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WORD COUNT	2802	TIME SUBMITTED	21-MAR-2023 10:04AM
		PAPER ID	97829134

Name of Journal: *World Journal of Gastrointestinal Surgery*

Manuscript NO: 83625

Manuscript Type: ORIGINAL ARTICLE

Retrospective Study

Efficacy and Influencing Factors of Bevacizumab Combined with Cyclophosphamide and Oxaliplatin in the Treatment of Advanced Pseudomyxoma Peritonei: a Single Center Retrospective Study

Chemotherapy for Advanced Pseudomyxoma Peritonei

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

Abstract

BACKGROUND

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

AIM

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

METHODS

A total of 32 patients were enrolled, after 2 cycles, objective response rate and disease control rate 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.

RESULTS

Stratified analysis showed that the PFS of patients with preoperative increase of Ca125 (8.9 vs. 2.1, P = 0.022) and CC 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). Our retrospective assessment confirmed that Bev + CTX + OXA regimen is certain effective in the posterior line treatment of advanced pseudomyxoma peritonei, and the adverse reactions can be tolerated.

CONCLUSION

The preoperative increase of Ca125 is an independent prognostic factor of PFS.

Key Words: Peritoneal pseudomyxoma; Bevacizumab; Oxaliplatin; Cyclophosphamide

Zhang Y, Zhao X, Gao C, Lin LY, Li Y. The Efficacy and Influencing Factors of Bevacizumab Combined with Cyclophosphamide and Oxaliplatin in the Treatment of Advanced Pseudomyxoma Peritonei: a Single Center Retrospective Study. *World J Gastrointest Surg* 2023; In press

Core Tip: For systemic chemotherapy of advanced PMP, there are currently few studies and insufficient evidence. In this study, the Bevacizumab + Oxaliplatin + Cyclophosphamide 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.

INTRODUCTION

Pseudomyxoma peritonei (PMP) is a rare peritoneal malignant tumor syndrome with an incidence of about 2 to 4 per 1 million[1]. It is characterized by the 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 studies have shown that PMP patients have obvious clinical benefits after standardized CRS+HIPEC treatment, and the median survival time after surgery is 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 combined with bevacizumab, etc[5]. The disease control rate (DCR) is 65.0% to 88.0%, with a median progression-free survival (PFS) is 8 to 13 mo[6-8]. But

there is no uniform standard for posterior treatment. Therefore, exploring more feasible treatment options is still a clinical problem that needs to be solved.

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

MATERIALS AND METHODS

Patients

This was a retrospective study of 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 to Capital Medical University from December 2015 to December 2020.

Inclusion criteria were: (1) pathologic confirmation of PMP; (2) Patients received incomplete CRS+HIPEC treatment, or recurrence and metastasis after complete CRS+HIPEC treatment, and could not be operated on again; (3) Have received at least first-line or above chemotherapy; (4) Karnofsky performance status（KPS）>60 points; (5) Have measurable target lesions; (6) Received at least 2 cycles of treatment with Bev+CTX+OXA regimen; (7) Complete clinical pathology and follow-up data.

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

Treatment plan

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/m^2, d1, ivgtt (120 min), q3w. Cyclophosphamide (Cyclophosphamide (Endoxan), CTX, Baxter Oncology GmbH, 200 mg/bottle), 500 mg/m^2, ivgtt (about 30 min), q3w. Patients received this regimen until the disease progresses or an intolerable adverse reaction occurs or the patient withdraws the 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 change the chemotherapy regimen. This case was the censored data.

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

Efficacy and safety evaluation

All patients received baseline examinations before treatment, including blood routine, liver and kidney function, tumor markers, electrocardiogram, and CT scan of measurable target lesions. Imaging evaluation was carried out before and every 2 cycles of treatment, we identified the most defined and clearly assessable lesions, that we chose as target lesions. The efficacy was evaluated according to the "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 objective response rate (ORR) by (CR+PR)/total number of cases×100%, and disease control rate (DCR) by (CR+PR+SD)/total number of cases×100%. The short-term efficacy of 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 adopts the National Cancer Institute Common Terminology Criteria (NCI-CTC).

