Clinics in Oncology

Research Article
Published: 26 Jan, 2023

Clinical Factors Affecting Patients with Advanced Gastrointestinal Cancer with Weak Physical Status Receiving Low-Dose Chemotherapy and the Establishment of Risk Prediction Scoring System

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Abstract

Introduction: To explore the risk factors affecting patients with advanced gastrointestinal cancer in weak physical status receiving low-dose chemotherapy and establish a prediction scoring system for the risks.

Methods: 141 patients with advanced gastrointestinal tumors who received low-dose chemotherapy from July 2018 to March 2021 were enrolled to analyze the clinical factors that may affect the prognosis.

Results: Univariate analysis revealed that body mass index, physical status score, pain, type of primary tumor, number of metastatic sites, symptom based qualitative evaluation of gastrointestinal function, CT image-based intestinal dilatation, ascites, hemoglobin, albumin, C-reactive protein, prothrombin time, D-dimer were all factors associating the prognosis of patients (all $P<0.05$); multivariate analysis revealed that pain; the type of primary tumor was gastric cancer; the qualitative evaluation of gastrointestinal function based on symptoms was gastrointestinal dysfunction, ascites positive and elevated C-reactive protein were the five independent risk factors affecting the prognosis. The prognostic risk prediction scoring system was established according to the results of multivariate regression analysis. Patients with pain, gastric cancer, gastrointestinal dysfunction, ascites positive and elevated C-reactive protein were scored 1 point respectively. In higher scores group, the median survival time of patients was shorter.

Conclusion: Pain, gastric cancer, gastrointestinal dysfunction, ascites positive and elevated C-reactive protein were independent risk factors for the prognosis of patients with advanced gastrointestinal cancer in weak physical status receiving low-dose chemotherapy. The prognostic risk prediction scoring system combined with the above indicators may effectively predict the low-dose chemotherapy benefit population.

Keywords: Gastrointestinal cancer; Weak physical status; Low-dose chemotherapy; Risk prediction scoring system

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Received Date: *27 Dec 2022*
Accepted Date: *20 Jan 2023*
Published Date: *26 Jan 2023*

Citation:
Su Z, Zhang X, Cheng L, Gan H, Li Z, Wang Z, et al. Clinical Factors Affecting Patients with Advanced Gastrointestinal Cancer with Weak Physical Status Receiving Low-Dose Chemotherapy and the Establishment of Risk Prediction Scoring System. Clin Oncol. 2023; 8: 1983.

ISSN: 2474-1663

Introduction

Due to the unbalanced economic level and health development in China, there are still many patients with gastrointestinal cancer who are already in advanced stage of disease when they are first diagnosed. Patients with advanced gastrointestinal cancer are usually accompanied by malnutrition, weak physical status and difficulty in receiving standard dose of chemotherapy. Compared with the best supportive treatment, low-dose chemotherapy can improve the quality of life of some patients and prolong their survival, and there are also certain toxic and side effects [1]. Low dose chemotherapy has become an important direction of clinical exploration, but it is often ignored in clinical practice and research. Therefore, it is urgent to find the factors affecting the prognosis of patients receiving low-dose chemotherapy and rationally select the potential beneficiaries. In previous clinical practice, we had found that hemoglobin level, pain and gastrointestinal function are

risk factors affecting the prognosis of patients [2], but the tumor types are complex, the factors are not comprehensive, and the sample size is small, which requires further study. In this study, we retrospectively analyzed the clinical data of patients with advanced gastrointestinal cancer with a Performance Status (PS) score of 2 to 3 receiving low-dose chemotherapy, explored the factors affecting the prognosis, and established a risk prediction scoring system to provide evidence for the selection of clinical treatment strategies.

Materials and Methods

Patient preparation

Clinical data of inpatients in the oncology department of our hospital from July 2018 to March 2021 were collected. Inclusion criteria: (1) 18 to 80 years old; (2) Pathologically diagnosed primary gastrointestinal cancer, including gastric cancer, colon cancer and rectal cancer; (3) Clinical stage was stage IV; (4) The PS score is 2 to 3; (5) Received low-dose chemotherapy, the chemotherapy dose is 1/4 to 1/2 of the standard dose (or even lower), which can be administered intravenously or orally. Exclusion criteria: (1) complicated by neurological diseases seriously affecting digestive tract function; (2) complicated digestive tract infection; (3) complicated by decompensated heart failure, renal failure, nephrotic syndrome, cirrhosis, tuberculous peritonitis and other diseases causing ascites; (4) Incomplete medical history.

