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ORIGINAL ARTICLE

Retrospective Study

Effects of omeprazole in improving concurrent chemoradiotherapy efficacy in rectal cancer

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Abstract

AIM

To explore the effects of omeprazole on chemoradiotherapy efficacy and tumor recurrence in rectal cancer.

METHODS

The medical data of 125 rectal cancer patients who received the same neoadjuvant chemoradiotherapy (CRT) followed by surgery were retrospectively collected. Patients who received omeprazole (OME) orally at a dose of 20 mg at least once daily for six days and/or intravenously at 40 mg a day were recognized as eligible OME users (EOU). Otherwise, patients were regarded as non-eligible OME users (non-EOU).

Moreover, a preferred OME dose cut-off of 200 mg on tumor recurrence was obtained by receiver operating characteristic (ROC) curves. Patients were divided into two groups: the effective OME group (EOG, OME ⩾ 200 mg) and the non-effective OME group (non-EOG, OME < 200 mg).

RESULTS

The good response rate of CRT efficacy (50.8%) in EOU was significantly increased compared with non-EOU (30.6%) (P = 0.02). The recurrence rate in the EOG was 10.3%, which was significantly lower compared with 31.3% in non-EOG (P = 0.025). The good response rate of CRT efficacy in EOG was 55.2%, which was obviously higher compared with 36.5% in non-EOG, with a significant difference (P = 0.072). Multivariate Cox analysis demonstrated that OME (non-EOG and EOG) was an independent and significant impact factor for DFS (P = 0.048, HR = 0.30, 95%CI: 0.09-0.99).

CONCLUSION

When applied as an adjuvant drug in cancer treatment for relieving common side effects of chemotherapy, omeprazole has a synergetic effect in improving CRT efficacy and decreasing rectal cancer recurrence.

Key words: Omeprazole; Chemoradiotherapy efficacy; Recurrence; Rectal cancer

Core tip: In *in vitro* and *in vivo* studies, proton pump inhibitors (PPIs) induce apoptosis of gastric cancer cells, B-cell tumors and hepatoblastoma cells and promote autophagy in melanoma cells and pancreatic cancer cells. PPIs also sensitize chemo-resistant tumors to cytotoxic drugs and improve the efficacy of T-cell-based cancer immunotherapy. However, whether PPIs affect chemoradiotherapy (CRT) efficacy, decrease tumor recurrence and improve survival in rectal cancer patients remains unclear. In the present study, when used as adjuvant drug in cancer treatment, omeprazole has a synergetic effect in improving CRT efficacy and decreasing recurrences in rectal cancer.

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INTRODUCTION

Rectal cancer is one of the worldwide leading causes of cancer related death[1]. Preoperative chemoradiotherapy (CRT) followed by radical surgery is a preferred treatment for patients with advanced rectal cancer for its reduced local recurrence and high sphincter preservation rate[2-4]. However, disease relapse is still a critical factor that affects patient survival[2]. The exploration of factors that affect CRT efficacy and tumor recurrence is important to improve cancer management.

Abnormal pH gradients in the tumor microenvironment are involved in tumorigenesis, tumor progression and drug resistance[5-11]. Vacuolar type H+-ATPases (V-ATPases) are proton pumps expressed on the membrane of endolysosomal organelles and plasma membranes[5], which could modulate the tumor acidic microenvironment[12,13]. V-ATPases are overexpressed in chemo-resistant cancer cells and are induced by cytotoxic drugs[14,15], playing a key role in cancer cells with a multidrug resistance phenotype[16]. Proton pump inhibitors (PPIs), such as omeprazole (OME) and esomeprazole, are used to relieve common side effects of chemotherapy, such as nausea and emesis. In addition to targeting the gastric acid pump, PPIs inhibit the activity of V-ATPases[17-20]. Moreover, PPIs induce apoptosis in gastric cancer cells[21], B-cell tumors[22] and hepatoblastoma cells[23] and promote autophagy in melanoma cells[24] and pancreatic cancer cells[25]. PPIs improve the efficacy of T-cell-based cancer immunotherapy[26-28]. In colorectal cancer, it is reported that PPIs re-sensitize drug-resistant cancer colon adenocarcinomas cell lines to cytotoxic drugs[26]

These study results suggest that the application of PPIs may be helpful in improving cancer treatment. However, whether PPIs could affect CRT efficacy, reduce tumor recurrence and improve survival in rectal cancer patients remain unclear.

