Original Article

Clinical study of the radiosensitization effect of sodium glycididazole in treatment of recurrent cervical carcinoma after postoperation radiotherapy

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ABSTRACT

Oblective: To observe the sensitization effect, toxicity and survival rate of CMNa for patients with cervical cancer and recurred at cavitas pelvis after operative radiotherapy. **Method:** Sixty patients with cervical cancer and limited recurrence at cavitas pelvis after operative radiotherapy from January 2005 to April 2009 were divided into CMNa group and control groups. Patients in the two groups both received three dimensional conformal radiation therapy while the sensitization group adding CMNa（800mg/m2）for sensitization. The follow-up results of two groups were compared. **Results:** Tumor remission rate of patients in CMNa group after radiotherapy 4 weeks, 6 weeks and 3 months were 56.7%, 83.3%, 90.0%, respectively, which had significant statistic difference compared with control group ($P<0.05$). One-year survival rate of patients in CMNa group was 56.7% , while that was 26.7% in control group, the different between the two groups had notabl significance in statistics. There was no significant difference in 3-year survival rate of two groups. Patients in both groups had obvious analgesic effect and there were no significant difference in toxicity between two groups.

Conclusion: CMNa has positive radiotherapy sensitization for patients of cervical cancer and recurred at cavitas pelvis after operation and radiotherapy.

Key Words: CMNa; Recurrent Cervix Cancer; post-operation radiotherapy; Three dimensional conformal radiation therapy; Radiotherapy Sensitization

Cervical cancer has the highest incidence rate in female reproductive neoplasm in China. Radiotherapy is the most important therapeutic method for this disease. The main type of treatment failure of radiotherapy is intrapelvic relapse [1]. The two factors impacting the radiotherapy effects include: (1) the dose restriction of normal tissues and risk organs; (2) radioresistance of anaerobious cancer cells. Sodium glycididazole (CM-Na) is a new type radiosensitizer of nitroimidazoles family which act on anaerobious cancer cells. It was independently developed by China and was applied in clinical in 2002. In this research, we studied the radiosensitization effect of CM-Na in three dimensional conformal radiation therapy (3DCRT) of intrapelvic relapse cervical cancer after postoperation radiotherapy.

SUBJECTS AND METHODS

Subjects

Sixty patients in 404 Hospital of Liberation Army and

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Radiotherapy Center of Xinqiao Hospital of the Third Military Medical University From January 2005 to April 2009 were selected for this study. The selected standards: Intropelvic relapse cervical cancer patients after postoperation radiochemotherapy and have complete records of clinical history. Excluding standards:Intrapelvic relapse patients without postoperation radiotherapy; or＜24 months after conventional postoperation radiotherapy; or patient with sever system diseases can not bear radiotherapy; or KPS ＜ 80; or with distant metastasis; or patient whose expect life span is less than 3 months; or lost of following-up. The primary pathologic classification were squamous cell carcinoma in all of the 60 patients. The median age was 46.3 years (ranged 27~71years), the median time from radiotherapy to relapse was 31.5 months (24.2~92 months, average 29.3 months). The 60 cases were divided into to two groups. CMNa group: included 30 relapse patients treated with 3DCRT and sensitized by CM-Na; Control group: included 30 relapse patients treated with 3DCRT without CM-Na sensitization.

We compared the curative effect of the two groups in the same treatment period, the first visit date of the patients after relapse was considered as the enrolment date, and it is the baseline time according to which the 1 and 3 years survival rate was estimated.

Methods

All the patients did not receive any chemotherapy, biological therapy or immunotherapy before operation, except for nutrition support and symptomatic treatment.

