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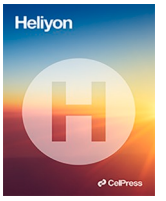

Research article

Capecitabine enhances sensitivity to oxaliplatin in advanced gastric cancer and the effects on patients' FOXP1 and GGT levels☆

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ABSTRACT

Objective: To investigate the effect of capecitabine on the sensitivity of oxaliplatin and on the level of transcription factor forkhead box P1 (FOXP1) and gamma-glutamyl transpeptidase (GGT) in patients with intermediate and advanced gastric cancer.

Methods: A total of 152 patients with intermediate and advanced gastric cancer diagnosed and treated in our hospital from April 2018 to May 2019 was selected as the research objects, and their clinical data were retrospectively analyzed. According to the different treatment methods, they were divided into the study group and the control group, with 76 cases in each group. The patients in the control group received with oxaliplatin, while the patients in the study group received with capecitabine on the basis of the control group. The therapeutic effect was evaluated according to the therapeutic effect evaluation criteria of solid tumors. The FOXP1 expression level in gastric cancer tissues was detected using immunohistochemistry. Serum levels of GGT were measured by chemiluminescence. The prognostic factors were analyzed by COX regression model, and the Kaplan-Meier survival curve was used to analyze the relationship between the influencing factors and the survival of gastric cancer.

Results: The effective rate of capecitabine combined with oxaliplatin and oxaliplatin alone in the treatment of patients with intermediate and advanced gastric cancer were 94.74 % and 76.32 % respectively. Capecitabine enhanced the sensitivity of intermediate and advanced gastric cancer to oxaliplatin ($P < 0.05$). Compared with adjacent normal tissues, the expression level of FOXP1 in gastric cancer tissues was lower ($P < 0.05$). Before treatment, the expression of FOXP1 was low, and no significant difference was observed in the GGT level between the two groups ($P > 0.05$). After treatment, the low expression rate of FOXP1 and serum GGT level were both significantly decreased, and those in the study group were lower than those in the control group ($P < 0.05$). There was no difference in the incidence of adverse reactions between the two groups ($P > 0.05$). The 1-year survival rates of the study group and the control group were 90.79 % and 78.95 %, while the 3-year survival rates of the study group and the control group were 75.00 % and 51.32 %, respectively. Both the 1-year and 3-year survival rate of the study group was higher than that in the control group ($P < 0.05$). The 1-year survival rate of 152 patients with gastric cancer was 84.87 % (129/152) and the 3-year survival rate was 63.17 % (96/152). Age, tumor diameter, tumor-node-metastasis (TNM) stage, lymph node metastasis, chemotherapy regimen and the expression of FOXP1 and GGT had significant effects on the survival rate ($P < 0.05$). Gastric cancer patients with age <60 years, TNM stage of I ~ II, lymph node metastasis N0 ~ N1, high

☆ This is a retrospective study, all data were analyzed retrospectively. This research was approved by the Ethics Review Committees of Fuwai Central China Cardiovascular Hospital (approval number: 2023-EC-015).

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expression of FOXP1, GGT <387.2, and combined with drug chemotherapy had higher survival rate.

Conclusion: Capecitabine effectively enhanced the sensitivity of intermediate and advanced gastric cancer to oxaliplatin, improved the therapeutic effect, reduced the proportion of patients with low FOXP1 expression rate and serum GGT level, decreased the recurrence rate and ameliorated the prognosis of patients.

1. Introduction

Gastric cancer is one of the most common malignant tumors of digestive tract. According to the 2020 Global Cancer Burden Data, the incidence rate of gastric cancer in China ranks second in the incidence rate of all malignant tumors, and the mortality rate ranks third in the mortality rate of malignant tumors, indicating a high incidence and mortality rates of gastric cancer in China [1]. However, the incidence of gastric cancer in developed countries is gradually decreasing. The prognosis of gastric cancer is closely related to the timing of diagnosis and treatment. The five-year survival rate of advanced gastric cancer is still less than 30 % even after comprehensive treatment with surgery [2,3]. Moreover, the quality of life of patients is low, which brings a heavy burden to the families and country. However, the 5-year survival rate of most early-stage gastric cancers can exceed 90 % after treatment [4], and even achieve a curative effect. Therefore, early diagnosis of gastric cancer is undoubtedly the key to improving the survival rate and survival time of gastric cancer patients. The pathogenesis of gastric cancer is complex. Its early onset is relatively insidious, only manifested as nausea and vomiting, and the symptoms are not obvious and lack certain specificity. As a result, most patients are in the intermediate and advanced stages at the time of diagnosis, missing the optimal time for treatment [5]. Surgery combined with radiotherapy and chemotherapy is the main method for the treatment of intermediate and advanced gastric cancer. Among them, chemotherapy based on oxaliplatin is considered as the first-line treatment against gastric cancer, which has achieved good results [6]. However, some tumor cells are less sensitive to chemotherapy drugs, so the effect of conventional chemotherapy is not satisfactory, especially for the treatment of advanced colorectal cancer. The emergence of chemoresistance poses a threat to long-term clinical benefits and may be an important factor contributing to treatment failure in patients with advanced gastric cancer [7]. Therefore, finding a safe and effective method that can enhance the sensitivity of tumor cells to oxaliplatin plays a momentous role in improving the treatment effect and prognosis of patients.

Capecitabine is an oral fluorouracil antitumor drug that inhibits the growth of tumor cells by inhibiting the activity of thymidine phosphatase (TPP) and hindering deoxyribonucleic acid (DNA) synthesis [8]. Capecitabine has a small gastrointestinal reaction, activates in liver and tumor tissues after oral administration, and is converted into 5-FU to exert anti-tumor effects, which is mainly used for the treatment of colorectal cancer, breast cancer, and gastric cancer, and can also be used as a rescue therapy for breast cancer after anthracycline and taxane therapy failure [9]. Oxaliplatin is a platinum-based antitumor drug that can hinder DNA replication and transcription of tumor cells through cross-linking with DNA strands, leading to tumor cell death [10]. The combined application of the two drugs can exert a synergistic anti-tumor effect and improve the efficacy of gastric cancer patients. However, it is not clear whether it can enhance the sensitivity of oxaliplatin and improve the therapeutic effect of patients with intermediate and advanced gastric cancer.

