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ABOUT COVER

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The primary aim of *World Journal of Gastrointestinal Surgery* (WJGS, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, etc.

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Retrospective Study

Treatment outcome analysis of bevacizumab combined with cyclophosphamide and oxaliplatin in advanced pseudomyxoma peritonei

Ying Zhang, Xin Zhao, Chao Gao, Lin-Yu Lin, Yan Li

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Abstract

BACKGROUND

Pseudomyxoma peritonei (PMP) is a rare peritoneal malignant tumor syndrome. Cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy is its standard treatment. However, there are few studies and insufficient evidence regarding systemic chemotherapy of advanced PMP. Regimens for colorectal cancer are often used clinically, but there is no uniform standard for late-stage treatment.

AIM

To determine if bevacizumab combined with cyclophosphamide and oxaliplatin (Bev+CTX+OXA) is effective for treatment of advanced PMP. The primary study endpoint was progression-free survival (PFS).

METHODS

Retrospective analysis was conducted on the clinical data of patients with advanced PMP who received Bev+CTX+OXA regimen (bevacizumab 7.5 mg/kg ivgtt d1, oxaliplatin 130 mg/m² ivgtt d1 and cyclophosphamide 500 mg/m² ivgtt d1, q3w) in our center from December 2015 to December 2020. Objective response rate (ORR), disease control rate (DCR) and incidence of adverse events were evaluated. PFS was followed up. Kaplan-Meier method was used to draw survival curve, and log-rank test was used for comparison between groups. Multivariate Cox proportional hazards regression model was used to analyze the independent influencing factors of PFS.

RESULTS

A total of 32 patients were enrolled. After 2 cycles, the ORR and DCR were 3.1% and 93.7%, respectively. The median follow-up time was 7.5 mo. During the

follow-up period, 14 patients (43.8%) had disease progression, and the median PFS was 8.9 mo. Stratified analysis showed that the PFS of patients with a preoperative increase in CA125 (8.9 *vs* 2.1, $P = 0.022$) and a completeness of cytoreduction score of 2-3 (8.9 *vs* 5.0, $P = 0.043$) was significantly longer than that of the control group. Multivariate analysis showed that a preoperative increase in CA125 was an independent prognostic factor for PFS (HR = 0.245, 95%CI: 0.066-0.904, $P = 0.035$).

CONCLUSION

Our retrospective assessment confirmed that the Bev+CTX+OXA regimen is effective in second- or posterior-line treatment of advanced PMP and that adverse reactions can be tolerated. A preoperative increase in CA125 is an independent prognostic factor of PFS.

Key Words: Pseudomyxoma peritonei; Bevacizumab; Oxaliplatin; Cyclophosphamide

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Core Tip: For systemic chemotherapy of advanced pseudomyxoma peritonei (PMP), there are currently few studies and insufficient evidence. In this study, the bevacizumab combined with cyclophosphamide and oxaliplatin regimen was used for advanced PMP for the first time. The scheme used in this study was based on clinical experience and had achieved good results.

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INTRODUCTION

Pseudomyxoma peritonei (PMP) is a rare peritoneal malignant tumor syndrome with an incidence of approximately 2 to 4 per 1 million[1]. It is characterized by accumulation and redistribution of mucus produced by mucinous tumor cells in the abdominal cavity, mainly from appendiceal mucinous tumors. Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is the standard treatment for PMP[2,3]. Our previous work showed obvious clinical benefits after standardized CRS + HIPEC treatment, with a median survival time after surgery of 55.4 mo[4], but the postoperative recurrence and metastasis rate is still high. For patients with advanced PMP who have no chance of surgery, systemic chemotherapy regimens for colorectal cancer are often used clinically, such as FOLFOX, FOLFIRI, or FOLFOX combined with bevacizumab[5]. The disease control rate (DCR) is 65.0% to 88.0%, with a median progression-free survival (PFS) of 8 to 13 mo[6-8]. However, there is no uniform standard for second- or posterior-line treatment. Therefore, exploring feasible treatment options is still a clinical problem that needs to be solved.

