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

JINFEN XU[1], XIA LI[1] and XINMING LV[2]

Departments of [1]Oncology and [2]Tumor Radiotherapy, Laigang Hospital Affiliated to Taishan Medical University, Laiwu, Shandong 271100, P.R. China

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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 fuorouracil 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.

Correspondence to: Dr Jinfen Xu, Department of Oncology, Laigang Hospital Affiliated to Taishan Medical University, 68 Xinxing Road, Laiwu, Shandong 271100, P.R. China
E-mail: erkqq@163.com

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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.

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% CO_2).

Methods. Patients were randomly divided into 3 groups: oxaliplatin group (25 cases): intravenous infusion of oxaliplatin (100 mg/m^2; 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/m^2, state approval no. H20030345) from day 1 to day 5; combination group (24 cases), intravenous infusion of oxaliplatin (100 mg/m^2) on the first day and intravenous infusion of fluorouracil (375 mg/m^2) 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 was 1 course of treatment, and efficacy and safety were evaluated after 2 courses of treatment. Treatment was performed until disease progression or until toxicity could not be tolerated by patients (no more than 6 courses of treatment).

Efficacy evaluation criteria (12): Efficacy was evaluated the first time after 2 courses of diseases. Patients were divided into complete remission (CR), partial remission (PR), stable disease (SD), and progression disease (PD) groups according to conditions of solid tumors. Remission rate (RR) = (CR+PR)/number of patients; disease control rate (DCR) = (CR+PR+SD)/number of patients.

SW837 cells were cultured in RPMI-1640 medium containing oxaliplatin (5 mg/l), fluorouracil (18 mg/l), or oxaliplatin (5 mg/l) and fluorouracil (18 mg/l) for 6 h. Then radiotherapy was performed with a dose of 6 Gy. MTT assay was used to observe the inhibitory effects of oxaliplatin, fluorouracil, and oxaliplatin combined with fluorouracil on proliferation of SW837 cells at 12, 24, 48 and 72 h after radiotherapy. Cell proliferation and sensitization ratio were compared. Each experiment was performed 3 times.

MTT assay to detect in vitro proliferation of SW837. SW837 was used to prepare single cell suspension. Cells were routinely cultured in a 96-well cell culture plate. Part of the cultured cells was taken at 6 h and 20 μl of MTT (5 mg/ml) was added, followed by incubation at 37˚C for 4 h. Supernatant containing the impurities was exhausted, and dimethyl sulfoxide formulation 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 χ^2 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 fluororacil 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

Table I. General information.

Variables	Oxaliplatin group	Fluorouracil group	Combination group	χ^2/F	P-value
No. of cases	25	24	24		
Sex (n, %)				0.013	0.987
Male	16 (64.0)	15 (62.5)	16 (66.67)		
Female	9 (36.0)	9 (37.5)	8 (33.3)		
Age (years)	67.59±7.88	69.13±7.24	68.57±8.13	0.248	0.781
Ethnicity (n, %)				0.073	0.931
Chinese	21 (84.0)	20 (83.3)	21 (87.5)		
Minority	4 (16.0)	4 (16.7)	3 (12.5)		
Clinical stage (n, %)				0.027	0.974
T1+T2	16 (64.0)	14 (58.3)	15 (62.5)		
T3+T4	9 (36.0)	10 (41.7)	9 (37.5)		
Place of residence (n, %)				0.006	0.994
Urban	12 (48.0)	12 (50.0)	11 (45.8)		
Rural region	13 (52.0)	12 (50.0)	13 (54.2)		
Degree of differentiation (n, %)				0.058	0.945
Highly differentiated	19 (76.0)	17 (70.8)	18 (75.0)		
Medium-low differentiation	6 (24.0)	7 (29.2)	6 (25.0)		

Table II. Analysis of treatment effects after two courses of treatment (n, %).

Variables	Oxaliplatin group	Fluorouracil group	Combination group	χ^2	P-value
No. of cases	25	24	24		
RR	7 (28.0)	6 (25.0)	15 (62.5)[a]	6.437	0.013
DCR	16 (64.0)	16 (66.7)	21 (87.5)	3.431	0.068
CR	0 (0.0)	1 (4.2)	2 (8.3)	2.163	0.146
PR	7 (28.0)	5 (20.8)	13 (54.2)	3.733	0.057
SD	9 (36.0)	10 (41.7)	6 (25.0)	0.814	0.370
PD	9 (36.0)	8 (33.3)	4 (16.7)	2.219	0.141

[a]P<0.05, compared with the oxaliplatin and the fluorouracil groups. RR, remission rate; DCR, disease control rate; CR, complete remission; PR, partial remission; SD, stable disease; PD, progression disease.