Transcription factor Fork-head box prote1 (FOXP1) belongs to the Fox family and participates in many processes, such as cell cycle, embryonic development, apoptosis and differentiation [11]. FOXP1 is found to be abnormally expressed in ovarian cancer, renal cancer, prostate cancer and other malignant tumors, and is closely related to the malignant degree [12]. In addition, the study has found that the FOXP1 transcription factor can promote epithelial-mesenchymal transition by directly affecting gastric tumor cells or indirectly affecting the tumor microenvironment, which may accelerate the invasion and metastasis of cancer [13]. γ- Glutamyl transpeptidase (GGT) is an enzyme bound to the cell membrane, which enables to hydrolyze glutathione and effectively maintains the homeostasis of glutathione and cysteine. It has been found that serum GGT can be used as a marker for the progression of colorectal cancer and other malignant tumors [14]. In addition, the study has shown that the effects of elevated GGT further increase the risk of gastric and colorectal cancer in diabetic patients, and that elevated GGT levels are associated with an increased risk of gastrointestinal cancer, regardless of the location of the cancer [15]. At present, there have been studies on the expression of FOXP1 and GGT in gastric cancer and their relationship with prognosis, but it is not known whether capecitabine can affect the treatment of gastric cancer patients with FOXP1 and GGT levels.

Thus, this study aimed to explore the effects of capecitabine on oxaliplatin sensitivity and the levels of FOXP1 and GGT in patients with intermediate and advanced gastric cancer.

2. Materials and methods

2.1. General materials

This study was approved by the hospital Ethics Committee. A total of 225 patients with intermediate and advanced gastric cancer who were diagnosed and treated in our hospital from April 2018 to May 2019 were enrolled, and their clinical data were retrospectively analyzed. 152 cases were finally selected as the study subjects after screening according to inclusion and exclusion criteria. The general information on the front page of the hospitalization medical record was retrieved through the medical record information

management system. Among them, there were 83 males and 69 females, aged from 29 to 75 years, with an average age of (50.37 ± 8.32) years. Inclusion criteria: (1) All patients met the diagnosis and treatment criteria for gastric cancer [16], and were confirmed by pathological examination. Patients were inoperable or patients with recurrence and metastasis after surgery. (2) Before enrollment, all patients confirmed by pathological examination were in TNM stage IIIb ~ IV. (3) All patients were diagnosed for the first time and had not received radiotherapy and chemotherapy one year before the chemotherapy in the study. The patients were aged over 18 years, and the expected survival was more than 6 months before treatment. (4) All subjects signed the informed consent form and they were willing to cooperate with this study. (5) The patient's clinicopathological data were complete and could cooperate with the study. (6) Imaging studies had at least one measurable lesion and vital organ function was generally normal. (7) The score of the patient in the Eastern Cooperative Group (ECoG) of the United States was less than 2 points, and the card score was more than 70 points. Exclusion criteria: (1) Patients combined with diabetes, metabolic syndrome and other diseases. (2) Patients with severe impairment of liver and kidney function or heart function. (3) The patient who was seriously allergic to the drugs used in the treatment process. (4) Patients with abnormal coagulation and hematopoiesis. (5) Pregnant or lactating patients. (6) Patients who were intolerant to chemotherapy. These objects were divided into the study group and the control group according to the different treatment methods, with 76 cases in each group. The selection process of general materials was shown in Fig. 1.

2.2. Methods

The control group: The patients in the control group treated with oxaliplatin. Oxaliplatin injection with a dose of 130 mg/m^2 (purchased from Shenzhen Haiwang Pharmaceutical Co., Ltd., production batch No.: 20171048, specification: 20 ml: 40 mg) was mixed with 5 % glucose solution. 250 ml mixture was infused intravenously once every 3 weeks. Calcium folinate solution (purchased from Jiangsu Hengrui Pharmaceutical Co., Ltd., production batch No.: 20170584, specification: 10 ml: 0.1 g) was infused intravenously at the dose of 250 mg/m^2, once a day. Fluorouracil (purchased from Hainan Sinochem United Pharmaceutical Industry Co., Ltd., production batch No.: 20171627, specification: 0.5g) was infused intravenously at the dose of 300 mg/m^2, and each intravenous infusion time should not be less than 8 h. The medication cycle was 3 weeks, with two courses of treatment.

The study group: The patients in the study group treated with capecitabine on the basis of the control group. Patients received capecitabine (purchased from Shanghai Roche Pharmaceutical Co., Ltd., production batch No.: 20173024, specification: 0.5g * 12 s) orally, once every 30 min after breakfast and dinner at the dose of 1000 mg/m^2. After 2 weeks of treatment, the drug was stopped for one week, with 3 weeks as a course of treatment.

All patients were treated for two consecutive courses.

2.3. Immunohistochemistry [17]

The tumor tissues of the gastric cancer patient were taken and placed in a 60 °C oven for 15 min. After dewaxing with xylene (Beijing Ita Biotechnology Co., Ltd., catalog number: YT2267), hydrating with gradient alcohol and washing with phosphate buffer (Beijing Ita Biotechnology Co., Ltd., catalog number: SY5774), citric acid repair solution was used for antigen repair. Endogenous peroxidase was used to block with hydrogen peroxide (Beijing Biolebo Technology Co., Ltd., catalog number: YTB1101-FJH). The slices were incubated with FOXP1 primary antibody in a refrigerator (Shanghai Lianqiao Biotechnology Co., Ltd., catalog number: DH. SWUF00400) at 4 °C overnight. After rewarming at room temperature, horseradish peroxidase labeled secondary antibody was added and incubated with the slices at room temperature for 60 min. Then the slices were washed with phosphate buffer solution and were administrated with DAB (Beijing Ita Biotechnology Co., Ltd., catalog number: SY2448) color development and hematoxylin counterstaining. After differentiation with hydrochloric acid and alcohol, the slices were sealed with neutral gum. Yellow, brown yellow or brown staining in the nucleus, cytoplasm and cell membrane of gastric cancer tissues was considered as the positive staining. Four high-power fields were randomly selected, among which 0, 1, 2 and 3 points were scored respectively if the percentage of positive cells was ≤5 %, 6 %–25 %, 26 %–75 % and ≥76 %. According to the staining intensity of positive cells, no staining, light yellow, yellow and

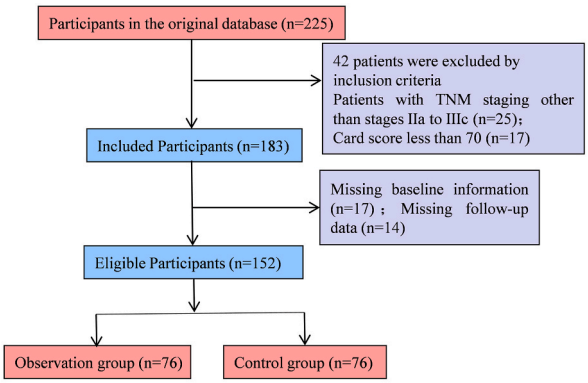

Fig. 1. The selection process of general materials.

brown yellow were recorded as 0, 1, 2 and 3 points respectively. If the sum of the two scores was lower than 1 (including 1), it was regarded as low expression, otherwise it was high expression.

