curative effect for NPC.

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MATERIALS AND METHODS

Clinical Data

Thirty patients with pathologically confirmed NPC but without distance metastasis who had not received previous treatment were used as the trial (test group). Their liver, kidney function and hemogram were normal, and their Karnofsky score was ≥70. Of the patients, 22 were male and 8 female. They were between 28 and 60 years of age. Clinical stages: 18 cases were in Stage III, and 12 cases Stage IV. Pathological classification: 26 cases were poorly differentiated squamous cell carcinoma, and 4 cases undifferentiated carcinoma. Fifty cases of advanced NPC patients treated in the same period of time with radiotherapy alone served as control. In these two groups, the median age, sex, pathological classification and clinical stage were all similar.

Methods

To find out the blood supply arteries of the carcinoma and their trends, we used external carotid arteriography by Seldinger's percutaneous femoral arteriopucture with 6.0 F H_1H catheter or SP catheter. According to the findings of the arteriography, the catheter was sent to the ascending pharyngeal artery or superior maxillary artery with the guidance of a guide thread. After confirmation by arteriography, the drugs were perfused into the artery. The combined drugs included cisplatin (DDP) 100 mg, 5-fluorouracil (5-Fu) 1000 mg and bleomycin (BLM) 16 mg. In some cases, whose arteriography images of ascending pharyngeal artery or superior maxillary artery were not clear, infusion of drugs could only be conducted in the external carotid artery. If the lesion had extended over the midline, the intervention chemotherapy encompassed both sides; 2/3 of the dose was infused to the side with the major lesion and 1/3 to the other side. Radiotherapy started one week after intervention chemotherapy. A total dose of 60–70 Gy was given to the primary tumor and 50–60 Gy to the cervical metastases in 8 weeks. For the residual tumor, another 10 Gy was given. The patients in the control group received radiotherapy alone. Both groups were treated with ^{60}Co; the duration

and method of treatment and dose fracture were the same.

Evaluation of Treatment Response

Before treatment, the extent, shape and size of primary tumor, and the place, size, texture and number of cervical metastases were recorded; during treatment, checked the reduction of the tumor was checked weekly, and the cumulative radiation dose recorded when the primary lesion and cervical metastases remitted completely. Liver function, kidney function and hemogram were examined before and after treatment; during the treatment, the hemogram was re-examined weekly, and the reaction of radiotherapy in oral mucous membrane and digestive canal was observed. The general curative effect index for solid carcinoma recommended by International Union Against- cancer (UICC) as reference for evaluation of treatment response was taken. As for the toxic and side effects, the toxic grading standards of WHO was used. The follow-up, by either correspondence or outpatient visit, lasted for half a year to two year. The follow-up rate was 100%.

RESULTS

Response to the Intervention Chemotherapy

After the intervention chemotherapy and before the radiotherapy, 22 patients felt remission in nasal obstruction, tinnitus and hypacusis, and 8 patients felt relief from headaches. Nasopharynx lesions of 16 patients had shrunk to varying degrees, and cervical lymphnodes of 12 patients had shrunk.

The Relationship of Tumor Remission and Radiation Dose

The radiation dose for complete remission of primary tumor mass (T) and cervical lymph nodes (N) in the treatment group was lower than that in control group. Their difference was significant ($P<0.05$, Table 1).

Table 1 The relationship between tumor regression and radiation dose ($\bar{x}\pm s$)

Group	Number of case	Dose (Gy)	
		T	N
Treatment	30	48.5±11.8	45.7±14.5
Control	50	60.5±12.0	58.6±13.8
P		<0.05	<0.05

Evaluation of Treatment Response 4 Weeks after Radiotherapy

In the treatment group, 25 cases (83.3%) had complete remission, and 5 cases (16.7%) partial remission; while in the control group, 36 cases (72.0%) had complete remission, and 14 cases (28.0) partial remission. The difference of the remission rate between the two groups was significant ($P<0.05$).