MATERIALS AND METHODS

Patients

From May 2008 to March 2016, the medical records of consecutive rectal cancer patients who received the same neoadjuvant CRT followed by radical surgery were retrospectively collected. Neoadjuvant CRT included three-dimensional conformal radiotherapy (3D-CRT) using a total dose of 46 Gy concurrent with two cycles of oxaliplatin plus capecitabine. The disease was diagnosed by a combination of medical history, physical examination, biopsy, and staging examination, including abdominal ultrasound, abdominal-pelvis computed tomography, colonoscopy and endoscopic or trans-rectal ultrasonography. Tumors were staged according to the AJCC (2010 edition). Tumor stages before CRT and after surgery were classified as cTNM and ypTNM, respectively. Patients lacking detailed medical records or those with a second tumor or distant metastasis were excluded. Finally 125 patients met the criteria. The patients were aged 15-78 years, with a mean age of 55.8 ± 12.01 years. The mean

body weight and mean height of the patients was 60.1 ± 9.3 kg and 164.1 ± 6.85 cm, respectively. Pre-treatment serum carcinoembryonic antigen (CEA) and CA19-9 data were available in 120 of the 125 patients. The study was approved by the Medical Ethics Committee of Sun Yat-Sen University Cancer Center. Written informed consent was obtained from all patients.

Neoadjuvant concurrent CRT

Radiation treatment planning was designed according to the three-dimensional conformal radiation therapy (3D-CRT), with one posterior field and two lateral fields. Patients were treated using a range of 6-15 MV photons. Radiation was delivered at a total dose of 46 Gy (23 fractions with 2 Gy per fraction in 5 wk). Gross tumor volumes (GTVs) included rectal tumors and enlarged lymph nodes. Clinical target volumes (CTVs) included lymphatic drainage areas around the rectum and sacrum. Planning target volume (PTV) included areas with a 0.8-1.0 cm radial margin around the CTV. Patients were treated in the prone position, and a belly board was used to exclude the small bowel out of the radiation field. Oxaliplatin (130 mg/m^2) was delivered intravenously over 2 h on the first day of radiation treatment and on day 21. Capecitabine was administered orally twice daily at 1000 mg/m^2 on days 1-14 and days 21-34.

Dosage of omeprazole

Omeprazole usage was recorded in detail. Omeprazole was administered orally at 20 mg twice a day (Omeprazole Magnesium Entericcoated Tablets, AstraZeneca AB), 40 mg (Omeprazole Sodium for Injection, AstraZeneca AB) or 60 mg (Omeprazole Sodium for Injection, Changzhou Siyao Pharmaceuticals Co., Ltd.) intravenously one hour before the start of chemotherapy and was continuously administered in the following days if the patients complained of digestive discomfort. The reduction in gastric peak acid secretion after continuous oral administration of 20 mg OME once daily for six days was comparable with the effect of a single intravenous dose of 40 mg OME[29]. Thus, patients who received 20 mg OME orally at least once a day for six days and/or intravenous infusion of 40 mg OME daily were recognized as eligible OME users (EOU); otherwise, the patients were regarded as non-eligible OME users (non-EOU). Among the 125 patients, 63 patients met the criteria as EOU. Moreover, the bioavailability of oral enteric-coated omeprazole granules was initially low (approximately 35%-40%); however, it increased to approximately 65% on repeated dosing[30-33]. Therefore, the oral dose of EOU was multiplied by 65% to convert to a dose comparable with the intravenous dose for the intention of equal drug bioavailability.

Surgery, tumor regression evaluation and adjuvant chemotherapy

Radical surgery was performed 4-6 wk after CRT completion. Primary tumor regression grade (TRG) was determined semiquantitatively according to a modified Dworak scale[34] based on the amount of viable tumor *vs* the amount of fibrosis as follows: 0, no regression; 1, dominant tumor mass with obvious fibrosis and/or vasculopathy; 2, dominantly fibrotic changes with few tumor cells or groups (easy to find); 3, very few (difficult to find microscopically) tumor cells in fibrotic tissue with or without a mucous-like substance; and 4, no tumor cells and only fibrotic mass (total regression or response). A Dworak grade of 2 or 3 was determined by two experienced pathologists. CRT efficacy was classified as either a "good response" or a "poor response". Good response cases were those whose tumor regression was classified as TRG 3 or 4; poor response cases were those whose tumor regression was graded as TRG 0, 1 or 2. Patients were advised to undergo four to six cycles of adjuvant chemotherapy that was the same as neoadjuvant chemotherapy 4-6 wk after surgery completion. When patients could not endure the side effects of adjuvant chemotherapy, capecitabine monotherapy was adopted. Finally, 125 patients received 479 cycles of adjuvant chemotherapy.