2.4. Outcome measures

(1) Efficacy analysis: The treatment effect of patients after two courses of treatment was evaluated according to the evaluation criteria for the efficacy of solid tumors [18], including progressive disease, stable disease, partial response and complete response. Among them, the lesion volume increased by more than 35 % or new lesions appeared after treatment was regarded as progressive disease. Partial response was considered when the volume of the lesion decreased by more than 30 % after treatment. It is considered as stable disease, when it was between progressive disease and partial response. The complete disappearance of the lesion after treatment was regarded as complete response. The effective rate = (complete response + partial response + stable disease)/total number of cases × 100 %.
(2) Expression of FOXP1 in gastric cancer tissues and GGT in serum: The expression of FOXP1 in gastric cancer tissues before treatment and after two courses of treatment was detected by immunohistochemistry. The venous blood was collected and centrifuged at 4 °C with 3000 r/min (centrifugation radius 13.5 cm) for 20 min, and the supernatant was taken for the examination. Serum GGT level was detected by chemiluminescence. 50 μL of the standard and the sample to be measured were placed in a row of microwells and labeled. An appropriate amount of enzyme markers was added to the standard and the wells of the sample to be measured, fully mixed, and incubated at 37 °C, and then 50 μL of substrate was added to fully mix, incubated for 20 min at room temperature in the dark, and stopped the reaction by adding a stop solution. The absorbance value at 470 nm was detected by a microplate reader. All steps were strictly in accordance with the detection steps of chemiluminescence analyzer (Beijing Bell Bioengineering Co., Ltd., model: VI-200), and the results were measured at least 3 times to reduce errors.
(3) Patients were followed up for 4 years. The survival rate of patients at 1 year and 3 years after treatment was recorded.
(4) The occurrence of adverse reactions during and after treatment was recorded in the two groups.

2.5. Statistical analysis

SPSS 21.0 statistics software package was used to calculate different observation indicators and data. Enumeration data such as gender, curative effect, complications and overall incidence, survival rate, low expression rate of FOXP1 in gastric cancer tissues were expressed in [cases (%)] and compared using χ^2 test or Fisher's exact test. The expression rate of FOXO1 in each group before and after treatment was analyzed by McNerma paired test. Grading data, such as clinical effects, were compared using the nonparametric Wilcoxon rank test. Serum GGT level and other measurement data were tested for normal distribution, and all of them were in line with normal distribution and expressed in the form of ($\bar{x} \pm s$). Repeated measures data, two-way (treatment mode, treatment time) ANOVA and post-hoc test were used to compare the GGT levels of the two groups before and after treatment. The non-normally distributed continuous data were expressed as median (interquartile range) [M(Q1, Q3)], and the Kruskal-WallisH test was used for comparison between groups. The prognostic factors were analyzed by the COX regression model. The relationship between the influencing factors and the survival time of gastric cancer was analyzed using Kaplan-Meier survival curve. $P < 0.05$ was indicated as the statistical significance.

3. Results

3.1. Analysis of capecitabine enhancing the sensitivity of intermediate and advanced gastric cancer to oxaliplatin

The effective rates of capecitabine combined with oxaliplatin and oxaliplatin alone in the treatment of patients with intermediate to advanced gastric cancer were 94.74 % and 76.32 % respectively. The effective rates in the study group were much higher than these in the control group. Capecitabine significantly enhanced the sensitivity of intermediate and advanced gastric cancer to oxaliplatin ($P < 0.05$, Table 1).

Table 1
Analysis of capecitabine enhancing the sensitivity of intermediate to advanced gastric cancer to oxaliplatin [cases (%)].

Groups	The study group (n = 76)	The control group (n = 76)	Z/χ^2	*P*
Clinical outcome			3.859[a]	<0.001
Complete remission	8 (10.53)	2 (2.63)		
Partial remission	28 (36.84)	16 (21.05)		
Stability	36 (47.37)	40 (52.63)		
Deterioration	4 (5.26)	18 (23.68)		
Effective rate	72 (94.74)	58 (76.32)	10.417[b]	0.001

Note.
[a] represented the difference in the clinical outcome (ranked variables) between the two groups using the Wilcoxon rank-sum test.
[b] represented the difference in the effective rate (binary variable) with the use of Fisher's exact test.

3.2. Expression of FOXP1 in gastric cancer tissues and GGT level in serum

The results of immunohistochemical detection showed that FOXP1 was mainly localized in the cytoplasm and nucleus in gastric cancer tissues, with a brown yellow staining (Fig. 2A–D). In control group, the expression level of FOXP1 in gastric cancer tissues was decreased compared with the adjacent normal tissues ($P < 0.05$). Before treatment, both the low expression of FOXP1 and the level of GGT had no significant difference between the two groups ($P > 0.05$). After treatment, both the low expression rate of FOXP1 and the serum level of GGT were prominently decreased, which was lower in the study group ($P < 0.05$, Fig. 2A–D, Table 2).

3.3. Comparison of the incidence of adverse reactions between the two groups

There was no difference in the incidence of adverse reactions between the two groups ($P > 0.05$, Table 3).

3.4. Analysis of 1- and 3-year survival rate and recurrence rate of patients with intermediate to advanced gastric cancer after treatment

The 1-year survival rate of the study group and the control group was 90.79 % and 78.95 %, respectively. The 3-year survival rate of the study group and the control group was 75.00 % and 51.32 %, respectively. The 1-year and 3-year survival rates in the study group were higher than these in the control group ($P < 0.05$, Table 4).

3.5. Univariate analysis of prognostic factors in patients with gastric cancer

The 1-year survival rate of 152 patients with gastric cancer was 84.87 % (129/152) and the 3-year survival rate was 63.16 % (96/152). Age, tumor diameter, tumor-node-metastasis (TNM) stage, lymph node metastasis, chemotherapy regimen and the expression of FOXP1 and GGT had statistically significant effects on the survival rate ($P < 0.05$, Table 5).

