

Hyperthermic intraperitoneal perfusion chemotherapy and response evaluation in patients with gastric cancer and malignant ascites

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Abstract. The present study describes the use of bidirectional chemotherapy in the treatment of patients with gastric cancer and peritoneal carcinomatosis (PC), using newly developed response criteria for the treatment of malignant ascites. In addition, the association between effusion response and survival was analyzed. Between June 2010 and May 2014, patients affected by malignant ascites secondary to unresectable PC of gastric origin were treated with a combination of systemic and loco-regional chemotherapy. Cisplatin (75 mg/m²) at an inflow temperature of 43°C was infused intraperitoneally, and docetaxel (75 mg/m²) was infused simultaneously via a peripheral vein, on day 1 every 3 weeks. The primary endpoint was overall survival rate, and the secondary endpoint was efficacy against malignant ascites using new response criteria. In total, 41 patients were enrolled, the majority of whom received 6 cycles of intraperitoneal chemotherapy in combination with hyperthermia. The majority of patients exhibited clinical regression of ascites and relief of associated symptoms. Malignant ascites disappeared [complete response (CR)] or decreased by 50% [partial response (PR)] in 73.2% of patients. No mortalities associated with the procedures occurred. The median survival time was 8.6 months, and the 1-year survival rate was 24.4%. As these new response criteria for the treatment of malignant ascites were found to be feasible, bidirectional chemotherapy may be the preferred strategy for the treatment of gastric cancer with PC. The CR, PR and non-PR groups showed significant differences in overall survival, indicating

that decreased effusion was associated with improved patient survival.

Introduction

Although the incidence of gastric cancer has decreased worldwide, particularly in Western countries, it remains the fourth most common type of cancer and the second-most common cause of cancer-associated mortality worldwide (1,2). Peritoneal carcinomatosis (PC) is the most frequent mode of recurrence and is responsible for ~60% of gastric cancer-associated mortalities (3). Patients with gastric cancer exhibiting PC are considered not to be curable and are usually treated with systemic chemotherapy without surgical resection (4,5). Patients with PC and ascites have very poor prognoses, with a median survival of 3-6 months, and there are no long-term survivors (4,5). PC is a common event in the natural history of gastrointestinal tract cancers, with a high 6-month mortality rate (6). Malignant ascites, one of the most frequent comorbid conditions complicating PC (7), may severely affect patient quality of life, and its symptoms may be particularly painful and life threatening (7,8).

PC from gastrointestinal cancers has been considered an incurable condition, for which the role of surgical intervention is limited (9). Systemic chemotherapy is the treatment of choice, with significant survival benefits compared with best-supportive care, but even systemic chemotherapy is relatively ineffective against PC due to the blood-peritoneal barrier, which consists of a monolayer of mesothelial cells and submesothelial connective tissue ~90 µm thick between the basement membrane and vasculature (10).

Intraperitoneal (IP) chemotherapy is designed to increase the dose and exposure time of intra-abdominal cancer cells to anticancer drugs, while minimizing systemic toxic effects (11,12). Prolonged retention in the peritoneal cavity and clearance from the systemic circulation are regarded as key attributes for IP chemotherapy drugs (11,12). Heat has been exhibited to be synergistic with the antitumoral effects of mitomycin C, cisplatin (CDDP) and oxaliplatin (13,14).

Drugs regarded as ideal for IP administration are those that maintain a high concentration in the peritoneum, exhibit high

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penetration into the tumors and have low systemic concentrations; CDDP and carboplatin have been shown to penetrate 1–2 mm from the surface of PC nodules (15). These two drugs are easily absorbed from the peritoneal cavity and are suitable for IP chemotherapy (15). CDDP, an alkylating agent used for treating gastric cancer, ovarian cancer and diffuse malignant peritoneal mesothelioma, is the most common agent used during heat-enhanced IP chemotherapy (HIPC) (16). A combination of systemic and loco-regional chemotherapy may be effective in patients with carcinomatosis from gastric cancer, particularly in patients with small volumes of disease and symptomatic ascites (16).

The present study describes the use of bidirectional chemotherapy in the treatment of gastric cancer with PC, using newly developed response criteria regarding the treatment of malignant ascites. The present study also investigated the association between effusion response and patient survival.