Cyclophosphamide (CTX) is a nitrogen mustard alkylating agent that has been used in the treatment of a variety of solid tumors. Application of CTX for treating PMP can be traced back to the 1950s[9]. Recent studies have reported that the DCR of CTX combined with capecitabine for PMP is 87.0%[10]. To date, there has been no report on the use of bevacizumab combined with CTX and oxaliplatin (hereinafter referred to as the Bev+CTX+OXA regimen) to treat PMP. This single-center, retrospective study aimed to evaluate the efficacy, safety, and prognosis of the Bev+CTX+OXA regimen for patients with unresectable PMP.

MATERIALS AND METHODS

Patients

This was a retrospective study involving clinical data of patients with advanced PMP who received the Bev+CTX+OXA regimen in the Department of Peritoneal Cancer Surgery in Beijing Shijitan Hospital affiliated with Capital Medical University from December 2015 to December 2020.

The inclusion criteria were as follows: (1) Pathologic confirmation of PMP; (2) Incomplete CRS + HIPEC treatment or recurrence and metastasis after complete CRS + HIPEC treatment that could not be operated on again; (3) Received at least first-line or above chemotherapy; (4) Karnofsky performance

status > 60 points; (5) Measurable target lesions; (6) Received at least 2 cycles of treatment with the Bev+CTX+OXA regimen; and (7) Complete clinical pathology and follow-up data.

Exclusion criteria were: (1) Concomitant other malignant tumors; (2) Unable to complete the efficacy evaluation; (3) PMP from a noncolorectal origin; and (4) Follow-up time < 3 mo. In this study, application of chemotherapy regimens was carried out with the informed consent of patients and their families.

Treatment plan

The following drugs were used: Bevacizumab (bevacizumab, Bev, Avastin, Germany/Roche Diagnostics GmbH, 400 mg (16 mL)/bottle), 7.5 mg/kg, d1, ivgtt (60-90 min), q3w; oxaliplatin (oxaliplatin, L-OHP, Jiangsu Hengrui Pharmaceuticals Co., Ltd., National Medicine Standard H20000337, 50 mg/bottle), 130 mg/m², d1, ivgtt (120 min), q3w; and CTX [CTX (endoxan), CTX, Baxter Oncology GmbH, 200 mg/bottle], 500 mg/m², ivgtt (approximately 30 min), q3w. Patients received this regimen until the disease progressed or an intolerable adverse reaction occurred or the patient withdrew informed consent. When patients had drug-related grade III or above adverse reactions during treatment, the dose was reduced by 25%; if it was still not tolerated, we adjusted to single-agent maintenance therapy or changed the chemotherapy regimen. Such cases were censored.

The primary study endpoint was PFS, as defined as the time from when a patient started receiving treatment to disease progression, death, or the follow-up deadline. The last follow-up date was July 4, 2021.

Efficacy and safety evaluation

All patients received baseline examinations before treatment, including routine blood, liver and kidney function, tumor marker, electrocardiogram, and CT scans of measurable target lesions. Imaging evaluation was carried out before and every 2 cycles of treatment, and we identified the most defined and clearly assessable lesions that we chose as target lesions. Efficacy was evaluated according to "Response Evaluation Criteria in Solid Tumors" (RECIST) version 1.1 criteria by a radiologist with special expertise to define complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). We calculated the objective response rate (ORR) by (CR + PR)/total number of cases × 100% and the DCR by (CR + PR + SD)/total number of cases × 100%. Short-term efficacy in all patients was determined at the end of the second cycle. Serum tumor markers were evaluated once a month. The level of serum tumor markers at the beginning of treatment and the lowest level of serum tumor markers during treatment were used to evaluate chemotherapy response. The safety evaluation adopted National Cancer Institute Common Terminology Criteria.

Statistical analysis

SPSS 19.0 software (SPSS Inc., Chicago, IL, United States) and R studio 4.1.0 software (<http://www.rstudio.com/>) were used for statistical analysis. Measurement data are expressed as the median (range) or $\bar{x} \pm s$, and enumeration data are expressed as the rate. The Kaplan-Meier method was used to draw survival curves, and the log-rank test was used for comparisons between groups. The Cox proportional hazard regression model was employed to perform univariate analysis, and factors with $P < 0.1$ were included in multivariate analysis. The Wilcoxon paired signed rank test was used to compare changes in tumor markers before and after treatment. Bilateral $P < 0.05$ was considered statistically significant.