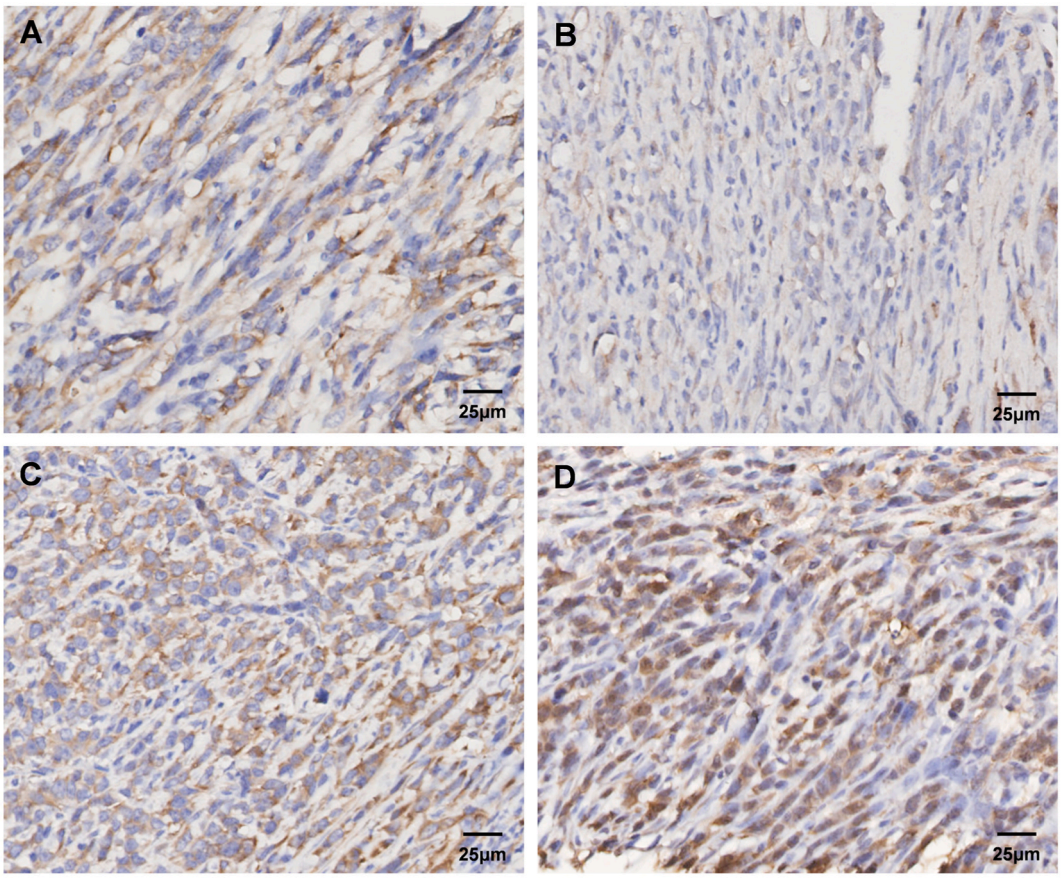

Fig. 2. Detection of FOXP1 expression by immunohistochemistry (× 200).
A: FOXP1 expression in the control group before treatment; B: FOXP1 expression in the study group before treatment; C: FOXP1 expression in the control group after treatment; D: FOXP1 expression in the study group after treatment.

Table 2
Expression of FOXP1 in gastric cancer tissues [cases (%)], ($\overline{x} \pm s$).

Groups	Cases	FOXP1 low expression		*P1*
		Before treatment	After treatment	
The study group	76	34 (44.74)	4 (5.26)	<0.001 [a]
The control group	76	32 (42.11)	16 (21.05)	0.005 [b]
χ^2/*Fisher test*		0.107	–	
P2		0.743 [c]	0.020 [d]	

Note.
[a] McNemar test was used to compare the differences before and after treatment in the study group.
[b] McNemar test was used to compare the differences before and after treatment in the control group.
[c] $\chi 2$ test was used to compare the differences between the study group and the control group before treatment.
[d] Fisher exact test was used to compare the differences between the study group and the control group after treatment; *P1* is the comparison of before and after treatment data for the same group of patients; *P2* showed the comparison of data between the study and control groups at the same time point.

Table 2
Expression of GGT in serum, ($\overline{x} \pm s$).

Groups	Cases	GGT (U/L)		*F*	*P2*
		Before treatment	After treatment		
The study group	76	542.79 ± 186.16	292.16 ± 91.53[ab]	$F_{time} = 19.149$	$P_{time}<0.001$
The control group	76	552.38 ± 205.15	421.15 ± 135.76 [a]		
F		$F_{treatment} = 9.610$		$F_{time\times treatment} = 16.552$	$P_{time\times treatment}<0.001$
P1		$P_{treatment} = 0.001$			

Note.
[a] $P<0.05$ compared with the same group before treatment.
[b] $P < 0.05$ compared with the control group after treatment. *P1* indicates the comparison between the study group and the control group. *P2* represents the comparison between the same group before and after treatment.

Table 3
Comparison of the incidence of adverse reactions between the two groups [Case (%)].

Group	The study group (n = 76)	The control group (n = 76)	χ^2	*P*
Complications				
Nausea and vomiting	10 (13.16)	13 (17.11)		
Oral mucositi	8 (10.53)	6 (7.89)		
Granulocytopenia	10 (13.16)	7 (9.21)		
Peripheral neurotoxicity	7 (9.21)	5 (6.58)		
Total incidence	35 (46.05)	31 (40.79)	0.429	0.513

Note: *P* indicates the comparison between the study group and the control group.

Table 4
Analysis of 1- and 3-year survival rate of patients with intermediate to advanced gastric cancer after treatment [cases (%)].

Group	Cases	Survival rate	
		1 year	3 years
The study group	76	69 (90.79)	57 (75.00)
The control group	76	60 (78.95)	39 (51.32)
χ^2 (independent-unpaired)		4.150	9.161
P		0.042	0.002

Note: *P* indicates the comparison between the study group and the control group.

3.6. COX regression analysis of prognostic factors in patients with gastric cancer

COX regression analysis was performed with survival as the dependent variable, age (1 = ≥60 years, 0=<60 years), TNM (1 = stage IV, 0 = stage III), lymph node metastasis (1 = N2~N3, 0 = N0~N1), FOXP1 (1 = low expression, 0 = high expression), and GGT (1 = ≥387.2 U/L, 0=<387.2 U/L) as independent variables. The results showed that gastric cancer patients with age ≥60 years, TNM stage of III ~ IV, lymph node metastasis N2 ~ N3, low expression of FOXP1, and GGT ≥387.2 were risk factors affecting the prognosis of patients with gastric cancer, while combined treatment with drug chemotherapy was protective factor ($P < 0.05$, Table 6).

Table 5
Univariate analysis of prognostic factors in patients with gastric cancer [cases (%)].

Factors		Cases	1-year survival rate	χ^2	*P*	3-year survival rate	χ^2	*P*
Gender	Male	83	73 (87.95)	1.354	0.245	55 (66.27)	0.759	0.384
	Female	69	56 (81.16)			41 (59.42)		
Age	<60 years old	51	48 (94.12)	5.113	0.024	40 (78.43)	7.695	0.006
	≥60 years old	101	81 (80.20)			56 (55.44)		
Tumor location	Upper 1/3	77	68 (88.31)	1.441	0.230	48 (62.34)	0.045	0.832
	Lower 1/3	75	61 (81.33)			48 (64.00)		
Tumor diameter	<5 cm	112	105 (93.75)	26.143	<0.001	85 (75.89)	29.664	<0.001
	≥5 cm	40	24 (60.00)			11 (27.50)		
TNM stage	I ~ II	102	98 (96.08)	30.343	<0.001	70 (68.63)	3.987	0.046
	III ~ IV	50	31 (62.00)			26 (52.00)		
Degree of differentiation	Low differentiation	69	58 (94.06)	0.065	0.799	48 (62.34)	2.229	0.135
	Medium and high differentiation	83	71 (85.54)			48 (64.00)		
Lymph node metastasis	N0 ~ N1	95	90 (94.74)	19.211	<0.001	69 (72.63)	9.771	0.002
	N2 ~ N3	57	39 (68.42)			27 (47.37)		
Chemotherapy regimen	Oxaliplatin	76	69 (90.79)	4.150	0.042	41 (53.95)	5.542	0.019
	Capecitabine + oxaliplatin	76	60 (78.95)			55 (72.37)		
FOXP1	Low expression	66	50 (75.76)	7.540	0.006	36 (53.03)	5.142	0.023
	High expression	86	79 (91.86)			61 (70.93)		
GGT	<387.2 (U/L)	58	55 (94.82)	7.244	0.007	47 (81.03)	12.881	<0.001
	≥387.2 (U/L)	94	74 (78.72)			49 (52.13)		

Table 6
COX regression analysis of prognostic factors in patients with gastric cancer.