Clinical data

Clinical data collected include: gender, age, weight, height, Body Mass Index (BMI), pain number score, PS score, type of primary tumor, number of metastatic sites, hemoglobin, white blood cell count, neutrophil count, blood sedimentation, total bilirubin, serum albumin, prealbumin, urea nitrogen, creatinine, uric acid, c-reactive protein, prothrombin time, D-dimer, ascites, based on the symptoms of digestive tract function the intestinal expansion of qualitative evaluation, based on CT images.

Gastrointestinal function evaluation

Qualitative evaluation criteria for gastrointestinal function based on symptoms refers to this literature [2].

Ascites evaluation based on CT images

The ascites assessment method based on CT images refers to the five-point CT method studied by Japanese scholar Yamagata et al.

Intestinal dilatation evaluation

The evaluation methods of Intestinal dilatation based on CT images were as follows: The range of involvement was divided into small intestine and colorectal by anatomical site; Evaluation criteria: Small intestine diameter ≤ 30 mm was normal, >30 mm was dilated, colon diameter ≤ 60 mm was normal, >60 mm was dilated. The presence of dilatation of the bowel in either location was assessed as positive. The survival status and survival time of patients were determined through medical history review, outpatient follow-up and telephone follow-up.

Ethics approval and consent to participate

The Ethics Committee of Zhongshan Hospital (Xiamen), Fudan University Biomedical Research Department provided ethical approval. This study was carried out in accordance with the principles of the Helsinki Declaration and informed consent for collecting and preserving samples and details was obtained from each patient.

Statistical analyses

SPSS 22.0 was used for all analyses. A two-sided test was performed. P value or an adjusted P value of less than 0.05 was considered statistically significant. Continuous variables are expressed as mean ± Standard Deviation (SD) or median and quartile ranges, and categorical variables are expressed as percentages (%). Univariate regression method was used to analyze the correlation between clinical indicators and overall survival time of patients. Kaplan-Meier survival analysis log-rank method was used for univariate analysis of the influence of different clinical factors on OS, and Cox proportional risk model was used for multivariate analysis.

Results

Baseline characteristics of patients

A total of 141 patients were included for statistical analysis, and the clinical characteristics were shown in Table 1. The median survival of all patients was 11.37 months (95% CI: 6.861-15.874).

Univariate analysis

Univariate analysis showed that factors that may be associated with the prognosis of low-dose chemotherapy in patients with advanced gastrointestinal malignancy with weak physical status included: BMI, PS score, pain, type of primary tumor, number of metastatic sites, qualitative evaluation of gastrointestinal function based on symptoms, intestinal dilation based on CT images, ascites, hemoglobin, serum albumin, C-reactive protein, prothrombin time, d-dimer (Table 1).

Logistic regression analysis

The results of multivariate regression analysis suggested that pain (Figures 1a-1e and Table 2), type of primary tumor, qualitative evaluation of gastrointestinal function based on symptoms, ascites, and C-reactive protein were independent factors affecting the prognosis of patients with advanced gastrointestinal malignancy with weak physical status receiving low-dose chemotherapy (all P values <0.05). BMI, PS score, number of metastatic sites, CT image-based intestinal dilation, hemoglobin, serum albumin, prothrombin time and D-dimer were not independent factors affecting the prognosis of low-dose chemotherapy in patients with advanced gastrointestinal cancer with weak physical status (all P values >0.05).

Risk prediction scoring system

Risk prediction scoring system according to the results of multi-factor regression analysis (Table 3). Score 0~1 was group A, 2~3 was group B, and 4~5 was group C. The median survival time of group A was not reached, HR=1; Median survival in group B was 7.46 months, HR=4.702, 95% CI (2.599-8.507), P<0.001; Median survival in group C was 1.77 months, HR=25.535, 95% CI (10.43-62.516), P<0.001 (Figure 1f).

