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Original Article

Efficacy of paclitaxel-based doublet regimens combining with intraperitoneal chemotherapy for advanced gastric cancer with peritoneal metastasis

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Abstract: We aim to evaluate the efficacy and safety of paclitaxel-based doublet intravenous chemotherapy (IVC) with and without intraperitoneal chemotherapy (IPC) as the first-line treatment in advanced gastric cancer (AGC) with peritoneal metastasis (PM). 173 AGC patients with peritoneal metastasis were enrolled. All patients received paclitaxel-based doublet systemic chemotherapy Among them, 117 patients received IVC+IPC and 56 patients received IVC alone. The median OS of patients in the IP+ group was longer than the IP- group, however, there was no statistical difference between the two groups (11.1 months vs. 10.1 months, P = 0.072). In the multivariate analysis, the ECOG PS and IVC±IPC were independent prognostic factors for PFS and OS. There were no significant differences in the incidence of grade 3 and 4 toxicity between the IP+(DDP), IP+(FUDR) and IP- groups. Paclitaxel-based doublet regimens combining with IPC is effective, feasible and tolerated in AGC patients with PM.

Keywords: Advanced gastric cancer, peritoneal metastasis, intraperitoneal chemotherapy, intravenous chemotherapy, paclitaxel

Introduction

Gastric cancer is the fourth most common malignant disease worldwide and the second most common cause of death from cancer [1, 2]. About 1 million new cases of gastric cancer were diagnosed in 2008, 74% of which were in Asia (47% in China) [3].

The peritoneal cavity is also a frequent site for metastatic disease after resection, particularly in patients with serosa-infiltrating tumours [4]. Peritoneal metastasis (PM) is the most frequent and most life-threatening modality of disease progression in patients with gastric cancer. Patients with gastric cancer and peritoneal carcinomatosis, have a poor prognosis, with a median survival without treatment of 3.1 months [5].

For many years 5-fluorouracil (5-FU)-based or cisplatin-based regimens were the most common treatments for advanced gastric cancer (AGC) used worldwide [6-8]. In some recently reported clinical trials, the third generation platinum compound, oxaliplatin, proved to be equal to, if not better than, cisplatin with regard to efficacy. Moreover, oxaliplatin was associated with slightly reduced toxicity and better tolerability compared to cisplatin [9-11]. To develop a more active and efficacious chemotherapy regimen, docetaxel, another cytotoxic agent against AGC, has been added to a doublet combination with 5-FU plus cisplatin. The global V325 phase 3 study showed the superiority of docetaxel plus cisplatin and fluorouracil (DCF regimen) over CF in terms of objective response rate, time to progression, and overall survival. However, the high toxicity profile, in particular

Table 1. Patient characteristics

Characteristics		IP+ group	IP- group	χ^2	*P* value
		N = 117	N = 56		
Sex	Male	76	36	0.007	0.931
	Female	41	20		
Age (years)	<65	102	47	0.335	0.563
	≥65	15	9		
Histological grade	G1-G2	46	26	0.788	0.375
	G3-G4	71	30		
ECOG PS	0-1	70	32	2.201	0.138
	2	47	34		

high incidences of grade 3/4 neutropenia and febrile neutropenia, limits the routine use of DCF [12]. Paclitaxel, another one of the taxanes, shows similar efficacy to docetaxel against advanced gastric cancer. However, compared to docetaxel, paclitaxel offers less toxicity and better tolerability [13, 14].

It has been suggested that IPC may improve survival in patients with peritoneal carcinomatosis [15-17]. IPC possesses a theoretical advantage over the systemic route by delivering high concentrations of drug directly to the peritoneal cavity with reduced systemic toxicity [18]. In addition, high drug concentrations are achieved in the portal vein. This may be important as the liver is a common site for metastases [19]. This study retrospectively analyzed the clinical efficacy of paclitaxel-based regimens combined with intraperitoneal chemotherapy as first-line treatment in AGC with PM, and the factors that affect the survival benefits from IPC were explored.

Methods

Ethics statement

All procedures were conducted in accordance with the Helsinki declaration, and with approval from the Ethics Committee of Fujian Provincial Cancer Hospital. Written informed consent was obtained from all participants.