Factors	*B*	*SE*	*Wald*	*P*	*OR*	95%*CI*
Age ≥60 years	2.046	0.436	4.045	0.014	3.297	1.367–5.252
Tumor diameter ≥5 cm	0.860	0.357	3.092	0.074	2.593	1.136–3.894
TNM stage of III ~ IV	2.160	0.936	4.297	0.023	7.526	3.684–12.412
lymph node metastasis N2 ~ N3	1.988	0.126	7.236	<0.001	4.297	1269~10.517
Combined drug chemotherapy	0.967	0.412	5.161	0.002	3.964	1128~5.169
Low expression of FOXP1	1.269	0.469	8.589	<0.001	7.266	2.169–9.259
GGT ≥387.2	1.115	0.419	6.335	<0.001	4.697	1.066–7.569

3.7. Kaplan-Meier survival curve was used to analyze the relationship between the influencing factors and the survival time of gastric cancer

The results of Kaplan-Meier survival curve analysis showed that the median survival of patients aged ≥60 years and <60 years was 23 months and 33 months, respectively. The survival of patients aged ≥60 years was significantly lower than that of patients aged <60 years (Fig. 3A). The median survival of patients with TNM stage III ~ IV and TNM I ~ II was 16 months and 27 months, respectively. The survival of patients with TNM stage III ~ IV was notably shorter compared with the patients with stage I ~ II (Fig. 3B). The median survival of patients with lymph node metastasis N2 ~ N3 and lymph node metastasis N0 ~ N1 was 17 months and 24 months, respectively. The survival of patients with lymph node metastasis N2 ~ N3 was markedly shorter than the patients with N0 ~ N1 (Fig. 3C). The median survival of patients with combined drug chemotherapy and single-drug chemotherapy was 28 months and 17.5 months, respectively. The survival of gastric cancer patients with single-drug chemotherapy was significantly lower than that of gastric cancer patients with combined drug chemotherapy (Fig. 3D). The median survival of patients with low FOXP1 expression and high FOXP1 expression was 14.5 months and 25.5 months, respectively. The survival of patients with low FOXP1 expression was observably lower than that of patients with high FOXP1 expression (Fig. 3E). The median survival of patients with GGT ≥387.2 and GGT <387.2 was 19.5 months and 29 months, respectively. The survival of patients with GGT ≥387.2 was notably shorter than the patients with GGT <387.2 ($P < 0.05$, Fig. 3F).

4. Discussion

Gastric cancer is a malignant tumor that seriously affects the lives of patients. Worldwide, mortality rates from gastric cancer are second only to those from lung cancer. Among the recently increased diagnoses of gastric cancer patients each year, more than half of cases occur in China [19]. Gastric cancer pathogenesis is relatively complex, and many studies believe that the mechanism of gastric cancer involves multiple stages and multiple factors [20,21]. Firstly, gastric cancer usually starts with chronic superficial gastritis, goes through atrophic gastritis, intestinal metaplasia, dysplasia, and finally develops into intestinal gastric cancer. In addition, *Helicobacter pylori* infection is one of the main causes of gastric cancer, which promotes the development of gastric cancer through a variety of mechanisms. EBV infection may also trigger gastric cancer by inducing DNA methylation. Long-term gastric mucosal damage and bacterial infections lead to the production of nitrite carcinogens, which further promote carcinogenesis. As gastric cancer is insidious in