RESULTS

Clinicopathological characteristics

A total of 41 patients with advanced unresectable PMP received the Bev+CTX+OXA regimen, and 9 cases were excluded according to the inclusion and exclusion criteria. Finally, 32 patients were enrolled in the study (Figure 1A), and the swimmer plot of the 32 patients was shown in Figure 1B. Among them, 24 (75%) were males and 8 (25%) females, with a median age of 57.5 (34-74) years. The main clinicopathological characteristics are shown in Table 1.

Short-term efficacy and PFS

The median chemotherapy cycle of 32 patients was 4 (2-11) cycles. After 2 cycles, 1 (3.1%) case of PR, 29 (90.6%) cases of SD, and 2 (6.3%) cases of PD were observed; the ORR and DCR were 3.1% and 93.7%, respectively. The median follow-up time was 7.5 mo. During the follow-up period, 14 (43.8%) patients experienced disease progression, and the median PFS was 8.9 mo (95%CI: 6.53-11.18), as shown in Figure 2A. By the end of follow-up, no deaths had occurred. The stratified analysis showed that patients with a preoperative increase in CA125 (8.9 vs 2.1, $P = 0.022$, Figure 2B) and a completeness of cytoreduction (CC) score of 2-3 (8.9 vs 5.0, $P = 0.043$, Figure 2C) had prolonged PFS, which was significantly different from the control group.

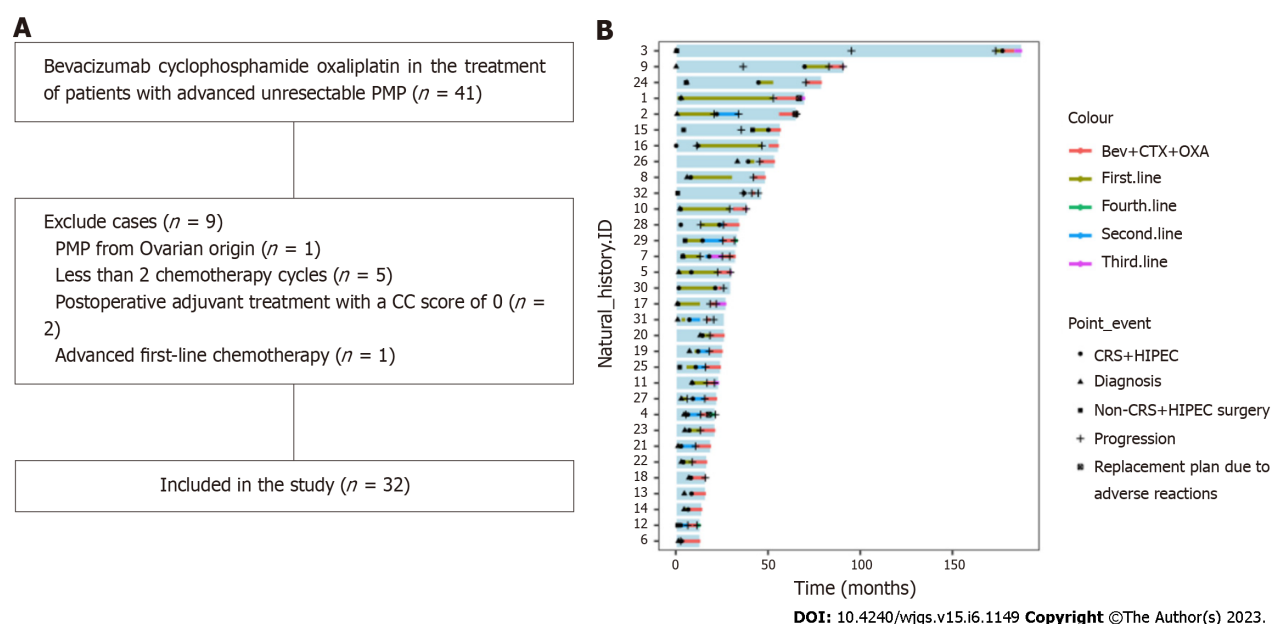


Figure 1 Study design. A: Flow chart; B: Swimmer plot of the 32 patients. PMP: Pseudomyxoma peritonei; CC: Completeness of cytoreduction; Bev+CTX+OXA: Bevacizumab combined with cyclophosphamide and oxaliplatin; CRS: Cytoreductive surgery; HIPEC: Hyperthermic intraperitoneal chemotherapy.