Follow-up

After completion of combined treatment, patients were followed up every 3 to 6 mo in the first 3 years and every 12 mo thereafter. Patient evaluation included a physical examination, abdominal ultrasonography or computed tomography scan, chest X-ray, and serum CEA and Ca19-9 levels. Diagnosis of recurrence was based on two types of radiologic examination with or without abnormal plasma tumor markers. Histopathological verification was performed when necessary. The survival status was verified by examination of clinical attendance records and direct telecommunication with the patient or their family in March 2016. Survival was censored at the time of the last follow-up on March 1, 2016, with a median follow-up time of 66 mo (range 17-99 mo).

End points and statistical analysis

The study end points were CRT efficacy, recurrence, disease-free survival (DFS) and overall survival (OS). DFS was defined as the interval from surgery to either confirmed recurrence or death, and OS was defined as the time interval between surgery and death.

Continuous variables were expressed as the mean ± SD. Student *t* test and χ^2 tests were used to compare differences between groups. A receiver operating characteristic (ROC) curve was plotted to identify a proper cut-off value. Kaplan-Meier analysis was used to compare survival using the log-rank test.

Table 1 Mean dose and duration of omeprazole administered orally and intravenously

OME	Cases	administered dose (mg)				OME administration (No. of days)			
		Mean ± SD	95%CI	Max	Min	Mean ± SD	95%CI	Max	Min
Oral[1]	7	260.0 ± 143.2	127.6-392.4	546	182	11.0 ± 8.0	3.6-18.3	28	7
IV[2]	47	217.2 ± 184.8	162.8-271.3	940	40	3.8 ± 3.0	2.9-4.6	16	1
IV + Oral[3]	9	406.2 ± 184.9	264.1-548.4	756	151	13.7 ± 7.0	8.2-19.1	28	7

[1]Oral OME multiplied by 65%; [2]OME received intravenously; [3]Oral OME multiplied by 65% plus OME received intravenously. OME: Omeprazole.

Table 2 Differences in the clinicopathological characteristics in eligible omeprazole users and non-eligible omeprazole users

Characteristics	Total	EOU		*P* value
		Non	Yes	
Sex				
Male	90	46	44	0.59
Female	35	16	19	
Age (yr)				
< 60	73	37	36	0.77
⩾ 60	52	25	27	
BMI				
< 25	100	47	53	0.25
⩾ 25	25	15	10	
Tumor size (cm)				
⩽ 3	49	24	25	0.95
3-6	61	30	31	
⩾ 6	15	8	7	
Tumor grade				
1	28	14	14	0.23
2	88	46	42	
3	9	2	7	
cTNM				
Ⅱ	39	22	17	0.31
Ⅲ	86	40	46	
CEA (ng/mL)				
< 5	62	28	34	0.47
⩾ 5	58	30	28	
CA19-9 (U/mL)				
< 35	102	50	52	0.72
⩾ 35	18	8	10	
TGR				
0	39	23	16	0.25
1	15	8	7	
2	20	12	8	
3	24	9	15	
4	27	10	17	
CRT efficacy				
Poor	74	43	31	0.02
Good	51	19	32	
ypTNM				
ypcr	25	9	16	0.34
Ⅰ	26	16	10	
Ⅱ	40	20	20	
Ⅲ	34	17	17	
Adjuvant CT				
No	21	9	12	0.5
Yes	104	53	51	
Recurrence				
No	92	46	46	0.66
Yes	33	16	17	

EOU: Eligible OME users; non-EOU: Non-eligible OME users; BMI: Body mass index; TGR: Tumor regression grade; adjuvant CT: Adjuvant chemotherapy.

Univariate and multivariate Cox proportional hazard models were used to assess the effect of risk factors on survival. Forward conditional methods were used to establish the multivariate Cox proportional hazards model. A two-tailed *P* value less than 0.05 was considered statistically significant. Statistical analysis was performed using the SPSS statistical software package (version 22).