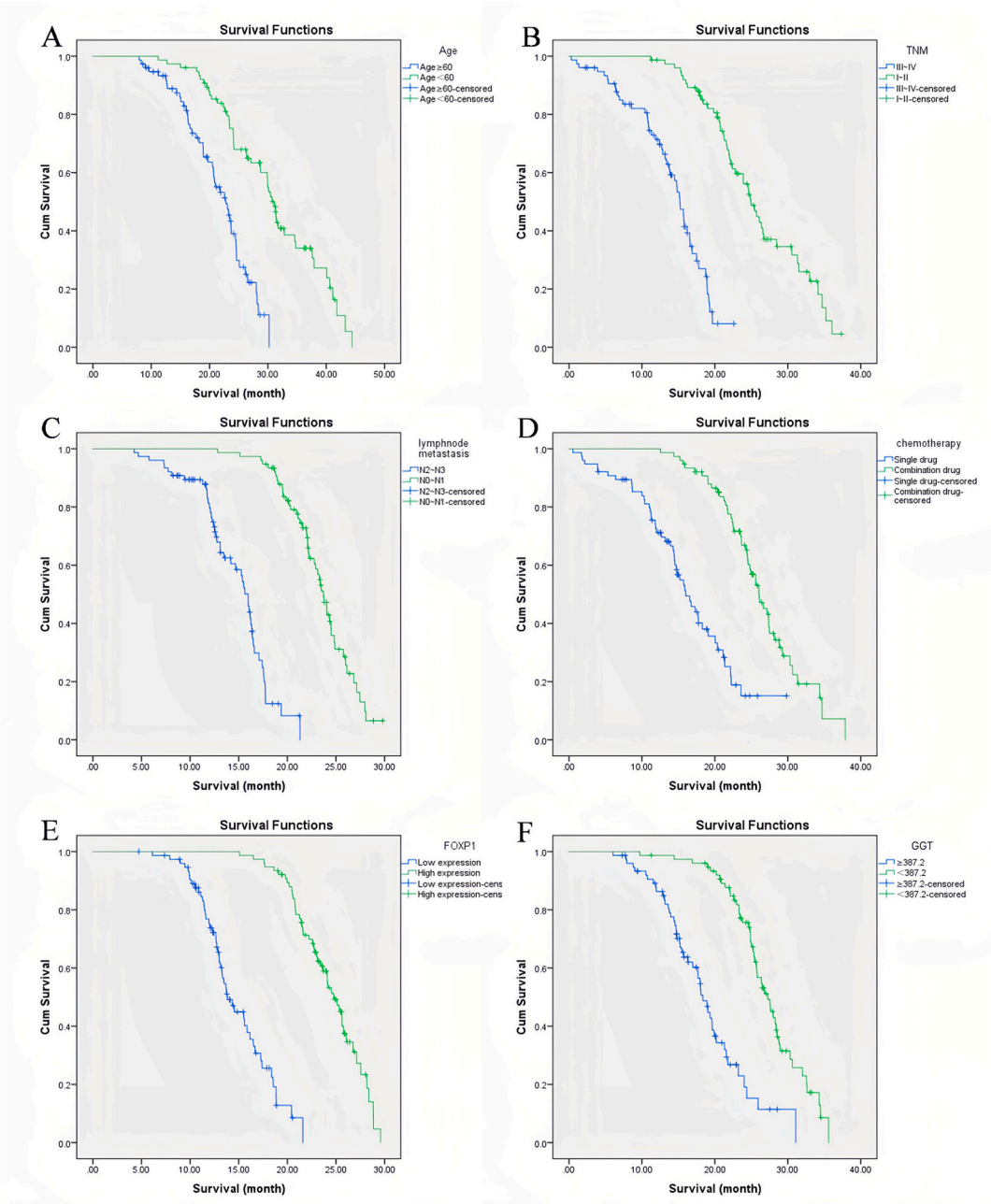

Fig. 3. The relationship between the influencing factors and the survival time of gastric cancer analyzed using Kaplan-Meier survival curve.
A: Survival curves of patients at different ages; B: Survival curves of patients at different TNM stages; C: Survival curve of patients with different lymph node metastasis; D: Survival curve of patients with different chemotherapy regimens; E: Survival curves of patients with different FOXP1 expression levels; F: Survival curves of patients with different GGT levels.

its early stages, most patients have mid- or late-stage disease at diagnosis.

Chemotherapy is the main method for treatment of advanced malignant tumors, and has an important role in reducing disease recurrence rates and prolonging patient survival. Oxaliplatin is a third-generation platinum-based chemotherapy drug whose main target is DNA. Oxaliplatin can bind to DNA to form intrastrand and interstrand crosslinks, thereby blocking DNA replication and transcription, and preventing the growth and division of cancer cells. Oxaliplatin also has the ability to induce apoptosis in cancer cells, which further enhances its antitumor effect [22]. Oxaliplatin combined with cisplatin is effective for the treatment of gastric cancer [23]. Further, folinic acid combined with oxaliplatin can effectively improve the survival rate of patients with intermediate to advanced gastric cancer, and an oxaliplatin-based combination regimen is considered an effective method to treat gastric cancer;

however, oxaliplatin often induces resistance to chemotherapeutic drugs, which is an important factor leading to treatment failure [24]. Therefore, it is important to identify methods that improve treatment efficacy, while minimizing adverse reactions. Capecitabine is a fluorouracil carbamate with a fast absorption rate that is selectively activated in tumors. Capecitabine can completely penetrate the liver and forms 5-fluorouracil under catalysis mediated by specific enzymes in the liver, thus exerting relevant anti-tumor effects [25]. Capecitabine is mainly used in clinical practice for the treatment of various types of cancer, and the mechanism of action includes inhibiting DNA synthesis and cell proliferation, blocking the neovascularization of cancer cells, activating immune cells, and inducing apoptosis [26]. In addition, higher concentrations of capecitabine has been found in tumor tissues than in normal tissues, which makes it highly selective and specific. Capecitabine has a wide range of clinical applications. For instance, in adjuvant chemotherapy for colon cancer, capecitabine was able to significantly prolong disease-free survival (DFS) and overall survival (OS) in patients with good tolerability and low side effects [27]. Capecitabine is established as effective for treatment of advanced gastric cancer [28,29]. Further, in terms of efficacy, toxicity, and convenience, the combination of cisplatin and capecitabine is effective and well tolerated in the treatment of patients with advanced gastric cancer, and may be among standard first-line treatment regimens [30]. Further, chemoresistance is a major problem in the treatment of malignant tumors. In this study, to explore whether capecitabine could enhance sensitivity to oxaliplatin, patients received an oxaliplatin regimen, or capecitabine combined with oxaliplatin, for treatment of advanced gastric cancer. Compared with the oxaliplatin regimen, capecitabine combined with oxaliplatin had higher clinical efficacy, and led to a higher three-year survival rate, indicating that capecitabine can enhance sensitivity to oxaliplatin, reduce disease recurrence rates, and prolong the patient survival. Relevant data [31] show that capecitabine combined with oxaliplatin is one of the classic regimens for the treatment of locally advanced rectal cancer, with definite efficacy, mild toxicity and side effects, and can significantly improve patients' symptoms. In addition, this protocol can inhibit the spread of cancer cells, prolong the life of patients, and improve the quality of life. Capecitabine and oxaliplatin have a synergistic effect on the anti-tumor mechanism. By upregulating the activity of thymidine phosphorylase, oxaliplatin promotes the metabolic activation of capecitabine, enabling it to produce more antitumor active substances in tumor tissues, and this synergistic effect makes the antitumor effect of the combination drug superior to that of the single agent [32]. In addition, due to the good targeting and selectivity of capecitabine, the combination of drugs can reduce the damage of oxaliplatin to normal tissues, thereby reducing the incidence of adverse reactions. At the same time, the oral administration of capecitabine avoids the discomfort and anxiety associated with indwelling vascular catheters or chemopumps [33]. However, this study found no difference in the incidence of adverse reactions between the two groups, which may be related to the small sample size included in the study.

FOXP1 is a transcription factor whose expression levels are greatly reduced in prostate cancer, breast cancer, and other malignant tumors, indicating that FOXP1 may act as a tumor suppressor gene [34]. FOXP1 is reported to have potentially important roles in diffuse large B-cell lymphoma occurrence and development, and high FOXP1 expression may be closely related to poor patient prognosis [35]. Further, FOXP1 expression levels are a potentially important factor affecting the survival of patients with gastric cancer, where those with high FOXP1 expression have higher survival rates than those with low expression [36].