Eligibility

We retrospectively studied all the AGC patients who were admitted in Department of Medical Oncology of Fujian Provincial Cancer Hospital from January 2003 to December 2010. One hundred and seventy-three patients with AGC were included in the study according to the following criteria: 1) Histologically proven gastric adenocarcinoma, 2) All the patients had PM confirmed by histological examination obtained from biopsy specimens during laparotomy, laparoscopic examination, or cytological examination of ascites, with or without metastasis to distant organ sites (such as the liver, lungs or bone), 3) Complete medical records were available, 4) Eastern Cooperative Oncology Group performance status between 0 and 2, 5) No prior chemotherapy except for postoperative adjuvant chemotherapy more than 12 months before entry into the study, 6) Adequate bone marrow function with leukocyte counts 3,000-12,000/mm^3, hemoglobin ≥8.0 g/dl, and platelet counts ≥100,000/mm^3, 7) Adequate liver function with total serum bilirubin ≤2.0 mg/dl and serum transaminases ≤100/UI, 8) Adequate renal function with serum creatinine within the upper limit of normal, 9) An expected survival period of >3 months, 10) All patients non-randomly received one of the systemic chemotherapy regimens, including PF, PO, for at least four cycles, and patients received intraperitoneal perfusion chemotherapy, including cisplatin (CDDP) or 5-fluoro-2'-deoxyuridine-5'-phosphate (FUDR), were given at least four cycles.

Treatment

The PF regimen consisted of a 3-hour infusion of paclitaxel (135 mg/m^2) followed by leucovorin (400 mg/m^2), administered simultaneously over a 2-hour infusion period. Subsequently, a 46-hour infusion of 5-florouracil (2400 mg/m^2) was administered using an ambulatory pump. The PO regimen consisted of a 3-hour infusion of paclitaxel (135 mg/m^2) followed oxaliplatin (85 mg/m^2). A total dose of 1,000 mg FUDR or 60 mg CDDP in 1.5 liters of normal saline was introduced into the peritoneal cavity with a catheter placed at the lower right or lower left abdominal wall. The catheter and drains were clamped for 24 h and no effort was made to drain the intraperitoneal solution unless it was necessary for patient comfort and the next IP infusion [20].

The treatment course was repeated every two weeks until observation of unacceptable toxicity, disease progression, or patient choice. All patients received a standard supportive regi-