RESULTS

Clinicopathological characteristics of patients treated at different doses of OME

Among 63 OME users, 7 patients only received OME orally, 47 patients only received OME intravenously, and 9 patients received OME both orally and intravenously. The detailed information of OME dosage is presented in Table 1. The good response rate (50.8%) in the EOU was significantly increased compared with non-EOU (30.6%) (*P* = 0.02, OR = 2.336, 95%CI: 1.124-4.856). No significant differences for other clinicopathological factors were found between the EOU and non-EOU groups (all *P* values > 0.05). The patient characteristics of EOU and non-EOU are summarized in Table 2.

PPIs inhibit cancer cell proliferation in a dose-dependent manner[25,35]. Therefore, in addition to arbitrarily applying a cut-off that meets the inclusion criterion, a preferred OME dose cut-off for tumor recurrence was investigated by ROC curves. The dose that was closest to the upper left corner (100% sensitivity and 100% specificity) was selected as the cut-off dose. The area under the ROC curve (AUC) was calculated to estimate the discriminatory power of the produced OME dose cut-off of the entire dose range on recurrence. A dose cut-off of 200 mg was identified by ROC as the optimized point that differentiated recurrence from non-recurrence with maximal sensitivity and specificity (Figure 1). The AUC was 0.66 (*P* = 0.053), and the OME dose of 200 mg differentiated recurrence from non-recurrence with a specificity of 82.4% and a sensitivity of 56.5%. Patients were then divided into the effective OME group (EOG, patients received OME ⩾ 200 mg) and non-effective OME group (non-EOG, patients received OME < 200 mg). Non-EOG and EOG patient characteristics are summarized in Table 3.

Table 3 Differences in clinicopathological characteristics of non-eligible omeprazole users and eligible omeprazole users

Characteristics	Total	EOG		*P* value
		Non	Yes	
Sex				
Male	90	71	19	0.380
Female	35	25	10	
Age(yr)				
< 60	73	58	15	0.410
⩾ 60	52	38	14	
BMI				
< 25	100	77	23	0.920
⩾ 25	25	19	4	
Tumor size (cm)				
⩽ 3	49	37	12	0.940
3-6	61	47	14	
⩾ 6	15	12	3	
Tumor grade				
1	28	22	6	0.960
2	88	67	21	
3	9	7	2	
cTNM				
Ⅱ	39	30	9	0.980
Ⅲ	86	66	20	
CEA (ng/mL)				
< 5	62	45	17	0.390
⩾ 5	58	46	12	
CA19-9 (U/mL)				
< 35	102	76	26	0.420
⩾ 35	18	15	3	
TGR				
0	39	34	5	0.330
1	15	11	4	
2	20	16	4	
3	24	17	7	
4	27	18	9	
CRT efficacy				
Poor	74	61	13	0.072
Good	51	35	16	
ypTNM				
ypcr	25	16	9	0.380
Ⅰ	26	21	5	
Ⅱ	40	31	9	
Ⅲ	34	28	6	
Adjuvant CT				
No	21	14	7	0.230
Yes	104	82	22	
Recurrence				
No	97	66	26	0.025
Yes	28	30	3	

EOG: Effective OME group; non-EOG: Non-effective OME group; BMI: Body mass index; TGR: Tumor regression grade; adjuvant CT: Adjuvant chemotherapy.

The recurrence rate in EOG was 10.3% (3/29), which was significantly lower than 31.3% (30/96) in non-EOG (P = 0.025, OR = 0.25, 95%CI: 0.07-0.90; Table 3). The response rate of CRT efficacy in EOG was 55.2% (16/29), which was obviously increased compared with 36.5% (35/96) in non-EOG, with a marginally significant difference (P = 0.072, OR = 2.15, 95%CI: 0.93-5.00; Table 3). There was no significant difference in other clinicopathological features between the non-EOG and EOG groups (all P > 0.05, Table 3). Non-EOG received a total of 371 cycles of adjuvant chemotherapy, with a mean value of 3.9 ± 2.2. EOG received 108 cycles, and the mean value was 3.7 ± 2.6. The mean adjuvant chemotherapy cycles were not significantly different (P = 0.77) between the EOG and non-EOG groups.

