Effect of oxaliplatin combined with 5-fluorouracil on treatment efficacy of radiotherapy in the treatment of elderly patients with rectal cancer

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Abstract. Efficacy of the combination of oxaliplatin, 5-fluorouracil and radiotherapy on rectal cancer in elderly patients was investigated. Seventy-three elderly patients with rectal cancer confirmed by histopathological examination were randomly divided into 3 groups: oxaliplatin group (25 cases): intravenous infusion of oxaliplatin; fluorouracil group (24 cases): intravenous infusion of fluorouracil; combination group (24 cases), intravenous infusion of oxaliplatin and fluorouracil. All patients were treated with radiotherapy, and efficacy and safety were evaluated after 2 courses of treatment. MTT assay was used to observe the inhibitory effects of the proliferation of human rectal cancer cells. Cell proliferation and sensitization ratios were compared. After 2 courses of treatment, there was no difference in complete remission (CR), partial remission (PR), stable disease (SD), progression disease (PD) and disease control rate (DCR). Remission rate (RR) was higher in the combination group than that in the oxaliplatin and the fluorouracil groups (P<0.05), and there was no difference between the oxaliplatin and the fluorouracil group (P>0.05). Incidence of neutropenia in the combination group was higher than that in the fluorouracil group (P<0.05). OD values of the combination group were lower than those of the oxaliplatin and the fluorouracil groups (P<0.05). Proliferation ability of SW837 cells of the combination group was significantly lower than that of the oxaliplatin and the fluorouracil groups (P<0.05). Intragroup comparison of sensitization ratio showed that sensitization ratios of three groups of cells at 24, 48 and 72 h were all higher than those at 12 h (P<0.05).

The combination of oxaliplatin and 5-fluorouracil is safe and effective in the treatment of rectal cancer in elderly patients, and it can be used for sensitization of radiotherapy. So it should be popularized in clinical practices.

Introduction

Rectal cancer is the most common type of malignant tumor in digestive tract and one of the leading causes of death in humans. It mainly occurs in people over 45 years, and the incidence is higher in men than in women (1,2). With the changes in people’s diet structure and the lack of physical exercise, incidence of rectal cancer has increased year by year, and 1,000,000 new cases were reported each year (3,4). With the growth of aging population, proportion of elderly patients with rectal cancer is gradually increased, but treatment of elderly patients with rectal cancer has not been well studied (5). Approximately 81% of rectal cancer occurs near the anal sphincter. Surgical resection is the only radical treatment for malignant tumors, while surgical treatment of rectal cancer is challenged by the retention of anus and anus function. Surgical treatment is also a very dangerous treatment for elderly rectal cancer patients (6,7).

Radiotherapy is one of the basic treatment methods for patients with malignant tumors. However, toxic effects of long-term radiotherapy are unbearable. Efficacy of radiotherapy will also decrease over time, so finding a mild and effective drug is critical (8,9). Oxaliplatin and fluorouracil are two widely used drugs in tumor treatment. There are also studies on the use of oxaliplatin and fluorouracil for the treatment of rectal cancer, but the efficacy and adverse reactions of the two drugs used for the treatment of rectal cancer are unclear. In addition, study of oxaliplatin combined with fluorouracil on treatment outcomes of conventional radiotherapy in the treatment of rectal cancer is rare (10,11).

Therefore, this study investigated the therapeutic efficacy and safety of oxaliplatin and fluorouracil combined with radiotherapy in treatment of rectal cancer. In addition, sensitization effects of oxaliplatin and fluorouracil on radiotherapy were also explored to investigate the application values of oxaliplatin and fluorouracil in treatment of patients with rectal cancer.

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Key words: oxaliplatin, 5-fluorouracil, elderly rectal cancer, SW837, radiosensitization, cell proliferation
Materials and methods

Research subjects. From March 2014 to March 2015, 73 patients with rectal cancer confirmed by histopathological examinations were selected in Laigang Hospital Affiliated to Taishan Medical University (Laiwu, China). All 73 patients were older than 60 years and had a mean age of 68.43±7.75 years. Among them, 40 were males and 33 were females. All patients were diagnosed as rectal cancer by histopathological examination. All patients received radiotherapy and chemotherapy for the first time. None had been treated with oxaliplatin and fluorouracil in the past or was allergic to these drugs. Patients had no liver, kidney and other organ dysfunction. Patients had no abnormal bleeding or coagulation abnormalities. Patients who had been treated, patients with large tumors, patients with other diseases of lung or chest wall, and patients with lymph node metastasis were excluded. This study was approved by the medical Ethics Committee of Laigang Hospital Affiliated to Taishan Medical University. Patients or their families signed an informed consent.

Human rectal cancer cell line SW837 (cat. no. C1258) was purchased from Shanghai Guandao Bioengineering Co., Ltd. (Shanghai, China) and cultured in RPMI-1640 medium (Shanghai Gaochuang Chemical Technology Co., Ltd., Shanghai, China) in an incubator (37˚C, pH 6.8-7.4, 5% CO₂).