Table III. Incidence of adverse reactions after 2 courses of treatment (n, %).

Variables	Oxaliplatin group	Fluorouracil group	Combination group	χ^2	P-value
No. of cases	25	24	24		
Vomiting	3 (12.0)	15 (62.5)	4 (16.67)	0.160	0.690
Diarrhea	4 (16.0)	11 (45.8)	6 (25.0)	0.511	0.477
Neutropenia	7 (28.0)	6 (25.0)	15 (62.5)[a]	6.437	0.013
Anemia	6 (24.0)	7 (29.2)	12 (50.0)	3.733	0.057
Thrombocytopenia	8 (32.0)	8 (33.3)	9 (37.5)	0.159	0.691
Transaminase elevating	11 (44.0)	10 (41.7)	12 (50.0)	0.169	0.682

[a]P<0.05, compared with the oxaliplatin and the fluorouracil groups.

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

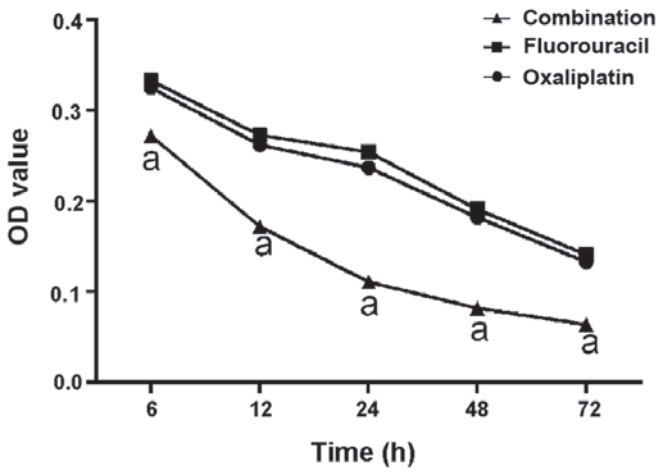

Figure 1. Proliferation of SW837 cells in oxaliplatin, fluorouracil and combination groups. *In vitro* proliferation assay of SW837 by MTT assay showed that OD values of three groups of cells decreased with time. No significant difference was found in OD values between oxaliplatin and fluorouracil groups 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 combination group was significantly lower than that in the oxaliplatin and fluorouracil groups (P<0.05). [a]P<0.05, compared with the oxaliplatin and fluorouracil groups.

Table IV. Radiosensitization of SW837 cells by oxaliplatin and fluorouracil.

Time period	Oxaliplatin group	Fluorouracil group	Combination group	F	P-value
12 h	0.84±0.12	0.73±0.11	0.89±0.13	1.389	0.319
24 h	1.58±0.24	1.42±0.23	2.01±0.41[a]	6.440	0.032
48 h	1.65±0.23	1.46±0.25	2.31±0.45[a]	3.698	0.042
72 h	1.83±0.35	1.80±0.33	3.44±0.56[a]	14.54	0.005

[a]P<0.05, compared with the oxaliplatin and the fluorouracil groups.

fluorouracil 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 the fluorouracil groups at 24, 48 and 72 h (P<0.05), while there was no significant difference in sensitization ratio between the oxaliplatin and the fluorouracil groups. Intragroup sensitization ratio comparison results showed that sensitization ratios of the three groups of cells at 24, 48 and 72 h were higher than those at 12 h (P<0.05). There was no significant difference in sensitization ratios among three groups of cells at 24 and 48 h (P>0.05), and sensitization ratio at 72 h in the combination group was higher than that at 24 and 48 h (P<0.05). Sensitization ratios of the oxaliplatin and the fluorouracil groups at 72 h were not significantly different from those at 24 and 48 h (P>0.05; Fig. 1; Table IV).

Discussion

Progression of rectal cancer in elderly is complicated and course of disease is long. Most patients are diagnosed in middle and advanced stages. Health conditions in elderly are poor and complications may easily happen. Old patients have low tolerance to chemoradiation. Many elderly patients with rectal cancer are also worried about the adverse reactions caused by chemoradiation (13,14). Therefore, it is critical for elderly patients to choose safe and effective drugs.