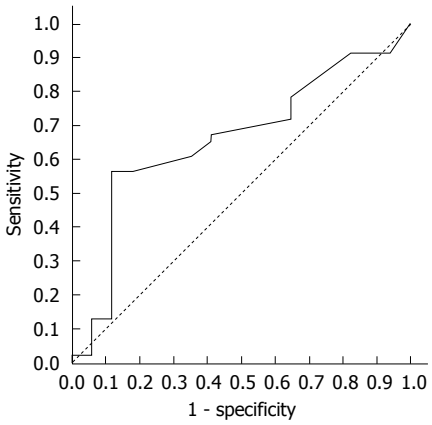

Figure 1 Receiver operating characteristic curve of omeprazole dose for recurrence.

Survival difference between the non-EOG and EOG

At the end of the study, 96 (76.8%) patients were still alive. The patients who did not survive all died from tumor-related causes, and no patient died of PPI-related severe infection[36] during the CRT treatment. The mean DFS and mean OS of all patients was 62.9 mo ± 25.5 mo, 95%CI: 58.4-67.4) and 66.6 mo ± 21.8 mo, 95%CI: 62.8-70.5), respectively. The 3- and 5-year DFS rates of all patients were 81.6% and 75.1%, respectively. The 3- and 5-year OS rates of all patients were 85.6% and 78.8%, respectively.

A significant difference in DFS was noted between non-EOG and EOG patients (P = 0.032; Figure 2A, Table 4). In addition, a marginally significant difference in OS was also observed (P = 0.092; Figure 2B and Table 4). BMI, ypTNM and CRT efficacy were significantly associated with DFS (P = 0.024, P < 0.005 and P = 0.031, respectively; Table 4), whereas cTNM was a marginally significant factor of DFS (P = 0.067; Table 4). ypTNM was the only significant impact factor of OS (P = 0.003; Table 4), and BMI was a marginally significant factor of OS (P = 0.05; Table 4).

Cox proportional hazards model analysis

The univariate Cox analysis revealed that OME (non-EOG and EOG), BMI, CRT efficacy, and ypTNM were significantly associated with DFS (P = 0.044, 0.039, 0.036 and P = 0.006, respectively; Table 5). The cTNM was significantly associated with DFS (P = 0.075; Table 5), and BMI was marginally significantly associated with OS (P = 0.069; Table 5). ypTNM was a significant impact factor for OS (P = 0.045). No other clinicopathological features significantly associated with DFS and OS (all P > 0.05; Table 5).

Furthermore, multivariate Cox analysis demon-

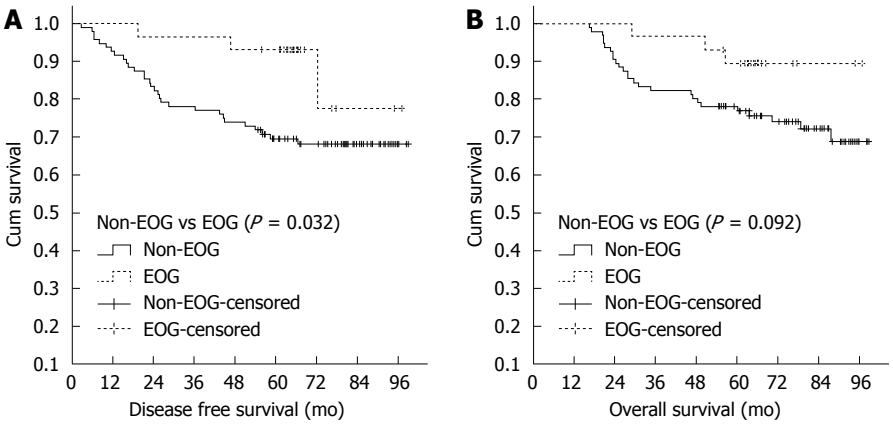

Figure 2 Disease-free survival curves (A) or OS curves (B) of non-omeprazole and omeprazole. EOG: Effective omeprazole.