Discussion

Low-dose chemotherapy refers to continuous chemotherapy with low dose and short interval in cancer patients, which can achieve similar or even better efficacy and survival with less toxic and side effects, improved tolerance and improved quality of life [3]. The dose of low-dose chemotherapy is generally 1/3 to 1/2 of the traditional dose, which can be administered intravenously or orally with a short time interval [4]. Meta-analysis showed that low-dose chemotherapy had similar anti-tumor effects to traditional chemotherapy, but the toxicity of low-dose chemotherapy decreased [5]. A number of studies on advanced gastrointestinal cancer have found that low-dose

Table 1: Clinical characteristics and univariate analysis.

Clinical data	Group	n	Overall Survival (OS)		
			Median time (month)	χ^2	P
Sex	male	98	11.37	0.002	0.97
	female	43	12.12		
Age	<60	69	8.77	1.502	0.22
	≥ 60	72	13.57		
BMI (kg/m^2)	<23.5	101	8.67	4.659	0.03
	≥ 23.5	40	20.11		
PS score	2	116	13.57	35.25	<0.01
	3	25	4.14		
Pain	yes	94	15.41	42.957	<0.01
	no	47	4.7		
Type of primary tumor	gastric	46	7.13	10.811	<0.01
	intestinal	95	14.19		
Number of metastatic sites	≤ 3	127	13.47	4.035	0.04
	>3	14	8.67		
Qualitative evaluation of gastrointestinal function	normal	97	17.84	56.289	<0.01
	disorder	44	4.93		
Intestinal dilation based on CT images	negative	48	NR	4.321	0.04
	positive	93	8.67		
Ascites	yes	124	13.5	12.4	<0.01
	no	17	6.37		
WBC (× 10^9/L)	<5.87	70	12.12	0.601	0.43
	≥ 5.87	71	10.28		
NEUT (× 10^9/L)	<3.60	71	14.16	1.53	0.22
	≥ 3.60	70	10.28		
HB (g/L)	<120	67	8.67	4.392	0.04
	≥ 120	74	13.57		
ESR (mm/h)	<40	72	13.57	1.782	0.18
	≥ 40	69	8.67		
TB (μmol/L)	<8.5	72	13.5	0.036	0.85
	≥ 8.5	69	11.01		
ALB (g/L)	<40	51	7.46	11.156	<0.01
	≥ 40	90	15.41		
BUN (mmol/L)	<4.9	72	12.12	1.255	0.26
	≥ 4.9	69	11.01		
Scr (μmol/L)	<71	71	12.12	0.835	0.36
	≥ 71	70	11.37		
UA (μmol/L)	<357	98	13.47	0.262	0.61
	≥ 357	43	8.77		
C-reactive protein (mg/L)	<5.0	73	15.41	7.375	<0.01
	≥ 5.0	68	7.95		
prothrombin time (s)	<11.8	73	13.57	5.802	0.02
	≥ 11.8	68	11.01		
Fibrinogen (mg/dL)	<352	72	13.57	0.886	0.35
	≥ 352	69	8.77		
D-dimer (mg/L)	<1.10	71	14.16	4.549	0.03
	≥ 1.10	70	10.28		

chemotherapy has achieved strong anti-tumor effects [6-10].

Gastrointestinal cancer is common in China with high morbidity and mortality, and have caused heavy economic burden [11-13]. Patients with gastrointestinal malignancy are often complicated by gastrointestinal structural changes and dysfunction, increased nutritional risk, reduced physical performance score [14], and intolerance standard dose chemotherapy. Therefore, low-dose chemotherapy has become the direction of clinical exploration.