In this study, no significant differences in DCR, CR, PR, SD and PD were found between the oxaliplatin and fluorouracil groups. RR was higher in the combination group than those in the oxaliplatin and fluorouracil groups. Rödel *et al* (15) showed that oxaliplatin combined with fluorouracil for adjuvant treatment of regional rectal cancer can effectively improve the patient's clinical staging. André *et al* (16) also stated that combination of oxaliplatin and 5-fluorouracil for treatment of colon cancer patients can effectively improve the survival rate of patients. Similar findings were found in this study, indicating that efficacy of oxaliplatin in combination with fluorouracil for the treatment of rectal cancer is promising. However, due to time constraints, we failed to obtain information on the survival rate of patients. We will further analyze and report on survival in future studies. Although the use of oxaliplatin in combination with fluorouracil increased the efficacy of rectal cancer treatment, it also increased the incidence of some adverse reactions. For example, incidence of neutropenia in patients receiving oxaliplatin and fluorouracil was higher than that of patients received oxaliplatin and fluorouracil alone, and incidence of anemia in patients treated with combination therapy also increased. Hong *et al* (17) also found that the incidence of neutropenia in patients with rectal cancer treated with oxaliplatin combined with fluorouracil increased. Similar findings were found in our study. However, incidence of vomiting and diarrhea showed decline trend in patients treated with combination therapy, compared with the fluorouracil group. 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 Laigang Hospital Affiliated to 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.