Table 4 Univariate analysis of impact of various characteristics on patient survival

Characteristics	*n*	DFS			*P* value	OS			*P* value
		Mean (mo)[1]	3-yr[2]	5- yr[2]		Mean (mo)[1]	3- yr[2]	5- yr[2]	
Sex									
Male	90	61.8 ± 25.9	81.1%	74.4%	0.803	65.5 ± 22.2	84.4%	79.9%	0.855
Female	35	65.6 ± 24.6	82.9%	76.9%		69.5 ± 20.1	88.6%	79.8%	
Age (yr)									
< 60	73	63.3 ± 26.3	80.1%	71.1%	0.533	68.4 ± 22.0	86.3%	80.7%	0.908
⩾ 60	52	62.4 ± 24.6	82.7%	80.7%		64.2 ± 21.5	84.6%	78.7%	
Tumor size (cm)									
⩽ 3	48	62.5 ± 26.1	81.2%	77.0%	0.571	65.0 ± 22.4	83.3%	79.2%	0.962
> 3	77	63.2 ± 25.3	81.8%	74.0%		67.7 ± 21.6	87.0%	80.3%	
BMI									
< 25	100	60.5 ± 26.8	77.0%	69.9%	0.024	65.3 ± 22.7	82.0%	76.9%	0.050
⩾ 25	25	72.7 ± 16.6	96.0%	96.0%		72.1 ± 17.0	96.0%	92.0%	
Tumor grade									
1	28	64.7 ± 28.0	78.6%	75.0%	0.852	69.4 ± 22.5	85.7%	78.6%	0.931
2, 3	97	62.4 ± 25.0	82.5%	75.2%		65.6 ± 21.7	85.6%	80.2%	
cTNM									
Ⅱ	39	69.2 ± 23.2	87.2%	84.6%	0.067	71.9 ± 18.8	92.3%	87.2%	0.137
Ⅲ	86	60.0 ± 26.2	79.1%	70.7%		64.2 ± 22.8	82.6%	76.4%	
CEA (ng/mL)									
< 5	62	77.0 ± 4.1	69.2%	69.2%	0.789	79.6 ± 3.7	80.6%	73.9%	0.384
⩾ 5	58	80.4 ± 4.3	82.8%	74.0%		86.1 ± 3.4	89.7%	84.5%	
CA19-9 (U/mL)									
< 35	102	81.3 ± 3.1	83.3%	75.4%	0.174	84.2 ± 2.7	86.3%	80.2%	0.597
⩾ 35	18	68.1 ± 9.2	72.2%	66.7%		78.3 ± 7.8	77.8%	72.2%	
CRT efficacy									
Poor	74	60.7 ± 27.2	78.4%	67.5%	0.031	66.2 ± 23.2	83.8%	75.6%	0.144
Good	51	66.1 ± 23.0	90.2%	86.0%		67.3 ± 19.9	88.2%	86.1%	
ypTNM									
ypcr, Ⅰ, Ⅱ	91	66.1 ± 24.0	85.7%	82.3%	0.005	68.5 ± 20.1	89.0%	84.4%	0.041
Ⅲ	34	54.3 ± 28.0	70.6%	55.6%		61.6 ± 25.5	76.5%	67.6%	
Adjuvant CT									
No	21	60.2 ± 31.5	71.4%	71.4%	0.385	63.5 ± 26.5	76.2%	66.3%	0.229
Yes	104	63.5 ± 24.3	83.7%	75.8%		67.3 ± 20.8	87.5%	82.7%	
OME									
Non- EOU	62	70.0 ± 25.8	85.5%	75.6%	0.658	73.9 ± 21.9	90.3%	82.0%	0.754
EOU	63	55.9 ± 23.5	77.8%	74.6%		59.5 ± 19.5	82.5%	77.6%	
OME (200 mg)									
Non-EOG	96	62.0 ± 28.2	77.1%	69.6%	0.032	66.9 ± 24.1	82.3%	76.9%	0.092
EOG	29	65.9 ± 13.3	96.6%	46.7%		65.8 ± 12.0	96.6%	89.5%	

[1]Mean ± SD (mo); [2]Three or 5 years survival rate. EOU: Eligible OME users; Non-EOU: Non-eligible OME users; EOG: Effective OME group; Non-EOG: Non-effective OME group; BMI: Body mass index; adjuvant CT: Adjuvant chemotherapy.