Adverse events

Adverse events occurred in 24 (75.0%) patients. The most common adverse events were neutropenia, anemia, and nausea and vomiting. One (3.1%) patient was allergic to oxaliplatin, and we replaced oxaliplatin with irinotecan. Five (15.6%) patients had grade 3 adverse events that were improved through dose reduction and symptomatic treatment, including 2 (6.3%) cases of neutropenia, 4 (12.5%) cases of anemia, 1 (3.1%) case of nausea and vomiting, and 1 (3.1%) case of proteinuria. In 2 (2.3%) patients, we replaced oxaliplatin with carboplatin due to grade 3 peripheral neurotoxicity (Table 2).

Changes in tumor markers

The mean values of serum CA199, carcinoembryonic antigen (CEA) and CA125 levels of 32 patients before chemotherapy were 844.17 ± 462.33 U/mL, 72.95 ± 25.22 ng/mL and 39.51 ± 6.15 U/mL, respectively. The mean minimum values during the treatment were 668.54 ± 384.65 U/mL, 71.65 ± 25.12 ng/mL and 27.41 ± 5.29 U/mL respectively. Both had a downward trend compared with that before treatment, but the difference was not statistically significant (Figure 3).

Analysis of influencing factors for PFS

Univariate analysis showed that the following two factors were related to PFS ($P < 0.1$): Preoperative increase of CA125 ($P = 0.035$), CC score was 2-3 points ($P = 0.054$). Multivariate analysis showed that preoperative increase of CA125 was an independent prognostic factor of PFS (HR = 0.245, 95%CI: 0.066-0.904, $P = 0.035$) (Table 3).

DISCUSSION

For systemic chemotherapy of advanced PMP, there are currently few studies and insufficient evidence. In this study, the Bev+CTX+OXA regimen was used for advanced PMP for the first time. The results showed that although the ORR was only 3.1%, the DCR reached 93.7%. This result is higher than the DCR with Pietrantonio *et al*'s FOLFOX4 and Hiraide *et al*'s mFOLFOX6 regimens, suggesting that this regimen has a certain effect on patients with advanced PMP[6,7]. We consider the following reasons. First, CTX was added to this regimen for the first time. Some studies have shown that CTX has a certain immunomodulatory effect[11]. Research suggests that low-dose CTX can induce secretion of interferon- γ , thereby enhancing the antitumor immune response in mice, which may be one of the underlying mechanisms[12,13]. Second, studies have shown that screening for gene mutations related to vascular endothelial growth factor (VEGF) signal transduction and administering anti-VEGF therapy may provide new options for treatment of patients with refractory/relapsed advanced PMP[14-16]. In this study, 59.4% of tumors were positive for VEGF expression. The higher DCR may be related to inhibition of VEGF and its downstream pathways by addition of bevacizumab. It is worth noting that 59.4% of the patients in this study had previously used bevacizumab; considering the clear evidence for