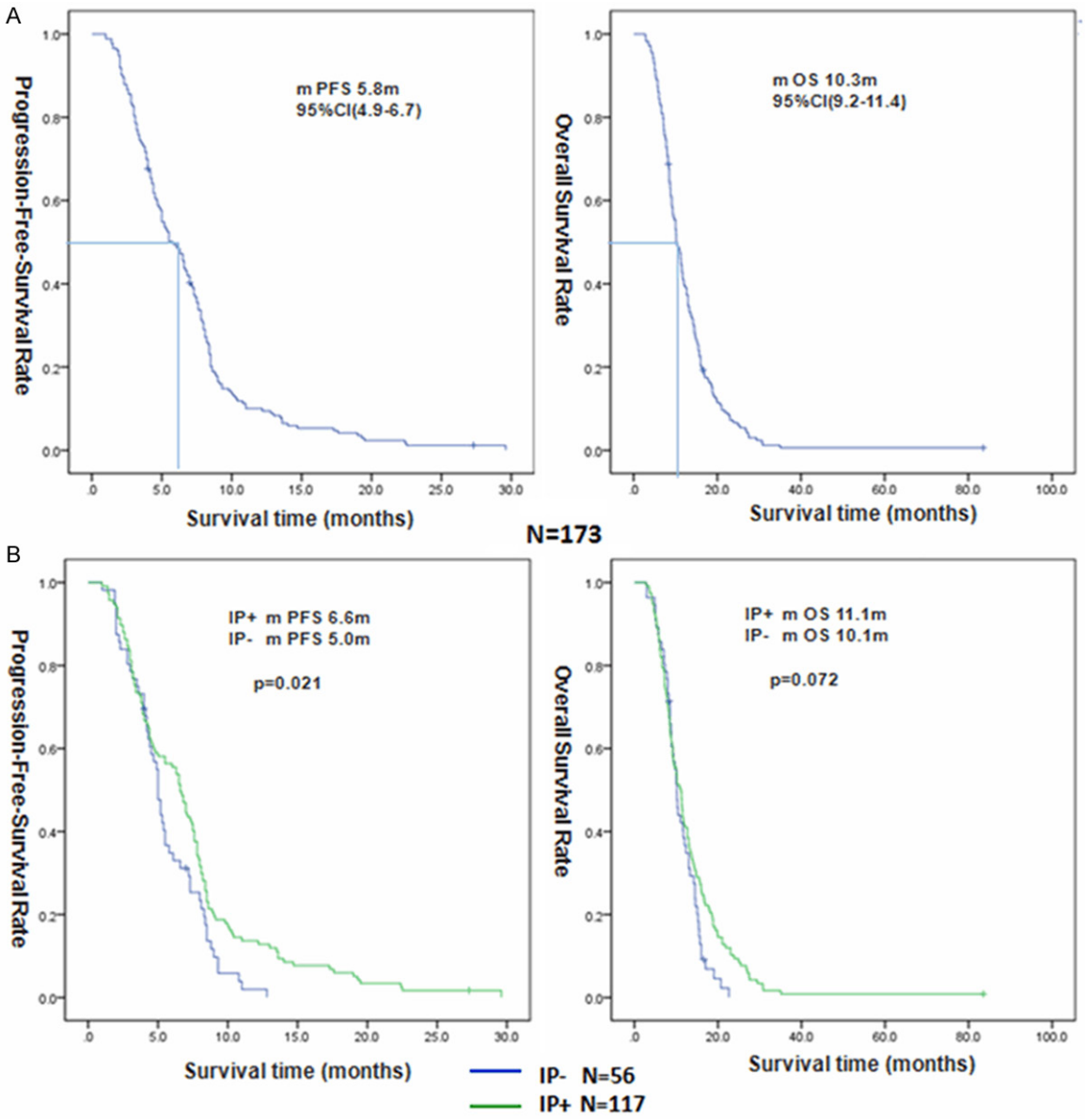

Figure 1. A. Kaplan-Meier curves for progression-free survival (PFS) and overall survival (OS) in 173 patients. B. PFS and OS in the patients who received intravenous chemotherapy with and without intraperitoneal chemotherapy.

men including oral corticosteroids, antihistamines, and antiemetics. With the eventual failure of this combination chemotherapy, second-line chemotherapy was recommended to all patients if their performance status was preserved.

Evaluation of toxicity and efficacy

A complete blood cell count and measurements of liver and renal function were assessed at least once a week during the treatment. Non-hematological toxicities were also verified at least once a week by patient interview and physical examination. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0 [21]. During the treatment, patients were evaluated with abdominal computed tomography (CT) scans and assessed for an objective response in measurable lesions every 1-2 months according to the Response Evaluation Criteria In Solid Tumors (RECIST) criteria [22]. Progression-Free-Survival (PFS) was measured from the day of initial treatment to the first evidence of progression or death. Overall Survival (OS) was defined from the date of initial treatment to death from any cause.

Table 2. Univariate analysis of factors associated with survival of 173 advanced gastric cancer patients with peritoneal metastasis

Variable		*n*	PFS (95% CI)	*P* value	OS (95% CI)	*P* value
Sex	Male	112	6.3 (5.00~7.60)	0.447	10.2 (8.45~11.96)	0.827
	Female	61	5.5 (3.89~7.11)		10.3 (8.61~11.94)	
Age (years)	<65	149	5.8 (4.69~6.91)	0.158	12.7 (10.54~14.86	0.186
	≥65	24	4.7 (1.68~7.12)		10.2 (8.87~11.53)	
Histological grade	G1~G2	72	6.7 (4.84~6.56)	0.143	11.3 (10.26~12.34)	0.481
	G3~G4	101	5.3 (4.15~6.45)		9.7 (8.65~10.75)	
ECOG PS	0~1	102	7.3 (6.42~8.18)	0.000	11.7 (10.56-12.84)	0.002
	2	71	4.2 (3.63~4.77)		8.5 (7.96~9.04)	
Regimens of IVC	PO	70	6.1 (4.76~7.45)	0.796	11.0 (9.47~12.53)	0.806
	PF	103	5.5 (4.25~6.75)		10.1 (8.53~11.67)	
IVC±IPC	IPC+	117	6.6 (5.79~7.42)	0.021	11.1 (8.97~11.23)	0.072
	IPC-	56	5.0 (4.49~5.51)		10.1 (9.59~12.61)	
Regimens of IPC	IPC (DDP)	78	6.8 (5.45~8.15)	0.057	11.5 (9.36~13.64)	0.106
	IPC (FUDR)	38	6.3 (3.59~9.02)		10.0 (7.50~12.50)	