The gastrointestinal cancer patients included in this study were all in advanced stage, and the overall population had a weak physical status score and short expected survival. The survival rate was 73.4% at 6 months, 24.6% at 24 months, and the median survival time was 11.37 months. Among 46 patients with gastric cancer, the 6-month survival rate was 54.8%, the 24-month survival rate was 11.3%, and the median survival time was 7.13 months. In colorectal cancer patients (n=95), the 6-month survival rate was 82.3%, the 24-month survival rate was 34.5%, and the median survival rate was 14.19 months. After low dose chemotherapy, the survival period of patients was prolonged, the quality of life was improved, and certain clinical benefits were produced. Although gastric cancer and colorectal cancer differ in biological behavior and degree of malignancy, the scoring system can distinguish the degree of risk of the two by different scores, which are applied to both cancer types. Multivariate analysis in this study showed that patients with PS=3 had no higher risk of death than patients with PS=2 (P>0.05). It was suggested that patients with PS=3, who had been previously recommended for optimal supportive therapy, were still likely to benefit from low-dose chemotherapy. Therefore, patients who might benefit from low-dose chemotherapy could be screened by combining this scoring system. Pain, gastrointestinal dysfunction, and physical weakness are common symptoms in patients with advanced gastrointestinal cancer. These patients are often complicated by systemic inflammatory reactions, which seriously affect the prognosis and quality of life of patients. Previous studies have shown that effective control of cancer pain [15], improvement of digestive tract function and physical status [16], and reduction of systemic inflammation can improve quality of life [17] and prolong survival. In this study, pain, ascites, c-reactive protein elevation, digestive tract dysfunction, and gastric cancer were risk factors for death in patients with advanced gastrointestinal cancer with weak physical status (HR: 3.150, 1.952, 1.789, 3.232, 2.136, respectively). Therefore, we suggest that patients with advanced gastrointestinal malignancy in weak physical status should actively control pain, correct digestive tract dysfunction, control ascites, and reduce systemic inflammatory response.

Low-dose chemotherapy is an important direction of clinical exploration for patients with advanced gastrointestinal cancer with weak physical status. However, not all patients can benefit from low-dose chemotherapy. Therefore, the establishment of a simple and effective risk prediction scoring system can promote the screening of potential benefit groups and provide a basis for the selection of clinical individualized treatment plans. In this study, we analyzed multiple clinical factors that may be associated with the prognosis of low-dose chemotherapy in patients with advanced gastrointestinal cancer with weak physical status, and established a risk prediction scoring system based on five independent factors influencing the prognosis. With the increase of risk prediction score, the risk of death increased. The risk of different evaluation groups had a strong distinction, which had good predictive value. These results suggest