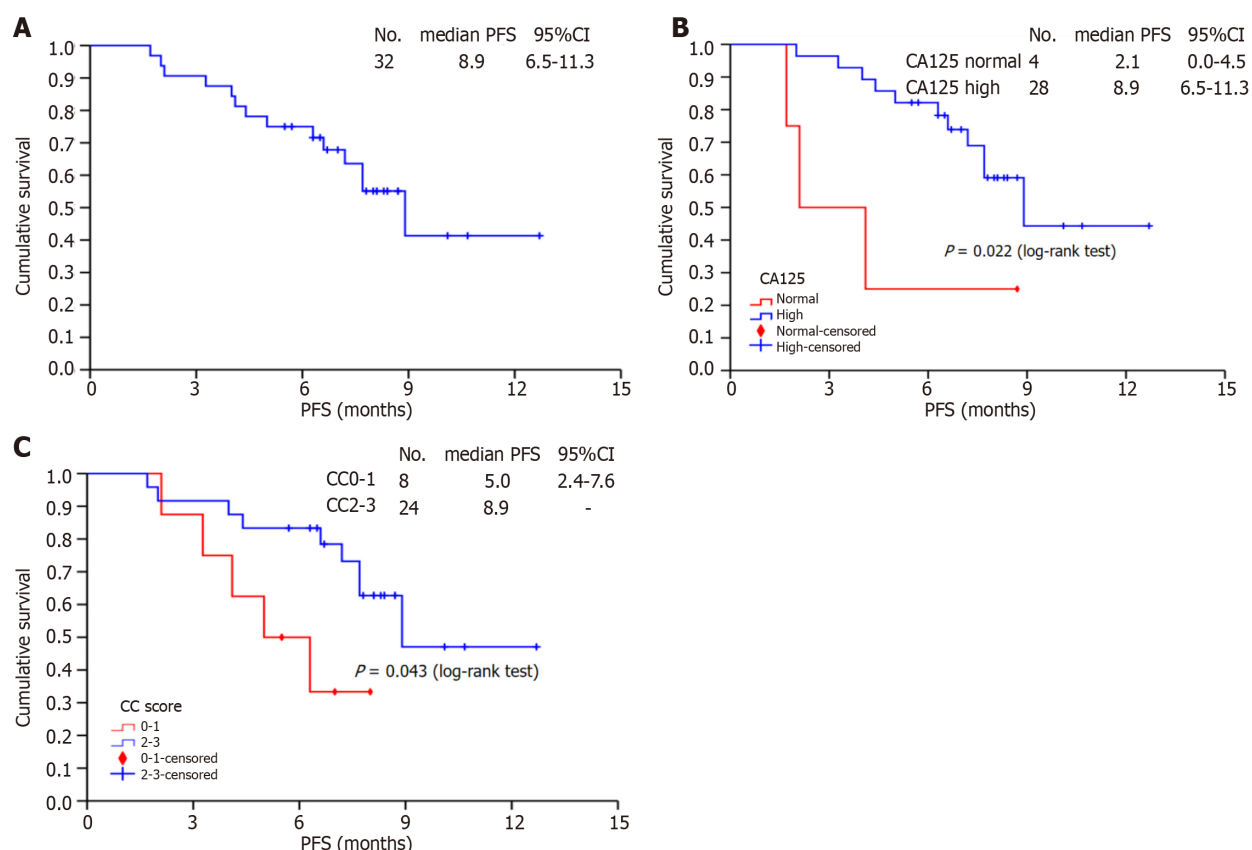
Table 1 Clinicopathological characteristics of 32 pseudomyxoma peritonei patients

Characteristic	No. of patients (%)
Sex	
Male	24 (75)
Female	8 (25)
Age (years), median (rang)	57.5 (34-74)
BSA (m²), median (rang)	1.69 (1.27-2.07)
KPS score, median (rang)	90 (60-100)
PCI score, median (rang)	31 (16-39)
Ca199 before chemotherapy, median (rang), U/mL	46.09 (4.68-10707.5)
CEA before chemotherapy, median (rang), ng/mL	16.63 (1.08-632.27)
Ca125 before chemotherapy, median (rang), U/mL	26.25 (5.3-146.7)
CC score	
0-1	8 (25)
2-3	24 (75)
Histological diagnosis	
Low-grade	12 (37.5)
High-grade	18 (56.2)
High-grade with signet ring cells	2 (6.3)
Lymph node metastasis	
Yes	2 (6.3)
No	30 (93.7)
Vascular tumor thrombus	
Yes	2 (6.3)
No	30 (93.7)
Nerve invasion	
Yes	2 (6.3)
No	30 (93.7)
VEGF expression	
Positive	19 (59.4)
Negative	3 (9.4)
Unknown	10 (31.2)
Microsatellite status	
MSS	14 (43.8)
MSI-L	1 (3.1)
Unknown	17 (53.1)
Past use of bevacizumab	
Yes	13 (40.6)
No	19 (59.4)
First-line chemotherapy (months), median (rang)	4.72 (0.01-34.73)

BSA: Body surface area; KPS: Karnofsky performance status; PCI: Peritoneal cancer index; CC: Completeness of cytoreduction; VEGF: Vascular endothelial growth factor; MSS: Microsatellite stability; MSI-L: Low microsatellite instability; CEA: Carcinoembryonic antigen.