GGT is a molecule located on the extracellular surface of cells and involved in glutathione metabolism. Since glutathione is the main water-soluble antioxidant in cells, GGT is often activated under oxidative stress, which can be induced by alcohol, drugs, or hepatitis-induced liver damage, and is widely used to monitor liver function [37]. GGT has been reported as a potentially important marker of colorectal cancer, esophageal cancer, and other diseases [38], and patients with high-level serum GGT have a much lower risk of morbidity than those with low-level serum GGT [39], which is comparable to the results of the present study. Here, we analyzed FOXP1 levels in gastric cancer tissues and serum GGT levels in the two groups of patients. Our results show that capecitabine combined with oxaliplatin can considerably reduce the proportion of patients with low FOXP1 expression, as well as serum GGT levels. Cox regression and Kaplan-Meier survival curve analyses both indicated that FOXP1 and serum GGT levels were risk factors affecting the prognosis of patients with gastric cancer, and that these two molecules may be effective biological markers of gastric cancer prognosis. The results of this study indicate that FOXP1 and GGT levels are related to the treatment of patients with gastric cancer; our data suggest that capecitabine combined with oxaliplatin can maintain low expression levels of FOXP1 and GGT in patients. Reducing FOXP1 expression can induce cell cycle G1/S phase arrest, resulting in inhibition of gastric cancer cell proliferation [40]. Further, decreasing GGT expression can reduce the redox state in cancer cells, ameliorate inflammation, and thereby inhibit the spread of cancer cells, control cancer development, and achieve improved therapeutic effects [41]. The analysis may be related to the fact that capecitabine is an oral fluorouracil drug that inhibits the growth of tumor cells by suppressing the activity of deoxynucleotide translocation enzymes and blocking DNA synthesis. In the treatment of gastric cancer, capecitabine represses the proliferation of gastric cancer cells by inhibiting DNA replication and RNA synthesis and inducing apoptosis [42]. FOXP1 has the function of regulating cell growth, differentiation and apoptosis in the occurrence and development of gastric cancer. Elevated expression of GGT may lead to increased glutathione synthesis and secretion, which in turn enhances the viability and drug resistance of gastric cancer cells. Therefore, it is believed that capecitabine may inhibit the growth and spread of gastric cancer cells by down-regulating the expression of FOXP1 and GGT, which provides a theoretical basis for further optimizing the treatment regimen of gastric cancer, and is expected to improve the treatment effect and prolong the survival of patients.

In summary, capecitabine can strongly enhance the sensitivity of intermediate and advanced gastric cancer to oxaliplatin, improve treatment efficacy, and reduce the proportions of patients with low FOXP1 expression and serum GGT levels, thereby lowering disease recurrence rates and improving patient prognosis. This study has some limitations. First, it was a single center retrospective study with limited sample size, which may have introduced bias in the results. Second, some predictive factors with potential significance, such as blood infiltration and *Helicobacter pylori* infection, were not included in our analysis because their influence is affected by numerous factors, such as tumor stage, grade, and pathology. The clinical effects of capecitabine combined with oxaliplatin warrant further exploration and confirmation in large-scale prospective clinical trials.

CRediT authorship contribution statement

Xinyu Guo: Writing – original draft, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Yi Liu:** Writing – review & editing, Software, Resources, Methodology, Data curation, Conceptualization.

Data availability statement

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

Ethical statement

This research was approved by the Ethics Review Committees of Fuwai Central China Cardiovascular Hospital (approval number: 2023-EC-015).

Consent for publication

Informed consent was obtained from all individual participants included in the study. The patients participating in the study all agree to publish the research results.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] H. Sung, et al., Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J Clin 71 (2021) 209–249, https://doi.org/10.3322/caac.21660.
[2] J. Lu, et al., Consideration of tumor size improves the accuracy of TNM predictions in patients with gastric cancer after curative gastrectomy, Surg Oncol 22 (2013) 167–171, https://doi.org/10.1016/j.suronc.2013.05.002.
[3] Z.N. Huang, et al., Potential survival benefits of open over laparoscopic radical gastrectomy for gastric cancer patients beyond three years after surgery: result from multicenter in-depth analysis based on propensity matching, Surg. Endosc. 36 (2022) 1456–1465, https://doi.org/10.1007/s00464-021-08430-0.
[4] R. Cristescu, et al., Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes, Nat Med 21 (2015) 449–456, https://doi.org/10.1038/nm.3850.
[5] N. Horii, et al., Psoas muscle depletion during preoperative chemotherapy for advanced gastric cancer has a negative impact on long-term outcomes after gastrectomy, Asia Pac. J. Clin. Oncol. 18 (2022) 61–69, https://doi.org/10.1111/ajco.13514.
[6] H. Li, et al., METTL3 promotes oxaliplatin resistance of gastric cancer CD133+ stem cells by promoting PARP1 mRNA stability, Cell. Mol. Life Sci. 79 (2022) 135, https://doi.org/10.1007/s00018-022-04129-0.
[7] M. Ishizuka, et al., Omentectomy does not affect the postoperative outcome of patients with locally advanced gastric cancer: a systematic review and meta-analysis, J. Surg. Res. 264 (2021) 287–295, https://doi.org/10.1016/j.jss.2021.02.033.
[8] X. Miao, et al., Clinical efficacy of acupuncture on neoadjuvant chemotherapy with capecitabine plus paclitaxel and radiotherapy in progressive gastric cancer, J Oncol 2022 (2022) 6156585, https://doi.org/10.1155/2022/6156585.
[9] S. Camera, et al., MOMENTUM: a phase I trial investigating 2 schedules of capecitabine with aflibercept in patients with gastrointestinal and breast cancer, Clin. Colorectal Cancer 19 (2020) 311–318.e311, https://doi.org/10.1016/j.clcc.2020.05.007.
[10] K. Harada, et al., Establishment of oxaliplatin-resistant gastric cancer organoids: importance of myoferlin in the acquisition of oxaliplatin resistance, Gastric Cancer 24 (2021) 1264–1277, https://doi.org/10.1007/s10120-021-01206-4.
[11] C. Gu, et al., MAb NJ001 inhibits lung adenocarcinoma invasiveness by directly regulating TIMP-3 promoter activity via FOXP1 binding sites, Thorac Cancer 11 (2020) 2630–2638, https://doi.org/10.1111/1759-7714.13593.
[12] Y.C.K. Ko, et al., Gene expression profiling of head and neck tumors identifies FOXP1 and SOX10 expression as useful for distinguishing ameloblastoma from basaloid salivary gland tumors, Am. J. Surg. Pathol. 44 (2020) 665–672, https://doi.org/10.1097/pas.0000000000001421.
[13] Y. Song, et al., Epstein-Barr virus-encoded miR-BART11 promotes tumor-associated macrophage-induced epithelial-mesenchymal transition via targeting FOXP1 in gastric cancer, Virology 548 (2020) 6–16, https://doi.org/10.1016/j.virol.2020.05.011.
[14] F. Ozcelik, Prognostic value of gamma-glutamyl transpeptidase in liver cirrhosis and hepatocellular cancer regardless of other parameters, Clin Res Hepatol Gastroenterol 45 (2021) 101708, https://doi.org/10.1016/j.clinre.2021.101708.
[15] S.W. Hong, et al., Risk of gastrointestinal cancer in patients with an elevated level of gamma-glutamyltransferase: a nationwide population-based study, PLoS One 16 (2021) e0245052, https://doi.org/10.1371/journal.pone.0245052.
[16] E.C. Smyth, et al., Gastric cancer, Lancet 396 (2020) 635–648, https://doi.org/10.1016/s0140-6736(20)31288-5.
[17] R. Guo, et al., A scoring method for immunohistochemical staining on Ki67, Appl. Immunohistochem. Mol. Morphol. 29 (2021) e20–e28, https://doi.org/10.1097/pai.0000000000000853.
[18] H.C. Chung, et al., First-line pembrolizumab/placebo plus trastuzumab and chemotherapy in HER2-positive advanced gastric cancer: keynote-811, Future Oncol. 17 (2021) 491–501, https://doi.org/10.2217/fon-2020-0737.