References

1. Péron J, Bylicki O, Laude C, Martel-Lafay I, Carrie C and Racadot S: Nonoperative management of squamous-cell carcinoma of the rectum. Dis Colon Rectum 58: 60-64, 2015.
2. Jeong BG, Kim DY and Kim SY: Concurrent chemoradiotherapy for squamous cell carcinoma of the rectum. Hepatogastroenterology 60: 512-516, 2013.
3. Cancer Genome Atlas Network: Comprehensive molecular characterization of human colon and rectal cancer. Nature 487: 330-337, 2012.
4. Musio D, De Felice F, Manfrida S, Balducci M, Meldolesi E, Gravina GL, Tombolini V and Valentini V: Squamous cell carcinoma of the rectum: The treatment paradigm. Eur J Surg Oncol 41: 1054-1058, 2015.
5. Nagpal K and Bennett N: Colorectal surgery and its impact on male sexual function. Curr Urol Rep 14: 279-284, 2013.
6. Rouanet P, Mourregot A, Azar CC, Carrere S, Gutowski M, Quenet F, Saint-Aubert B and Colombo PE: Transanal endoscopic proctectomy: An innovative procedure for difficult resection of rectal tumors in men with narrow pelvis. Dis Colon Rectum 56: 408-415, 2013.
7. Hendren S and Fiscella K: Patient navigation improves the care experience for patients with newly diagnosed cancer. J Clin Oncol 32: 3-4, 2014.
8. Moran MS, Schnitt SJ, Giuliano AE, Harris JR, Khan SA, Horton J, Klimberg S, Chavez-MacGregor M, Freedman G, Houssami N, *et al*: Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. Int J Radiat Oncol Biol Phys 88: 553-564, 2014.
9. Specht L, Yahalom J, Illidge T, Berthelsen AK, Constine LS, Eich HT, Girinsky T, Hoppe RT, Mauch P, Mikhaeel NG, *et al*; ILROG: Modern radiation therapy for Hodgkin lymphoma: Field and dose guidelines from the international lymphoma radiation oncology group (ILROG). Int J Radiat Oncol Biol Phys 89: 854-862, 2014.
10. Thuss-Patience PC, Hofheinz RD, Arnold D, Florschütz A, Daum S, Kretzschmar A, Mantovani-Löffler L, Bichev D, Breithaupt K, Kneba M, *et al*: Perioperative chemotherapy with docetaxel, cisplatin and capecitabine (DCX) in gastro-oesophageal adenocarcinoma: A phase II study of the Arbeitsgemeinschaft Internistische Onkologie (AIO){dagger}. Ann Oncol 23: 2827-2834, 2012.
11. Schwartzberg LS, Rivera F, Karthaus M, Fasola G, Canon JL, Hecht JR, Yu H, Oliner KS and Go WY: PEAK: A randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. J Clin Oncol 32: 2240-2247, 2014.
12. Lai Q, Avolio AW, Graziadei I, Otto G, Rossi M, Tisone G, Goffette P, Vogel W, Pitton MB and Lerut J; European Hepatocellular Cancer Liver Transplant Study Group: Alpha-fetoprotein and modified response evaluation criteria in solid tumors progression after locoregional therapy as predictors of hepatocellular cancer recurrence and death after transplantation. Liver Transpl 19: 1108-1118, 2013.
13. Marks J, Nassif G, Schoonyoung H, DeNittis A, Zeger E, Mohiuddin M and Marks G: Sphincter-sparing surgery for adenocarcinoma of the distal 3 cm of the true rectum: Results after neoadjuvant therapy and minimally invasive radical surgery or local excision. Surg Endosc 27: 4469-4477, 2013.
14. Muro K: Systemic chemotherapy for metastatic colorectal cancer - Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2016 for treatment of colorectal cancer. Nihon Shokakibyo Gakkai Zasshi 114: 1217-1223, 2017.
15. Rödel C, Graeven U, Fietkau R, Hohenberger W, Hothorn T, Arnold D, Hofheinz RD, Ghadimi M, Wolff HA, Lang-Welzenbach M, *et al*; German Rectal Cancer Study Group: Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer (the German CAO/ARO/AIO-04 study): Final results of the multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 16: 979-989, 2015.
16. André T, de Gramont A, Vernerey D, Chibaudel B, Bonnetain F, Tijeras-Raballand A, Scriva A, Hickish T, Tabernero J, Van Laethem JL, *et al*: Adjuvant fluorouracil, leucovorin, and oxaliplatin in stage II to III colon cancer: Updated 10-year survival and outcomes according to BRAF mutation and mismatch repair status of the MOSAIC study. J Clin Oncol 33: 4176-4187, 2015.
17. Hong YS, Nam BH, Kim KP, Kim JE, Park SJ, Park YS, Park JO, Kim SY, Kim TY, Kim JH, *et al*: Oxaliplatin, fluorouracil, and leucovorin versus fluorouracil and leucovorin as adjuvant chemotherapy for locally advanced rectal cancer after preoperative chemoradiotherapy (ADORE): An open-label, multicentre, phase 2, randomised controlled trial. Lancet Oncol 15: 1245-1253, 2014.
18. Dai X, Zhang X, Wang C, Jiang J and Wu C: Paclitaxel/oxaliplatin/fluorouracil (TOF) regimen versus S-1/oxaliplatin (SOX) regimen for metastatic gastric cancer patients. Oncotarget 8: 30495-30501, 2017.

19. Xiao H, Xiong L, Song X, Jin P, Chen L, Chen X, Yao H, Wang Y and Wang L: Angelica sinensis polysaccharides ameliorate stress-induced premature senescence of hematopoietic cell via protecting bone marrow stromal cells from oxidative injuries caused by 5-fluorouracil. Int J Mol Sci 18: 18, 2017.
20. Lee EM, Hong YS, Kim KP, Lee JL, Kim SY, Park YS, Choi DH, Kim JH, Lim SB, Yu CS, *et al*: Phase II study of preoperative chemoradiation with S-1 plus oxaliplatin in patients with locally advanced rectal cancer. Cancer Sci 104: 111-115, 2013.
21. Tang M, Lu X, Zhang C, Du C, Cao L, Hou T, Li Z, Tu B, Cao Z, Li Y, *et al*: Downregulation of SIRT7 by 5-fluorouracil induces radiosensitivity in human colorectal cancer. Theranostics 7: 1346-1359, 2017.
22. Gheidari F, Bakhshandeh B, Teimoori-Toolabi L, Mehrtash A, Ghadir M and Zeinali S: TCF4 silencing sensitizes the colon cancer cell line to oxaliplatin as a common chemotherapeutic drug. Anticancer Drugs 25: 908-916, 2014.
23. Amorim R, Pinheiro C, Miranda-Gonçalves V, Pereira H, Moyer MP, Preto A and Baltazar F: Monocarboxylate transport inhibition potentiates the cytotoxic effect of 5-fluorouracil in colorectal cancer cells. Cancer Lett 365: 68-78, 2015.