Table 2 Adverse events, *n* (%)

Adverse events	Total	Grade 1-2	Grade 3-5
Total	24 (75.0)	20 (62.5)	5 (15.6)
Neutropenia	14 (43.8)	12 (37.5)	2 (6.3)
Thrombocytopenia	1 (3.1)	1 (3.1)	0 (0)
Anemia	16 (50.0)	12 (37.5)	4 (12.5)
Peripheral neurotoxicity	8 (25.0)	6 (18.8)	2 (6.3)
Fatigue	9 (28.1)	9 (28.1)	0 (0)
Nausea and vomiting	15 (46.9)	14 (43.8)	1 (3.1)
Liver damage	7 (21.9)	7 (21.9)	0 (0)
Renal impairment	9 (28.1)	9 (28.1)	0 (0)
Proteinuria	5 (15.6)	4 (12.5)	1 (3.1)
Hypertension	5 (15.6)	5 (15.6)	0 (0)
Allergy	1 (3.1)	1 (3.1)	0 (0)



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Figure 2 Progression-free survival for 32 patients. A: Total progression-free survival; B: Stratified analysis of preoperative CA125; C: Stratified analysis of completeness of cytoreduction score. PFS: Progression-free survival; CC: Completeness of cytoreduction.

bevacizumab in cross-line treatment of a variety of solid tumors, we did not remove it. The results of the study also showed that whether bevacizumab has been used in the past did not affect PFS, suggesting that in second- or posterior-line treatment of patients with advanced PMP, cross-line application of bevacizumab may still bring survival benefits.

In terms of adverse events, 24 (75.0%) patients had adverse events, 2 (6.3%) patients had grade 3 neutropenia, and 4 (12.5%) patients had grade 3 anemia. These rates are slightly higher than those of Pietrantonio *et al*[7] and Hiraide *et al*[6], but lower than that of Raimondi[10]. This may be related to the fact that our enrolled population had received at least first-line chemotherapy in the past, which may

Table 3 Analysis of influencing factors for progression-free survival

Prognostic factors	Univariate analysis			Multivariate analysis		
	HR	95%CI	P value	HR	95%CI	P value
Sex (female <i>vs</i> male)	0.522	0.143-1.906	0.325	-	-	-
Age (< 60 <i>vs</i> ≥ 60)	0.630	0.208-1.910	0.414	-	-	-
Preoperative CEA (increased <i>vs</i> normal)	1.383	0.309-6.193	0.671	-	-	-
Preoperative CA199 (increased <i>vs</i> normal)	1.289	0.446-3.725	0.639			
Preoperative CA125 (increased <i>vs</i> normal)	0.245	0.066-0.904	0.035	0.245	0.066-0.904	0.035
KPS (≥ 80 <i>vs</i> < 80)	0.946	0.119-7.493	0.958			
CC (2-3 <i>vs</i> 0-1)	0.319	0.100-1.012	0.054	0.351	0.106-1.164	0.087
Pathology (high-grade with signet ring cells <i>vs</i> high-grade <i>vs</i> low-grade)	1.247	0.463-3.357	0.662			
Lymph node metastasis (yes <i>vs</i> no)	0.044	0.000-435.823	0.506			
Vascular tumor thrombus (yes <i>vs</i> no)	0.044	0.000-435.823	0.506			
Nerve invasion (yes <i>vs</i> no)	0.043	0.000-196.970	0.464			
VEGF expression (+ <i>vs</i> -)	0.764	0.157-3.712	0.739			
CA199 before chemotherapy (increased <i>vs</i> normal)	0.764	0.266-2.197	0.618			
CEA before chemotherapy (increased <i>vs</i> normal)	0.743	0.232-2.379	0.616			
CA125 before chemotherapy (increased <i>vs</i> normal)	1.401	0.489-4.014	0.530			

CEA: Carcinoembryonic antigen; KPS: Karnofsky performance status; CC: Completeness of cytoreduction.

have caused a decline in bone marrow hematopoietic function. In terms of proteinuria and peripheral neurotoxicity, the rate of grade 3 adverse events in this study was not high, and the grade 1-2 adverse events were all alleviated by symptomatic treatment, suggesting that the regimen can be tolerated.