Materials and methods

Patients. A total of 41 patients were enrolled in the present study, including 23 (56.1%) males and 18 (43.9%) females, with a median age of 42 (range, 31–69) years. The trial was conducted by the Department of Oncology, The Third Affiliated Hospital, Soochow University (Changzhou, China), between June 2010 and May 2014. Patients were eligible if they met the following criteria: Histopathological confirmation of gastric cancer; tumor cells in ascites, pathological findings of peritoneal metastasis or macroscopic PC diagnosed by laparoscopy; the absence of non-curative factors, including distant metastasis to the liver or lungs, with the exception of metastases to the peritoneum; Eastern Cooperative Oncology Group (ECOG) (17) performance status <2; age <75 years; no prior treatment; adequate bone marrow function (leukocyte count >3,000/ml and platelet count >100,000/ml); adequate liver function (serum bilirubin level <1.5 mg/dl and serum transaminase levels <2 times the upper normal limit); adequate renal function (serum creatinine level <1.5 mg/dl); no other severe medical conditions, including symptomatic infectious disease, intestinal pneumonia, active hemorrhage/bleeding or obstructive bowel disease; not pregnant or lactating; provision of written informed consent in accordance with hospital regulations; and an expected survival time >3 months. Gastric cancer ascites was observed with a light microscope (BX51; Olympus Corporation, Tokyo, Japan) with x200 magnification.

The present study was approved by the Ethics Committee of Soochow University. All patients provided written informed consent regarding their involvement in the study, in accordance with institutional guidelines.

Bidirectional chemotherapy and HIPC. IP catheters, ARROWg+ and blue central venous catheters (Arrow International, Inc., Reading, PA, USA) were inserted under local anesthesia prior to therapy. On day 1 of every 3-week cycle, heated ($43.0 \pm 0.5^\circ\text{C}$) CDDP perfusion solution (60 $\mu\text{g}/\text{ml}$ saline for a dose of $75 \text{ mg}/\text{m}^2$) was infused into the peritoneal cavity of all patients through an inflow tube using an automatic hyperthermia chemotherapy perfusion device (HGG-Z102; Hejia Medical Treatment Information Industry Co., Ltd., Zhuhai, China). Subsequent to perfusion, to allow the solution to

distribute itself throughout the entire peritoneal surface, the tilt of the patient was changed at 15 min intervals during continuous perfusion over 2 h as follows: (1) level; (2) Trendelenburg + left tilt; (3) Trendelenburg + right tilt; (4) level; (5) reverse Trendelenburg + left tilt; and (6) reverse Trendelenburg + right tilt. Approximately 30 min was required to deliver a volume of 1 l. Additionally, all patients were infused intravenously for 1 h with docetaxel ($75 \text{ mg}/\text{m}^2$) on day 1 of the 3 week cycle.

Evaluation and determination of efficacy. Baseline evaluations included patient history, physical examination, measurement of the serum concentration of carcinoembryonic antigen (CEA) (18) and an examination of the abdomen using B-mode ultrasound within 1 week prior to therapy. CEA and a B-mode ultrasound inspection of the abdomen were repeated prior to each cycle of chemotherapy.

Malignant ascites is considered a non-evaluable lesion, since it is difficult to detect by conventional radiological examinations. The present study used a new response criterion to assess the effect of treatment of PC: B-mode ultrasound examination above the bladder using longitudinal sections prior to and following therapy. Complete response (CR) was defined as complete absence of effusion on B-mode ultrasound or CT scans; partial response (PR) as a $\geq 50\%$ reduction in ascites depth on B-mode ultrasound; and non-PR (nPR) as a <50% reduction or an increase in ascites depth. Patients were assessed by B-mode ultrasound following every second treatment cycle. The majority of patients received 6 cycles of HIPC and systemic chemotherapy.

Statistical analysis. Survival time was calculated from the initial date of treatment to the date of the most recent follow-up visit of the event of patient mortality, using the Kaplan-Meier method. Univariate analysis was performed using the log-rank test, and multivariate analysis was performed using a Cox proportional hazards model. $P < 0.05$ was considered to indicate a statistically significant difference. The primary study endpoint was overall survival (OS) rate, and the secondary endpoints were efficacy and serious adverse events, defined as severe local and/or systemic infection, intestinal occlusion or mortality associated with the procedure. The statistical analyses were performed using SPSS version 16.0. (SPSS Inc., Chicago, IL USA).