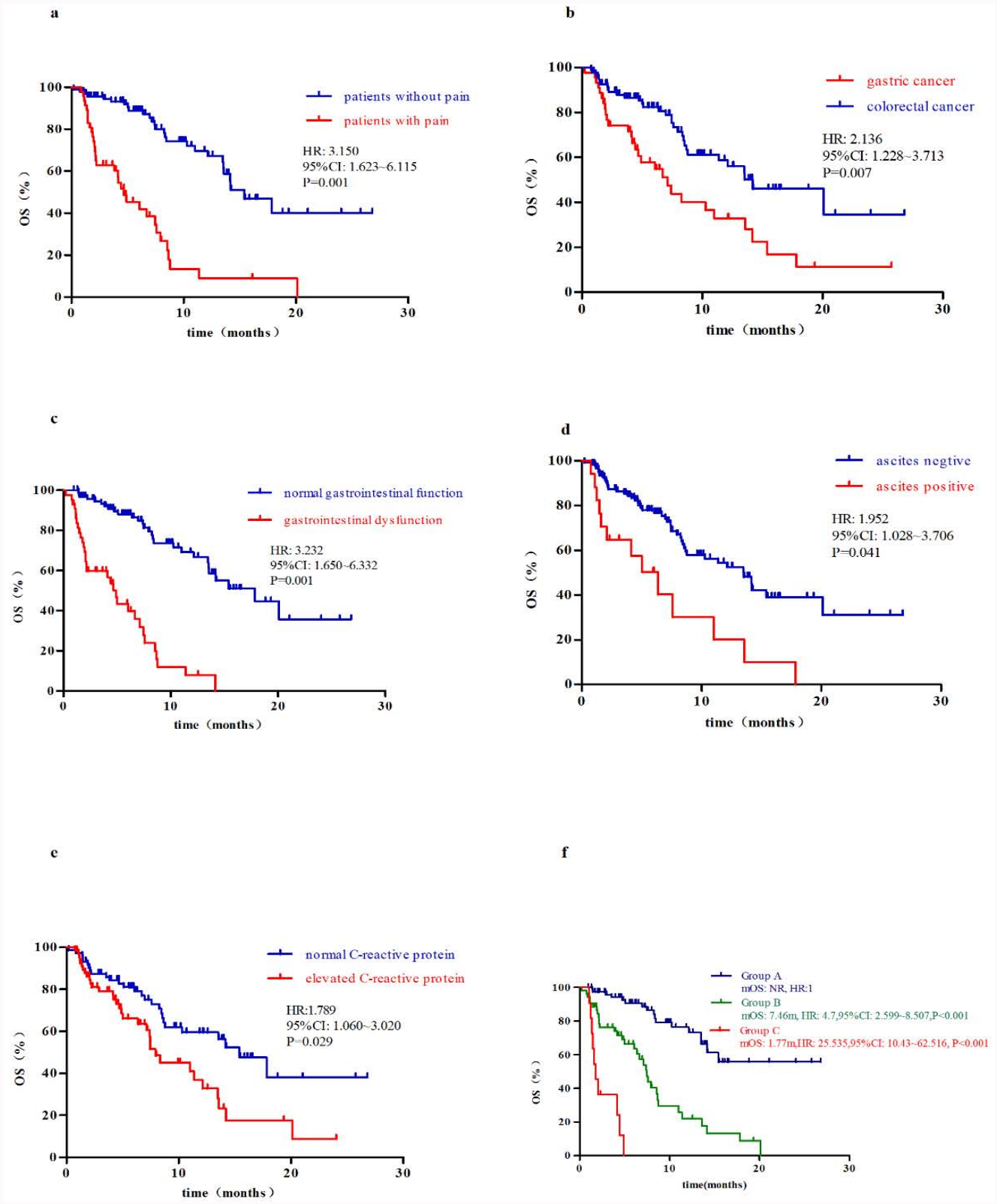

Figure 1: The results of multivariate regression analysis (n=141). (a-e) Pain, type of primary tumor, qualitative evaluation of gastrointestinal function based on symptoms, ascites, and C-reactive protein were independent factors affecting the prognosis (P<0.05). (f) The median survival time of group A was not reached; Median survival in group B was 7.46 months; Median survival in group C was 1.77 months, P<0.001.

Table 2: Multivariate regression analysis.

Factors		Regression coefficient	Standard error	*Wald* χ^2	HR	*HR 95% CI*	P
Pain	yes *vs.* no	1.147	0.338	11.499	3.15	1.623~6.115	0.001
Type of primary tumor	gastric *vs.* intestinal	0.759	0.282	7.227	2.136	1.228~3.713	0.007
Qualitative evaluation of gastrointestinal function	disorder *vs.* normal	1.173	0.343	11.687	3.232	1.650~6.332	0.001
Ascites	yes *vs.* no	0.669	0.327	4.183	1.952	1.028~3.706	0.041
C-reactive protein	≥ 5.0 *vs.* <5.0	0.582	0.267	4.748	1.789	1.060~3.020	0.029

Table 3: Risk prediction scores sheet.

Score	0	1
Pain	no	yes
Type of primary tumor	intestinal	gastric
Qualitative evaluation of gastrointestinal function	normal	disorder
Ascites	no	yes
C-reactive protein	<5.0	≥ 5.0

that low-dose chemotherapy is suitable for patients with low score. For patients with prognosis prediction score ≥ 4, prudent use of low-dose chemotherapy can reduce unnecessary economic expenditure and waste of medical resources. In the future, this risk prediction score needs to be validated in a large number of clinical patients to further test its effectiveness.

In conclusion, low-dose chemotherapy is the direction of clinical exploration for patients with advanced gastrointestinal cancer with weak physical status. It is crucial to explore the factors influencing the prognosis of low-dose chemotherapy for patients with advanced gastrointestinal cancer with weak physical status. Pain, ascites, elevated c-reactive protein, gastrointestinal dysfunction, stomach cancer is an independent prognosis risk factor for patients with advanced gastrointestinal cancer in weak physical status after receiving low-dose chemotherapy. Based on the above five clinical indicators, a risk prediction scoring system was established to help clinical screening of potential beneficiaries and development of individualized treatment plans.

Acknowledgment

We thank Fuyu Chen for excellent assistant in statistical assistance and constructive advice.

Funding

This study was supported by Zhongshan Hospital (Xiamen), Fudan University Incubation Program (2019ZSXMYS10).

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