During the treatment period of this study, serum CEA, CA125, and CA199 levels exhibited a downward trend. Although the difference was not statistically significant, this trend is still worth noting. The research of Randall *et al*[17] showed that in patients with epithelial ovarian cancer and peritoneal cancer continuously treated with bevacizumab, RECIST and CA125 are related in disease evaluation. Approximately 10% of patients may be found disease progression earlier through CA125. Hiraide *et al*[6] and others also used tumor markers as a method to monitor the efficacy. This provides a certain basis for monitoring efficacy in patients with no measurable lesions in the future. The median PFS in this study was 8.9 mo, which was lower than that with the FOLFOX4[6] and mFOLFOX6[7] regimens. However, considering that the median follow-up time of this study was only 7.5 mo, the median chemotherapy cycle was 4 cycles; thus, further follow-up is still needed to assess the PFS with this program. At the same time, 62.5% of patients with high-grade pathological types were included in this study, and patients with CC scores 2-3 accounted for 75%. These poor baseline data may limit the improvement in PFS. Stratified analysis and multivariate analysis showed that a preoperative increase in serum CA125 is an independent prognostic factor of prolonged PFS in this study. However, this trend was not observed in patients with elevated CA125 at the beginning of this regimen, which may be related to the surgical cytoreduction and previous chemotherapy that caused a significant decrease in serum CA125 before this regimen. The patients in this study had symptoms of abdominal and pelvic effusion during initial treatment. Previous studies have shown that an increase in CA125 is related to the degree of ascites. Anti-VEGF treatment can inhibit neovascularization and has obvious benefits for ascites control. This may be one of the reasons for the prolonged PFS of these patients. On the other hand, stratified analysis showed that the PFS of the patients with CC scores of 2-3 was prolonged, but the CC score in multivariate analysis was not an independent prognostic factor. This may be related to the large proportion of patients with CC scores of 2-3, and further research is needed for verification.

This study has certain limitations. First, this study was a single-center retrospective study. The previous treatment plan, clinical pathological data and biological characteristics of the enrolled patients were heterogeneous, which will lead to patient selection bias in the results. Second, the sample size was small, and the follow-up time was short, leading to some results that may be contrary to theory. In general, selection of beneficial regimens needs to be verified by expanding the sample and extending the follow-up time. Third, this study did not establish a control group.