Table 5 Univariate Cox analysis of the impact of various characteristics on patient survival

Characteristics	DFS		*P* value	OS		*P* value
	HR	95%CI		HR	95%CI	
Sex						
Male *vs* Female	0.91	0.42-1.65	0.800	0.93	0.41-2.09	0.860
Age (yr)						
< 60 *vs* ⩾ 60	0.80	0.40-1.62	0.530	1.05	0.50-2.19	0.910
BMI						
< 25 *vs* ⩾ 25	0.22	0.05-0.93	0.039	0.26	0.06-1.11	0.069
Tumor size (cm)						
⩽ 3 *vs* > 3	1.23	0.60-2.51	0.570	0.98	0.46-2.08	0.960
Tumor grade						
1 *vs* 2, 3	1.08	0.47-2.50	0.850	0.96	0.41-2.26	0.930
cTNM						
Ⅱ *vs* Ⅲ	2.23	0.92-5.41	0.075	1.96	0.80-4.80	0.144
CEA (ng/mL)						
< 5 *vs* ⩾ 5	0.91	0.46-1.81	0.790	0.72	0.34-1.51	0.390
CA199 (U/mL)						
< 35 *vs* ⩾ 35	1.77	0.77-4.08	0.180	1.30	0.50-3.40	0.600
CRT efficacy						
Poor *vs* good	0.43	0.19-0.95	0.036	0.55	0.24-1.24	0.150
ypTNM						
ypcr, Ⅰ, Ⅱ *vs* Ⅲ	1.61	1.14-2.27	0.006	1.46	1.01-2.11	0.045
Adjuvant CT						
Non *vs* yes	0.69	0.30-1.60	0.390	0.60	0.25-1.40	0.240
EOU						
Non *vs* yes	1.17	0.59-2.31	0.660	1.13	0.54-2.37	0.750
EOG						
Non *vs* yes	0.30	0.90-0.97	0.044	0.37	0.11-1.23	0.110

EOU: Eligible OME users; Non-EOU: Non-eligible OME users; EOG: Effective OME group; Non-EOG: Non-effective OME group; BMI: Body mass index; Adjuvant CT: Adjuvant chemotherapy.

strated that OME (non-EOG and EOG), BMI and ypTNM were independent and significant predictors of DFS (*P* = 0.048, HR = 0.30, 95%CI: 0.09-0.99, *P* = 0.038, HR = 0.22, 95%CI: 0.05-0.92 and *P* = 0.01, HR = 1.58, 95%CI: 1.12-2.22). ypTNM was also an independent and significant predictor of OS (*P* = 0.045, HR = 1.46, 95%CI: 1.01-2.11).

DISCUSSION

Neoadjuvant CRT could greatly improve the anus save rate and decrease local recurrence rate in advanced rectal cancer patients[2-4,37]. However, results addressing whether neoadjuvant CRT could improve survival are inconsistent[2,37]. The results of the present study showed that CRT efficacy is a significant clinicopathological factor associated with DFS (*P* = 0.031) and exhibits a favorable trend with OS (*P* = 0.144), indicating that CRT could decrease recurrence and potentially benefit OS. The results of the present study suggest that CRT efficacy is a significant clinicopathological factor associated with DFS, and this result is consistent with previous studies[2-4]. The present study results suggest that CRT has a potential benefit in OS, but is not a significant predictor. These results were consistent with the study by Sauer *et al*[37] but not with the study of Calogero Cammà *et al*[2]. As a potential chemotherapeutic agent[27,38-42], PPIs are safe to humans at high doses and with long-term treatment[37,38]. The mechanisms by which PPIs affect cancer include inhibiting V-ATPase activity[17,18], inducing apoptosis[21-23], promoting autophagy[24,25] and stimulating caspase-dependent cell death[35]. PPIs could sensitize chemo-resistant tumors to cytotoxic drugs[26] and could improve the efficacy of T-cell-based cancer immunotherapy[27,28], suggesting that PPIs may improve cancer treatment efficacy. In the present study, we found a good response rate (50.8%) in the EOU group that was significantly increased compared with the non-EOU group (30.6%) (*P* = 0.02), suggesting that OME could enhance the sensitivity of rectal cancer to concurrent CRT. We noticed that after the OME dose cut-off was increased, the good response rate of CRT efficacy between EOG (55.2%) and non-EOG (36.5%) patients exhibited a marginally significant difference (*P* = 0.072). This result was likely caused by an elevated cut-off that resulted in a decreased EOG sample size, which would reduce statistical power. To the best of our knowledge, this study is the first to investigate the effect of PPIs on CRT efficacy.