Statistical methods

Statistical analysis was performed with the SPSS software (Version 17.0, SPSS). For all analyses, the significance level was specified as P<0.05. Comparisons between proportions were analyzed using the χ^2 test and the Fisher exact probability test. OS and PFS variables were estimated by the Kaplan-Meier method and survival curves were plotted. Two-sided log-rank tests were used to compare survival rates between groups. Multivariate analyses using the Cox proportional hazards regression model were performed to assess the impact of the variables on PFS and OS.

Results

From January 2003 to December 2010, 173 AGC patients with PM were enrolled in this study and were fully evaluated for OS, PFS, and OS. One hundred and seventeen patients received intravenous chemotherapy +IP, 56 patients received intravenous chemotherapy alone. Of all the patients, 70 patients received PO and 103 patients received PF. Patient characteristics are listed in **Table 1**.

PFS and OS

For the 173 patients, the median PFS was 5.8 months, 95% CI = (4.9-6.7), and median OS was 10.3 months, 95% CI = (9.2-11.4), and the 1-year survival rate and 2-year survival rate were 39.6% and 6.6%, respectively (**Figure 1A**). The median PFS in the IP+ group was improved by 1.6 months compared with that in the IP- group; 6.6 months vs. 5.0 months, P = 0.021 (**Table 2** and **Figure 1B**). The median OS of patients in the IP+ group was longer than in the IP- group, however, there was no statistically significant difference between the two groups; 11.1 months vs. 10.1 months, P = 0.072 (**Table 2** and **Figure 1B**).

For the patients who received different regimens of IPC or intravenous chemotherapy (IVC), there was no significant difference in the PFS and OS (**Table 2** and **Figure 2A**, **2B**).

Survival analysis

In the univariate analysis, ECOG PS was associated with PFS and OS, but only the patients who received IVC combined with IPC had a prolonged PFS. While the sex, age, histological grade, regimens of IPC, and regimens of IVC were not correlated with PFS or OS (**Table 2**). In the multivariate analysis, the variables including sex, age, histological grade, regimens of IPC, regimens of IVC and IVC±IPC were tested to determine their independent effect on PFS and OS. The ECOG PS and IVC±IPC were independent prognostic factors for PFS and OS (**Table 3**).

Toxicity

All patients were analyzed for toxicity and a summary of toxicity is presented in **Table 4**. The incidence of grade 1 and 2 toxicity for nausea/vomiting and abdominal pain was higher for