Statistical analysis

SPSS 19.0 software (SPSS Inc., Chicago, IL, USA) and R studio 4.1.0 software(http://www.rstudio.com/) were used for statistical analysis. Enumeration data was expressed as median (range) or x±s, and measurement data was expressed as rate. Kaplan-Meier method was used to draw survival curve, and log-rank test was used for comparison between groups. The Cox proportional hazard regression model performed univariate analysis, and factors with P<0.1 were included in multivariate analysis. Wilcoxon paired signed rank test was used to compare the changes of 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 had 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 1). Among them, 24 (75%) were males and 8 (25%) were females, with a median age of 57.5 (34-74) years. The main clinicopathological characteristics are shown in Table 1.

Short-term efficacy and progression-free survival

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, 2 (6.3%) cases of PD were evaluated, 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 had disease progression, and the median PFS was 8.9 mo (95%CI 6.53-11.18). By the end of follow-up, no deaths occurred. The stratified analysis showed that patients with preoperative increase of Ca125 (8.9 vs. 2.1, P = 0.022) and the CC score of 2-3(8.9 vs. 5.0, P = 0.043) had prolonged PFS, which was statistically different from the control group (Figure 2).

Adverse events

Adverse events occurred in 24 (75.0%) patients. The most common adverse events were neutropenia, anemia, and nausea and vomiting. 1 (3.1%) patient was allergic to oxaliplatin, so we replaced oxaliplatin with irinotecan. 5 (15.6%) patients had grade 3 adverse events which 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, 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 of Pietrantonio's FOLFOX4 and Hiraide's mFOLFOX6 regimen, 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 the secretion of IFN-γ, thereby enhancing the anti-tumor immune response of mice, which may be one of the underlying mechanisms[12, 13]. Second, studies have shown that screening for gene mutations related to VEGF signal transduction and giving anti-VEGF therapy may provide new options for the treatment of patients with refractory/relapsed advanced PMP [14-16]. In this study, 59.4% of patients were positive for VEGF expression. The higher disease control rate may be related to the inhibition of VEGF and its downstream pathways by the addition of bevacizumab. It is worth noting that 59.4% of the patients in this study had previously used bevacizumab, but considering that bevacizumab has clear evidence in the cross-line treatment of a variety of solid tumors, we didn't remove it, and the results of the study also showed that whether or not bevacizumab has been used in the past didn't affect PFS, suggesting that in the posterior line treatment of patients with advanced PMP, the 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. This ratio is slightly higher than that of Pietrantonio[7] and Hiraide[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 cause the decline of 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 adverse events of grade 1-2 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 all have a downward trend. Although the difference was not statistically significant, this trend is still worth noting. The research of Randall [17] showed that in patients with epithelial ovarian cancer and peritoneal cancer who were continuously treated with bevacizumab, RECIST and Ca125 are related in the evaluation of the diseases. Approximately 10% of patients may find disease progression earlier through Ca125.

Hiraide[6] and others also used tumor markers as a method to monitor the efficacy. This provides a certain basis for monitoring the efficacy of patients with no measurable lesions in the future.The median PFS in this study was 8.9 mo, which was lower than that of the FOLFOX4[6] and mFOLFOX6[7] regimens. But considering that the follow-up time of this study was only 7.5 mo, the median chemotherapy cycle was 4 cycles, so the PFS of this program still needs further follow-up to determine. 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 of PFS.Stratified analysis and multivariate analysis showed that preoperative increase of serum Ca125 is an independent prognostic factor of prolonged PFS in this study. However, this trend was not seen 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 the initial treatment. Previous studies have shown that the 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, the stratified analysis showed that the PFS of the patients in the CC scores of 2-3 was prolonged, but the CC score in the multivariate analysis was not an independent prognostic factor. This may be related to the large proportion of patients with CC score of 2-3, and further research is needed to verify.

This study still has certain limitations. First, this study is 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 patients' 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. The selection of beneficiaries still needs to be verified by expanding the sample and extending the follow-up time. Third, this study did not establish a control group.

CONCLUSION

In summary, Bev + CTX + OXA regimen is certain effective in the posterior line treatment of advanced pseudomyxoma peritonei, and the adverse reactions can be tolerated. The preoperative increase of 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 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 posterior 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 the treatment of advanced PMP.

Research methods

A total of 32 patients were enrolled, after 2 cycles, objective response rate and disease control rate 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.

Research results

Stratified analysis showed that the PFS of patients with preoperative increase of Ca125 (8.9 vs. 2.1, P = 0.022) and CC 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). Our retrospective assessment confirmed that Bev + CTX + OXA regimen is certain effective in the posterior line treatment of advanced pseudomyxoma peritonei, and the adverse reactions can be tolerated.

Research conclusions

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.

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