Toxic and Side Effects

After the intervention chemotherapy, 20 cases had nausea, vomiting and anorexia of varying degrees; 10 cases had a sensation of medicine in the mouth; 10 cases had local temporooccipital alopecia; 6 cases had mild stomatitis; 5 cases had hypoleukocytosis; and 1 case had transient binocular blindness. All these symptoms disappeared after giving expectant treatment. During the radiotherapy, there were more cases of local stomatitis and hypoleukocytosis in the treatment group than in the control group, but they were all in grade I and grade II, and could be tolerated by the patients. All the patients received the whole treatment course according to the schedule.

Followed-up

All the patients received follow-up for one-half to two year, and they were all still living. In the treatment group, no case had a recurrence or distance metastases; in the control group, however, 2 cases had local metastases and received radiotherapy 2 times, and 1 case had bone metastases.

DISCUSSION

NPC is one of the common malignant tumors in China. Its morbidity ranks first place in cephalocervical malignant tumors. To get better therapeutic results, more and more attention has been paid to comprehensive treatment of chemotherapy combined with radiotherapy. But the conventional intravenous and intramuscular chemotherapy has the disadvantage of poor specificity and high toxic and side effects. Intraarterial intervention chemotherapy, however, injects anticancerdrugs into the nutritive arteries of the carcinoma directly, which has the

characteristics of a high local drug concentration, good treatment response and low systemic toxic and side effects. The predilection sites for NPC are lateral walls and posterior wall of the nasopharynx whose blood supply are from the ascending pharyngeal artery and maxillary artery.[2] Intervention chemotherapy by selective catheterization can kill large amounts of cancer cells and shrink the tumor in a short time. It is indicated by many experiments and clinical researches that DDP has not only the cytotoxic effect of other chemotherapy drugs, but also the effect of sensitivity enhancement for radiotherapy, especially for anaerobic tumor cells, which can reduce the radioreaction of normal mucous membrane and increase the radiation tolerance.[3] The synergism of DDP and 5-Fu has been proved, and BLM is very effective for cephlocervical squamous cell carcinoma. Most NPCs are poorly differentiated carcinomas and sensitive to chemotherapy.[4] Intraarterial intervention chemotherapy with DDP, 5-Fu and BLM shows good prospect in the treatment of advanced NPC. In the reported study among 30 advanced NPC patients, the primary tumor mass reduced in size in 16 patients and the enlarged cervical lymphnodes shrank or became loosened in 12 patients after intervention chemotherapy, and all the patients felt improvement. The radiation dose required to achieve complete response of the primary and metastatic lesions was significantly less than that of patients receiving radiotherapy alone ($P<0.05$). Four weeks following the completion of radiotherapy, the complete response rate in treatment and control groups was 83.3% and 72.0% respectively, with a significant difference ($P<0.05$). The results indicate that intervention chemotherapy combined with radiotherapy can alleviate improve the symptoms. Furthermore, intervention chemotherapy can increase the sensitivity of radiotherapy by enhancing the cancer cells killing effect, reducing the size of the lesion and accelerating the remission of the tumor.

The complications of comprehensive intervention chemotherapy were mild and the patients could tolerate them on the whole. The common complications and their treatment were as follows: (1) Complication of puncture and catheterization: such as local hematoma and endangium injury etc. These could be avoided by careful operation and observation, and usually did not need special treatment;. (2) Anaphylaxis to contrast medium: before operation, conduct a skin test; during operation, observe all the reactions of the patients closely; if anaphylaxis occurred, diagnose and treat it promptly; (3) Toxic reactions of chemotherapy: such as nausea, vomiting, low fever, leukocytopenia and alopecia, etc. They could be relieved by expectant treatment. Taking traditional Chinese medicine orally might reduce toxic and side effects remarkably; (4) Local toxic reactions: such as stomatitis, local skin swelling pain and numbness. They could be healed with Dobell's solution and a small amount of corticoid; and (5) Transient binocular blindness: it might be caused by contrast medium and usually happened 2-3 hours following the operation. After treatment with infusion (large amount), corticoid and neurenergen, the patient could recover 12-48 hours later.

We consider intervention chemotherapy combined with radiotherapy as a novel, safe and effective therapy for advanced NPC, because its near-term effect is significant and its toxic and side effects are mild. Since the duration of follow-up was not long enough, the long-term effect needs further observation. Besides, we also need to find out whether intervention chemotherapy combined with radiotherapy for advanced NPC can reduce the radiation dose and is there any sequel after radiotherapy.

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