Methods. Patients were randomly divided into 3 groups: oxaliplatin group (25 cases): intravenous infusion of oxaliplatin (100 mg/m²); Hubei Yuancheng Saichuang Science and Technology Co., Ltd., Wuhan, China; state approval no. H20020648) on the first day; fluorouracil group (24 cases): intravenous infusion of fluorouracil (375 mg/m², state approval no. H20030345) from day 1 to day 5; combination group (24 cases), intravenous infusion of oxaliplatin (100 mg/m²) on the first day and intravenous infusion of fluorouracil (375 mg/m²) from day 1 to day 5. All patients were treated with radiotherapy at the same time, radiation dose was 45.0-50.4 Gy and 21 days treatment was added and shaken on a horizontal shaker for 15 min. Finally, the absorbance at 570 nm was measured by using an enzyme-linked immunosorbent assay. The above steps were repeated at 12, 24, 48 and 72 h, respectively. MTT test kit was purchased from Shanghai LM Bioengineering Co., Ltd. (Shanghai, China).

Statistical analysis. SPSS 19.0 (Asia Analytics Formerly SPSS, Beijing, China) was used. Enumeration data were expressed as a rate and compared by χ² test. Measurement data was expressed as mean ± standard deviation, and ANOVA was used for comparison among groups, and repeated measures ANOVA was used for intra-group comparisons, and LSD tests were used for comparison between two groups, as post hoc tests. P<0.05 was considered to indicate a statistically significant difference.

Results

General information. Seventy-three patients with rectal cancer had a mean age of 68.43±7.75 years. Oxaliplatin group included 16 male and 9 female patients, with a mean age of 67.59±7.88 years. Fluorouracil group included 15 male and 9 female patients, with a mean age of 69.13±7.24 years. Combination group included 16 males and 8 females, with a mean age of 68.57±8.13 years. There was no difference in the basic data such as the average age, sex, and clinical stages among the three groups (P>0.05) (Table I).

Analysis of treatment effects after two courses of treatment. After two courses of treatment, ANOVA analysis showed no significant differences in DCR, CR, PR, SD and PD among the three groups (P>0.05), and there was statistical difference in RR (P<0.05). LSD test results showed that RR was higher in the combination group than in the oxaliplatin and the fluorouracil groups (P<0.05), and there was no difference between the oxaliplatin and the fluorouracil groups (P>0.05) (Table II).

Incidence of adverse reactions after 2 courses of treatment. ANOVA analysis showed that there were statistically significant differences in incidence of neutropenia among three groups (P<0.05), while there were no differences in incidence of other adverse reactions (P>0.05). LSD test showed that incidence of neutropenia was higher in the combination group than that in the oxaliplatin and the fluorouracil groups (P<0.05). Incidence of other adverse reactions in the combination group was not significantly different from those in the oxaliplatin and the fluorouracil groups (P>0.05) (Table III).

Radiosensitization of SW837 cells by oxaliplatin and fluorouracil. In vitro proliferation assay of SW837 by MTT assay showed that OD values of three groups of cells decreased with time. No significant difference was found in OD values between oxaliplatin and fluorouracil groups at 6, 12, 24, 48 and 72 h (P>0.05). However, OD values at 6, 12, 24, 48...
and 72 h points in the combination group were lower than those in the oxaliplatin and the fluorouracil groups (P<0.05). Proliferation ability of SW837 cells in the combination group was significantly lower than that in the oxaliplatin and fluorouracil groups (P<0.05).
flourouracil groups (P<0.05). ANOVA analysis showed that sensitization was not significantly different among the three groups of cells at 12 h (P>0.05), while significant differences were found at 24, 48 and 72 h (P<0.05). LSD test analysis showed that sensitization ratio of the combination group was higher than that of the oxaliplatin and fluorouracil groups (P<0.05). Proliferation ability of SW837 cells in combination group was significantly lower than that in the oxaliplatin and fluorouracil groups (P<0.05). Table IV showed that sensitization ratio of the combination group was significantly lower than that in the oxaliplatin and fluorouracil groups (P<0.05). Therefore, we speculate that oxaliplatin may improve the digestive system of patients and balance the adverse effects of fluorouracil on the digestive system. However, both oxaliplatin and fluorouracil have myelosuppressive effects (18,19), which may increase the incidence of neutropenia and anemia. Therefore, the safety still needs to be explored. This may be related to the small sample size, and we will conduct a further analysis with a large sample size to further confirm our findings.

In this study, human rectal cancer cell line SW837 was used to investigate the radiosensitization of oxaliplatin and fluorouracil. Results of this study found that oxaliplatin and fluorouracil have a certain radiosensitization effects on SW837 cells during radiotherapy, and combination of the two drugs showed stronger radiosensitization effects. After treatment with radiotherapy for 72 h, sensitization effect of combination group was twice higher than that of oxaliplatin and fluorouracil groups. Study of oxaliplatin combined with fluorouracil for radiosensitization is rare. Lee et al (20) reported that oxaliplatin can enhance the sensitivity of rectal cancer to radiotherapy. Tang et al (21) also reported that fluorouracil can increase the radiosensitivity of human colorectal cancer. Oxaliplatin (22) is a platinum-based drug that antagonizes DNA replication...
and transcription. Fluorouracil (23) exerts an antitumor effect by blocking the conversion of deoxyribose uric acid and interfering with the synthesis of DNA. Mechanism of action of the two drugs is different, so theoretically they can be used in combination to exert synergistic effects to increase the radiosensitivity of tumor cells. However, clinical studies are needed to verify the findings.

In conclusion, combination of oxaliplatin and fluorouracil is safe and effective for the treatment of rectal cancer in elderly. Combination of oxaliplatin and fluorouracil can increase sensitivity of cancer cells to radiotherapy. So it should be popularized in clinical practices.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

JX conceived the study and was responsible for the treatment of patients. XLi was responsible for MTT assay. XLv contributed to cell culture. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Taishan Medical University (Laiwu, China). Signed informed consents were obtained from the patients or the guardians.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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