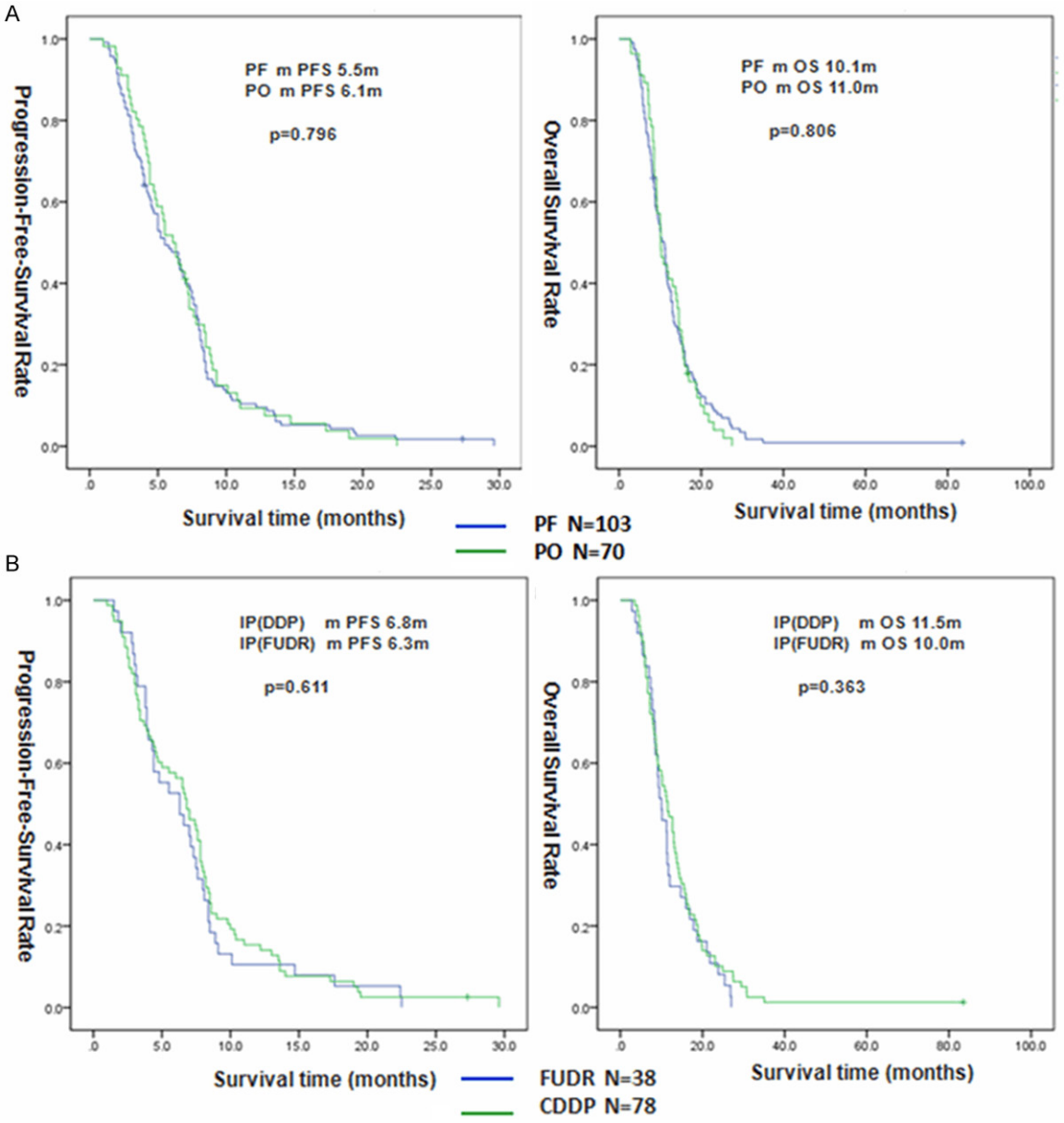

Figure 2. A. Progression-free survival (PFS) and overall survival (OS) in patients in relation to different intravenous chemotherapy. B. PFS and OS in patients in relation to different intraperitoneal chemotherapy.

Table 3. Multivariate analysis (Cox model) of factors associated with progression-free-survival (PFS) and overall survival (OS) of 173 advanced gastric cancer patients with peritoneal metastasis

	PFS			OS		
Variable	*P* value	HR	95% CI	*P* value	HR	95% CI
ECOG PS	<0.001	0.48	0.35-0.66	0.001	0.59	0.43-0.81
IVC±IPC	0.003	0.60	0.43-0.84	0.025	0.69	0.48-0.95

patients on the IP+ regimens. In general, the incidence of major grade 3 and 4 toxicity is less than 10%, and there were no significant differences in the incidence of grade 3 and 4 toxicity between the IP+(DDP), IP+(FUDR) and IP groups.

Discussion

PM is a poor prognostic factor in patients with advanced gastric cancer, and once established, is associated with poor survival, with median survival ranging from 1 to 7 months and no survival at 5 years [23, 24].