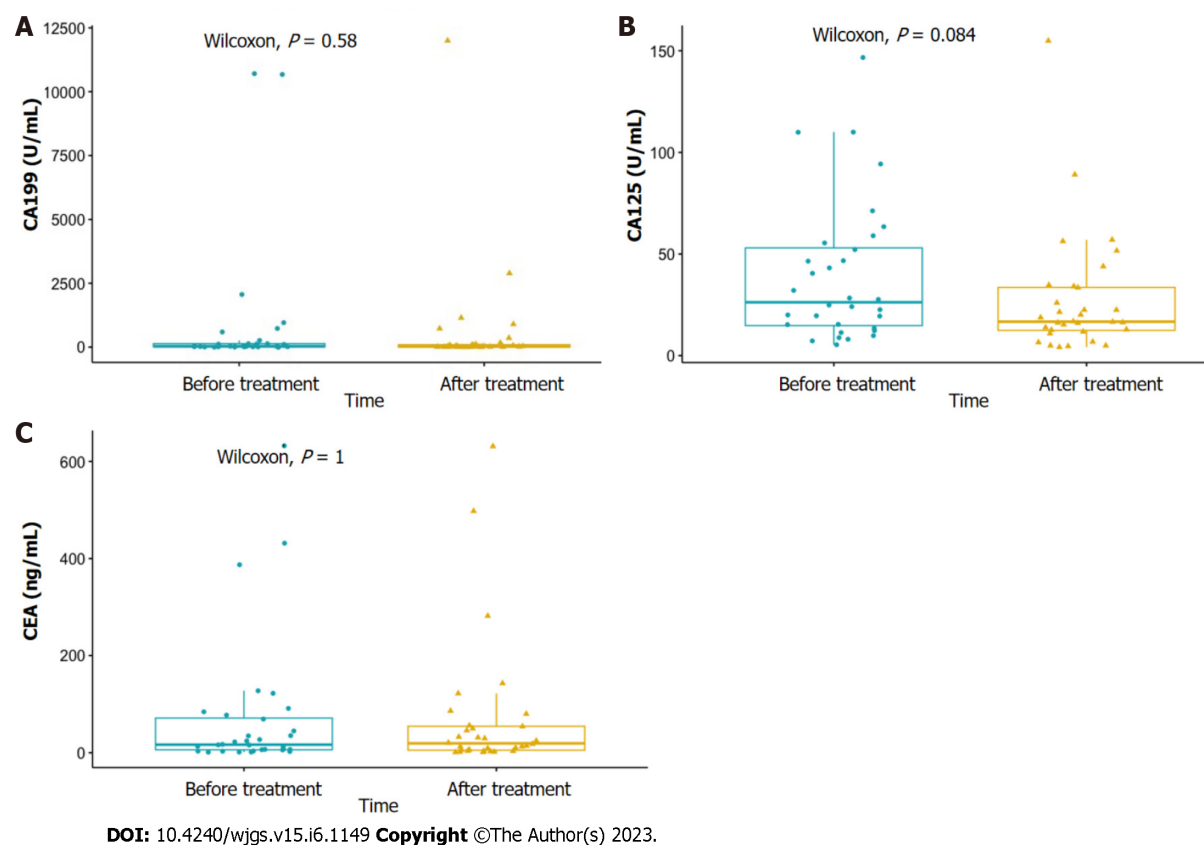


Figure 3 Changes in serum tumor markers in 32 patients before and after treatment. A: Changes in CA199 before and after treatment; B: Changes in CA125 before and after treatment; C: Changes in carcinoembryonic antigen before and after treatment. CEA: Carcinoembryonic antigen.

CONCLUSION

In summary, the Bev+CTX+OXA regimen is effective in second- or posterior-line treatment of advanced PMP, and adverse reactions can be tolerated. A preoperative increase in CA125 is an independent prognostic factor of PFS.

ARTICLE HIGHLIGHTS

Research background

Cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy is its standard treatment. But for systemic chemotherapy of advanced pseudomyxoma peritonei (PMP), there are currently few studies and insufficient evidence.

Research motivation

Regimens for colorectal cancer are often used clinically, but there is no uniform standard for late-stage treatment.

Research objectives

The purpose of this single-center, retrospective study was to determine if bevacizumab combined with cyclophosphamide and oxaliplatin (Bev+CTX+OXA) is effective for treatment of advanced PMP.

Research methods

Retrospective analysis was conducted on the clinical data of patients with advanced PMP who received Bev+CTX+OXA regimen from December 2015 to December 2020. Objective response rate (ORR), disease control rate (DCR) and incidence of adverse events were evaluated. Progression-free survival (PFS) was followed up.

Research results

A total of 32 patients were enrolled, after 2 cycles, ORR and DCR were 3.1% and 93.7% respectively. The

median follow-up time was 7.5 mo. During the follow-up period, 14 patients (43.8%) had disease progression, and the median progression-free survival (PFS) was 8.9 mo. Stratified analysis showed that the PFS of patients with preoperative increase of CA125 (8.9 *vs* 2.1, $P = 0.022$) and completeness of cytoreduction score of 2-3 (8.9 *vs* 5.0, $P = 0.043$) were significantly longer than those of the control group. Multivariate analysis showed that preoperative increase of CA125 was an independent prognostic factor for PFS (HR = 0.245, 95%CI: 0.066-0.904, $P = 0.035$).

Research conclusions

Bev+CTX+OXA regimen is certain effective in the posterior-line treatment of advanced PMP, and the adverse reactions can be tolerated. The preoperative increase of CA125 is an independent prognostic factor of PFS.

Research perspectives

More sample size should be conduct in the future to validate the conclusion of our study.

FOOTNOTES

Author contributions: Zhao X and Gao C collected the data; Zhang Y and Lin LY performed the data analysis; Zhang Y wrote the original draft preparation; Zhang Y and Li Y wrote the review and editing; Li Y contributed to the supervision.

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