Abnormal extracellular acidic pH could enhance the invasive capacity and metastatic behavior of cancer cells[43-46]. V-ATPase is involved in pH-dependent degradation of the extracellular matrix and promotion of tumor invasion and metastasis[39,47], suggesting that inhibition of V-ATPase may prevent metastasis. Consistent with these studies, the present study

results showed that the recurrence rate in EOG patients was 10.3%, which was significantly lower compared with 31.3% in non-EOG patients (P = 0.025). In addition, a significant difference in DFS was noted between non-EOG and EOG patients (P = 0.032), and a marginally significant difference in OS was noted (P = 0.092). Further multivariate Cox analysis demonstrated that OME (non-EOG and EOG) is an independent and significant predictor of DFS (P = 0.048). These results suggest that when administered as an adjuvant chemoradiotherapy drug, OME may exert synergistic effects with concurrent CRT to reduce tumor recurrence.

Whether the plasma concentration of the including criteria for dosage of OME in the present study could affect cancer cell vitality should be further discussed. The oral intake of 20 mg OME could produce a maximal plasma concentration of 2.5 mg/mL after two hours in patients[48]. The minimum OME dosage for the inclusion criteria in the present study was 40 mg intravenously administered, achieving a plasma concentration of 5 mg/mL. In *in vitro* studies, OME dissolved in normal saline at a concentration of 1 mg/mL induces apoptosis in B-cell cancers[22] and re-sensitizes drug-resistant cancer cell lines (22 melanomas, 2 colon adenocarcinomas, 2 breast cancers and 2 ovarian carcinomas) to cytotoxic drugs[26]. In *in vivo* studies, 0.4 mg/kg OME co-administered with dichloroacetate and tamoxifen exhibit a synergistically anti-proliferative effect on cholangiocarcinoma[49]. In addition, 2 mg/kg OME combined with dichloroacetate exhibited an antitumor effect on HT1080 fibrosarcoma cells inoculated in mice[50]. ESOM (2.5 mg/kg) reduced tumor growth in SCID mice engrafted with human melanoma[35]. In the present study, the minimum OME dose per kilogram of body weight was approximately 0.67 mg/kg (40 mg/60 kg), and the mean dose per kilogram of body weight was 3.6 mg/kg (217.2 mg/60.0 kg), which were higher than the least functional dosage reported above[49].

BMI was significantly associated with DFS (P = 0.024) and was a marginally significant factor associated with OS (P = 0.05). Further multivariate Cox analysis demonstrated that BMI was an independent and significant predictor of DFS (P = 0.038), which was consistent with a previous study[51].

Our study has several limitations. Although consecutive patients were included, it is a retrospective study. In addition, the patient sample of the study was relatively small. However, the effects of OME on CRT efficacy, tumor recurrence and patient survival were first investigated in the present study, which would be helpful for randomized and controlled trials in the future.

In conclusion, when used as an adjuvant drug in cancer treatment, omeprazole has a synergetic effect on improving CRT efficacy and decreasing rectal cancer recurrence.

COMMENTS

Background

Abnormal pH gradients of tumor microenvironment are involved in tumorigenesis, tumor progression and drug resistance. Vacuolar type H+-ATPases (V-ATPases) are proton pumps expressed on the membrane of endolysosomal organelles and the plasma membrane, which could modulate the tumor acidic microenvironment. Proton pump inhibitors (PPIs), such as omeprazole (OME) and esomeprazole, are used to relieve common side effects of chemotherapy, such as nausea and emesis. In addition to targeting the gastric acid pump, PPIs inhibit the activity of V-ATPases. Moreover, PPIs induce apoptosis in multiple cancer cells and promotes cancer cell autophagy. PPIs also sensitize chemo-resistant tumors to cytotoxic drugs and improve the efficacy of T-cell-based cancer immunotherapy. These study results suggest that application of PPIs may be helpful to improve cancer treatment. However, whether PPIs affect CRT efficacy, reduce tumor recurrence and improve survival in rectal cancer patients remain unclear.

Research frontiers

The present study investigates whether omeprazole used as an adjuvant drug in cancer treatment could improve cancer treatment efficacy.

Innovations and breakthroughs

In contrast with previous *in vitro* and *in vivo* studies, the present study clinically revealed that when used as an adjuvant drug in cancer treatment, omeprazole has synergetic effects on improving CRT efficacy and reducing rectal cancer recurrence.

Applications

When used as an adjuvant drug in cancer treatment, omeprazole has a synergetic effect on improving CRT efficacy and reducing rectal cancer recurrence and is helpful in improving cancer treatment efficacy.

Peer-review

Zhang *et al* retrospectively reviewed a series of 125 patients with rectal cancer and demonstrated that omeprazole users had better prognosis in term of response and recurrence rates and disease-free survival.

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