Facilities: ELEKTA 12 MV X-ray liner accelerator and Shandong Xinhua 6 MV X-ray liner accelerator, Sichuan Haitai multiple leaves collimator. Treatment planning system was brought from Shandong Xinhua Crop. The whole process of radiotherapy included 4 steps: position fixation by phantom, treatment planning, treatment plan validation and treatment execution. Patients were set supine, both hands were lifted above head, and markers were set on skin around the tumor. And then pelvic MRI scan was performed with 5mm slice thickness and 2mm slice interval. The images and raw data were transported to TPS workshop. GTV was defined by radiologists, radiotherapist and physicist together. PTV include GTV and a margin of 1.0~0.5cm. Radiation fields were set conformally according to the size and the shape of the tumor. GTV should be included in 80% isodose curve, and this curve should be defined as the prescription dose curve. Dose volume histogram (DVH) was used to evaluate the treatment plan. Conformation index, tumour control probability and normal tissue complication incident probability were referred to optimize the treatment planning. After optimization, 4~8 radiation field were set, 2Gy would be set on 80% isodose curve as prescription dose. The isodose curve was normalized to maximum dose point, therefore 2.5Gy was on 100% isodose curve line. Total dose of 40~60Gy was given in 4~6 weeks. When tumor dose reached 40Gy, MRI scan should be performed in order to reduce the tumor volume and another dose of 20Gy should be added.

Control group: only received radiotherapy, CMNa group: radiotherapy was the same with control group, and CM-Na were used with a dose of 800mg/m2, diluted by 100ml 0.9% normal saline. CM-Na should be given with 30 minute, and radiotherapy should be taken within 60 minutes after CM-Na was given. CM-Na was given three times a week (every Monday, Tuesdays, Friday) during radiation therapy. total treatment time was 4~6 weeks, 12~18 times.

valuation of Curative effects

Curative effects according to Response Evaluation Criteria in Solid Tumors (1981) were divided into complete remission (CR), partial remission (PR), no change (NC), progress of disease (PD). Overall effective rate = CR + PR. Acute radiation toxicities were assessed according to the grading standards of RTOG/EORTC. Numeric rating scale (NRS) was used to analyze pain grading. Effective pain relieving: pain grading score was reduced more than 50% and last at least for 4 weeks. The size of tumors in MRI were recorded before treatment, in the middle of the treatment course and 1~2weeks after treatment finished in order to assess the curative effects. Complete blood cell counts were checks before treatment and once a weeks during the whole treatment period. Biochemical indicators and ECG was checked before, after and in the middle of the treatment course.

Evaluation criterion: Objective indicators: (1) Tumor size analyzed by CT, MRI, ultrasonic. (2) Survival. 1 and 3 year survival rate of the two group were compared. (3) Toxicities. Early toxicities include myelosuppression, gastrointestinal toxicities and urinary toxicities. Late toxicities include radiocystitis, radiation proctitis, skin fibrosis and the forth. Subjective indicators: symptoms changes.

Statistical analysis

Statistical analysis was performed using statistical package SPSS 13.0, the data were analysed by x2 test, and $P<0.05$ was considered statistically significant.

RESULTS

Follow– up

Follow-up of the patients ended at May 20th, 2009. The median follow-up time was 28.6 month. 60 patients had received effective follow-up. Survival time was defined as from the beginning of 3DCRT to finish of follow-up or death.

Objective indicator : The tumor size of the two groups at the 4th and 6th week of the treatment course and 3 and 6 month after treatment are listed in table 1. 1 and 3 year-survival rate of control group are 26.7% and 6.7% respectively. 1 and 3 year-survival rate of CMNa group are 56.7% and 16.7%. The 1-year-suvial rates of the two groups have significant statistical differences($P<0.01$), 3-year-suvial rates of the two groups show no obvious statistical differences($P>0.05$).

Table 1. Overall effective rate of pelvic relapse patients at different time of treatment course

Time	Control group	sensitization group	X2	P
4th week of treatment coures	7 (23.3%))	17 (56.7%))	6.944	0.008
6th week of treatment course	16 (53.3%))	25 (83.3%))	6.239	0.013
3 month after treatment	19 (63.3%))	27 (90.0%))	5.936	0.015
12 month after treatment	20 (70.0%))	27 (90.0%))	4.812	0.028

Toxicities

In control group, the incidence of acute Ⅲ degree and above toxicities of bladder, rectum and bone marrow were 14.8%, 23.3% and 6.7% respectively. In CMNa group, they are 10.0%, 10.0% and 3.3% respectively. Most of the toxicity symptoms would be released after 1~2 month after treatment course. 1 patient of the control group developed radiocystitis, and another patient of control group developed radiation proctitis. No treatment relative death was observed.