Table 4. Most common treatment-related toxicities

Toxicities	IPC+(DDP)	IPC+(FUDR)	IPC-	χ^2	*P*-value
	N = 78	N = 38	N = 57		
Nausea/Vomiting					
Grade I/II	35	11	12	8.842	0.012
Grade III/IV	7	1	2	2.693	0.262
Diarrhea					
Grade I/II	12	4	5	1.469	0.482
Grade III/IV	4	1	1	1.222	0.543
Abdominal pain					
Grade I/II	27	14	5	13.891	0.001
Grade III/IV	3	1	0	2.179	0.336
Fatigue					
Grade I/II	22	9	15	0.271	0.873
Grade III/IV	2	1	1	0.118	0.941
Peripheral neuropathy					
Grade I/II	8	5	12	3.171	0.205
Grade III/IV	3	2	2	0.195	0.907
Leucopenia					
Grade I/II	19	14	14	2.304	0.316
Grade III/IV	2	0	1	0.986	0.611
Thrombocytopenia					
Grade I/II	9	3	4	0.908	0.635
Grade III/IV	2	0	0	2.464	0.292
Aminotransferase					
Grade I/II	26	14	17	0.518	0.772
Grade III/IV	5	1	1	2.091	0.352

Our previous studies showed that Paclitaxel-based doublet regimens (PF or PO), which had less toxicity, had similar survival to triplet regimen (POF) for the AGC patients [25]. Intraperitoneal administration of anticancer drugs enables an extremely high concentration of drugs to directly contact the target cancer lesions in the peritoneal cavity. The use of IPC as targeted adjuvant treatment after surgery may be a rational prophylactic/therapeutic approach, which could be effective for preventing peritoneal dissemination and liver metastasis [26, 27]. There have only been a few trials for treating AGC with PM reported [28-32]. There is limited good-quality data to determine the role of IPC in AGC with PM.

In this study, we evaluated the potential effects of paclitaxel-based doublet regiments (PO or PF) with or without IPC for treatment of AGC patients with PM. Generally, the effects of chemotherapy are determined by tumor response. However, the evaluation of tumor response in GC patients with PM is difficult because they frequently do not have a target lesion. Therefore, we adopted PFS and OS instead of an objective response rate (ORR) when evaluating the prognosis. For all the patients, the median PFS was 5.8 months and the median OS was 10.3 months.

Through single-factor analysis using the Kaplan-Meier estimator, it was found that the patients in IP+ group had better PFS compared with patients in IP- group (P = 0.021), but there was no significant difference for OS. However, further COX regression analysis showed that IPC treatment and ECOG PS can be used as one of the independent prognostic factors for PFS and OS. Although the incidence of grade 1 and 2 toxicity for nausea/vomiting and abdominal pain were higher for patients on the IPC+ regimens, there were no significant differences in the incidence of grade 3 and 4 toxicity between the IPC+(DDP), IPC+(FUDR), and IPC- groups. These results indicated that paclitaxel-based doublet regimens combining with IPC for treatment of AGC with PM is effective and tolerated.

Furthermore, from the univariate and multivariate analysis, we could see that there was no significant difference in the PFS and OS for the patients who received different regimens of IPC or intravenous chemotherapy (IVC). It means that there were more choices for doctors. For example, the PF regimen is a good option for patients with peripheral neuropathy because simultaneous administration of oxaliplatin and paclitaxel, which are both neurotoxic, would result in more significant peripheral neuropathy [33]. The PO regimen increases convenience and reduces the time spent at the chemotherapy clinic, as it does not need a protracted infusion of fluorouracil [34]. FUDR for IPC may be suitable for patients with renal impairment.

Our results are limited by the heterogeneity in the study design and the retrospective nature of the analysis. Therefore, a treatment model

for systemic chemotherapy with additional IPC for AGC with PM needs further investigation with an expanded sample size in further prospective clinical studies.

In conclusion, our opinion is that for AGC patients with PM, especially in those having a good performance status, paclitaxel-based doublet regimens combining with IPC is effective, feasible and tolerated. Doctors may choose drug combinations for peritoneal perfusion or systemic medication according to the actual situation. This provides an individualized treatment for gastric cancer, and a theoretical basis for future prospective studies using an expanded sample size.

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Disclosure of conflict of interest

None.

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