[19] Y. Ogata, et al., Predictors of early and late mortality after the treatment for early gastric cancers, Dig. Endosc. 34 (2022) 816–825, https://doi.org/10.1111/den.14172.
[20] Z.K. Wang, et al., ASO author reflections: long-term efficacy of splenic hilar lymph node dissection for proximal gastric cancer, Ann. Surg Oncol. 28 (2021) 6663–6664, https://doi.org/10.1245/s10434-021-09884-1.
[21] A. Seko-Nitta, et al., 18F-fluorodeoxyglucose uptake in advanced gastric cancer correlates with histopathological subtypes and volume of tumor stroma, Eur. J. Radiol. 145 (2021) 110048, https://doi.org/10.1016/j.ejrad.2021.110048.
[22] L. Kang, et al., Oxaliplatin-induced peripheral neuropathy: clinical features, mechanisms, prevention and treatment, J. Neurol. 268 (2021) 3269–3282, https://doi.org/10.1007/s00415-020-09942-w.
[23] D. Takahari, et al., Perioperative TAS-118 plus oxaliplatin in patients with locally advanced gastric cancer: APOLLO-11 study, Gastric Cancer 26 (2023) 614–625, https://doi.org/10.1007/s10120-023-01388-z.
[24] Y.K. Kang, et al., S-1 plus leucovorin and oxaliplatin versus S-1 plus cisplatin as first-line therapy in patients with advanced gastric cancer (SOLAR): a randomised, open-label, phase 3 trial, Lancet Oncol. 21 (2020) 1045–1056, https://doi.org/10.1016/s1470-2045(20)30315-6.
[25] J.N. Primrose, et al., Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study, Lancet Oncol. 20 (2019) 663–673, https://doi.org/10.1016/s1470-2045(18)30915-x.
[26] P.L. Kunz, et al., Randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors (ECOG-ACRIN E2211), J. Clin. Oncol. 41 (2023) 1359–1369, https://doi.org/10.1200/jco.22.01013.
[27] J. Park, et al., Comparison between oxaliplatin therapy and capecitabine monotherapy for high-risk stage II - III elderly patients with colon cancer, Asian J. Surg. 45 (2022) 448–455, https://doi.org/10.1016/j.asjsur.2021.07.067.
[28] F. Rivera, et al., Perioperative trastuzumab, capecitabine and oxaliplatin in patients with HER2-positive resectable gastric or gastro-oesophageal junction adenocarcinoma: NEOHX phase II trial, Eur. J. Cancer 145 (2021) 158–167, https://doi.org/10.1016/j.ejca.2020.12.005.
[29] F. Pietrantonio, et al., Bax expression is predictive of favorable clinical outcome in chemonaive advanced gastric cancer patients treated with capecitabine, oxaliplatin, and irinotecan regimen, Transl Oncol 5 (2012) 155–159, https://doi.org/10.1596/tlo.12151.
[30] Q. Zhang, et al., Comparison of S-1-based vs. capecitabine-based adjuvant chemotherapy for patients with gastric cancer: a systematic review and meta-analysis, Eur. J. Clin. Pharmacol. 77 (2021) 1791–1804, https://doi.org/10.1007/s00228-021-03187-w.
[31] M. Suenaga, et al., A feasibility study of capecitabine and oxaliplatin for patients with stage II/III colon cancer -actor study, Anticancer Res. 38 (2018) 1741–1747, https://doi.org/10.21873/anticanres.12410.
[32] Z. Pan, et al., A novel protein encoded by exosomal CircATG4B induces oxaliplatin resistance in colorectal cancer by promoting autophagy, Adv. Sci. 9 (2022) e2204513, https://doi.org/10.1002/advs.202204513.
[33] S. Miyazaki, et al., Pharmacokinetic model analysis of interaction between phenytoin and capecitabine, Int J Clin Pharmacol Ther 54 (2016) 657–665, https://doi.org/10.5414/cp202416.
[34] X. Chen, et al., The circACC1/miR-29c-3p/FOXP1 network plays a key role in gastric cancer by regulating cell proliferation, Biochem. Biophys. Res. Commun. 557 (2021) 221–227, https://doi.org/10.1016/j.bbrc.2021.04.028.
[35] W.E. Wright, et al., FOXP1 interacts with MyoD to repress its transcription and myoblast conversion, J Cell Signal 2 (2021) 9–26.
[36] D. Neyroud, et al., FoxP1 is a transcriptional repressor associated with cancer cachexia that induces skeletal muscle wasting and weakness, J Cachexia Sarcopenia Muscle 12 (2021) 421–442, https://doi.org/10.1002/jcsm.12666.
[37] C.H. Zhang, et al., Combined preoperative albumin-bilirubin (ALBI) and serum γ-glutamyl transpeptidase (GGT) predicts the outcome of hepatocellular carcinoma patients following hepatic resection, J. Cancer 10 (2019) 4836–4845, https://doi.org/10.7150/jca.33877.
[38] T. Dai, et al., Prognostic value of combined preoperative gamma-glutamyl transpeptidase to platelet ratio and fibrinogen in patients with HBV-related hepatocellular carcinoma after hepatectomy, Am J Transl Res 12 (2020) 2984–2997.
[39] L.L. Lin, et al., Activation and thermal stabilization of a recombinant γ-glutamyltranspeptidase from Bacillus licheniformis ATCC 27811 by monovalent cations, Appl. Microbiol. Biotechnol. 106 (2022) 1991–2006, https://doi.org/10.1007/s00253-022-11836-y.
[40] X. Wang, et al., Downregulation of FOXP1 inhibits cell proliferation in hepatocellular carcinoma by inducing G1/S phase cell cycle arrest, Int. J. Mol. Sci. 17 (2016), https://doi.org/10.3390/ijms17091501.
[41] F. Yu, et al., Poly-γ-glutamic acid derived nanopolyplexes for up-regulation of gamma-glutamyl transpeptidase to augment tumor active targeting and enhance synergistic antitumor therapy by regulating intracellular redox homeostasis, Biomater. Sci. 8 (2020) 5955–5968, https://doi.org/10.1039/d0bm01254h.
[42] F. Yuan, et al., Capecitabine metronomic chemotherapy inhibits the proliferation of gastric cancer cells through anti-angiogenesis, Oncol. Rep. 33 (2015) 1753–1762, https://doi.org/10.3892/or.2015.3765.