Subjective symptoms

Symptoms of pelvic relapse: At early stage, no specific symptoms can be detective. At advanced stage, irregular colporrhagia, increased leucorrhea or discharge in vagina, pelvic mass, lumbosacral and hypogastric pain.

Symptoms of control group: 90% (27/30) patients had pain, 85.2% (23/27) reached complete release after treatment, and 14.8% (4/27) reached partial release. Total release rate of pain was 100%. Unilateral lower limb edema and pain were presented in 14 patients before treatment, 42.9% (6/14) completely released, and 50.0% (7/14) partially released after treatment, and the total release rate of edema was 92.9%.

CMNa group: 93.3% (28/30) patients presented pain before treatment, 96.4% (27/28) completely released, 3.5% (1/28) partially released. Unilateral lower limb edema and pain were presented in 16 patients before treatment, 68.8% (11/16) was completely released, and 31.3% (5/16) partially released. Total release rate of pain and unilateral lower limb edema was 100%.

DISCUSSION

Radiotherapy is one of the most tools of malignant tumor therapy. About 70% malignant tumor need radiotherapy. The percentage of anaerobiosis cancer cells in solid tumor is about 10~15%, the bigger the tumor mass is, the higher percentage the anaerobiosis cells take. Anaerobiosis cancer cells can impact on the effectiveness of radiotherapy. The fundamental research and clinical research of CM-Na have both reached positive results that CM-Na has obvious radiosensitization effect with little harm to normal tissuses. Pharmacokinetic researches have shown that CM-Na distributes quickly in vivo and is compatible to tumor tissues. Its electrophilic habit can fix the damage of radiotherapy to the tumor tissue, accelerate the tumor cell death, and sensitize the effect of the radiotherapy. In the mean time, CM-Na can inhibit DNA repair enzyme and especially its function of repairing the lethal damage and sublethal damage caused by radiation.

There are few researches about the second therapy of pelvic relapse cervical cancer after radiation. Radiotherapy is usually used in second therapeutic course. However, the prognosis of

pelvic relapse is still bad. Some data showed that 1-year survival rate is 15.0%~20.0%, and 5-year survival rate is 3.2%~13%. The following two reasons lead to the bad prognosis: 1) the dose can be prescribed is very limited because of the first radiotherapy course, and the relapse focus can not receive enough radiation doses. 2) pelvic fibrosis caused by first radiation course lead to poor blood supply of the relapse focus and the high percentage of anoxic tumor cells, which decreased the sensitivity of the tumor cells to second radiation. Therefore, previous radiation dose distribution and tolerance dose of organ at risk should be taken into consider when making a second treatment plan.

3DCRT is a kind of multi-angle, highly accurate, converging radiation therapy, it can deliver enough doses to the target, and guarantee the distribution of the high dose area are conformal to the target. The isdose curve declined sharply on the margin of the target in order to protect normal tissues while treating the tumor.

In this research, a statistical difference of tumor remission rate of the two groups could be seen at the 4th week of treatment course($P<0.01$). The remission rate at 3 and 6 month after treatment course of the CMNa group remained higher compared to the control group, and statistical differences existed($P<0.05$). The 1-year survival rate of CMNa group was 56.7%, and much higher than that of control group (26.7%), ($P<0.05$). And 1-year-survival rate of CM-Na group was elevated obviously compared to previous research results of Li Hubin etc. However, there was none difference of 3-year-suvival rate between the two groups, which might be caused by small sample capacity of our research. The remission rate of pain was 100% of two groups, this account for the pain killing effect of radiotherapy. The remission rate of lower limb edema was higher in CM-Na group, which might be that the tumor shrinking speed in CM-Na group was quicker than control group, and the lymphatic circulation was proved more rapidly in CM-Na group. No obvious neurotoxicity was seen in CM-Na group. Complete blood cell count, ECG, liver and renal function test were no any differences between two groups. No statistical differences of early and late toxicities were observed between two groups. However, radiation proctitis, radiocystitis and bone marrow depression were a little less in CM-Na group, this may be that the tumor shrinked quicker in CM-Na group and the radiation field could be reduced on time. Above all, CM-Na has affirmative radiosensitization effects on radiation therapy of pelvic relapse cervical cancer after postoperative radiotherapy. Early treatment response (ETR) is satisfactory and toxicities can be accepted, however, long term results need a further demonstration.

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