Results

Between June 2010 and May 2014, 41 patients were enrolled in the present study, including 17 with primary tumors and peritoneal dissemination, and 24 with peritoneal recurrence (Table I). The 41 patients consisted of 23 (56.1%) males and 18 (43.9%) females, with a median age of 42 (range, 31–69) years. All patients had an ECOG performance status score of 0 or 1. Metastatic sites included the peritoneum (41/41; 100%), lymph nodes (13/41; 31.7%), liver (12/41; 12.2%) and lungs (2/41; 4.9%), with 34 patients (82.9%) having positive peritoneal cytology. Fig. 1 shows typical cancer cells in gastric cancer ascites. All patients presented with malignant ascites.

Fig. 2 shows a typical peritoneal effusion response imaged using B-mode ultrasound. Prior to treatment, numerous abdominal effusions were observed above the bladder (Fig. 2A).

Table I. Characteristics of patients.

Variables	Patients, n (%)
Age, years	42.1±13.2 ^a (31-69)
Sex	
Male	23 (56.1)
Female	18 (43.9)
ECOG performance status	
0	2 (4.9)
1	13 (31.7)
2	16 (39.0)
Ascites	
No	0 (0.0)
Yes	41 (100.0)
Peritoneal lavage cytology	
Negative	7 (17.1)
Positive	34 (82.9)
Primary or recurrence	
Primary	17 (41.5)
Recurrence	24 (58.5)
Cycles of hyperthermic intraperitoneal perfusion chemotherapy	2.2 ^b (1-4)
Total	41 (100.0)

^aRepresents the mean ± SD, and ^brepresents median; ECOG, Eastern Cooperative Oncology Group.

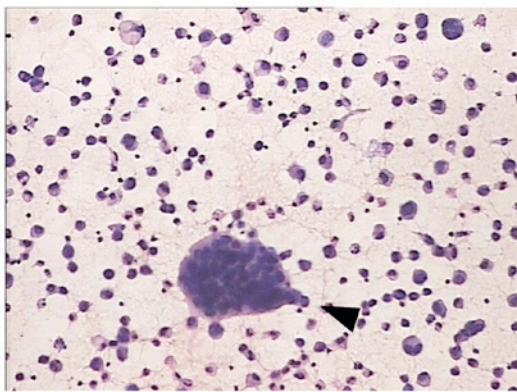


Figure 1. Cancer cells (indicated by arrow) in the ascites fluid of a patient with gastric cancer. Numerous cancer cells were present in the ascites prior to hyperthermic intraperitoneal perfusion chemotherapy (hematoxylin and eosin; magnification, x200).

Following two cycles of treatment, the peritoneal effusions had disappeared above the bladder (Fig. 2B), indicating that this patient had achieved CR. CT of another patient also showed a typical peritoneal effusion response during therapy (Fig. 3); this patient was also regarded as having achieved CR.

Table II shows the effects of therapy on peritoneal dissemination. The majority of patients showed clinical regression of ascites and associated symptoms. The peritoneal effusion response rate (RR=CR+PR) was 73.2%, including 7 patients (17.1%) who achieved CR and 23 (56.1%) who achieved PR,

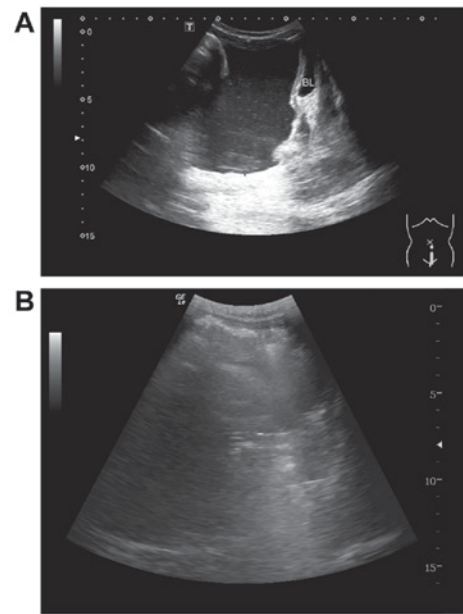


Figure 2. Longitudinal sections from B-mode ultrasound examinations above the bladder showing (A) symptomatic ascites prior to hyperthermic intraperitoneal perfusion chemotherapy and (B) disappearance of ascites following two cycles of therapy.

with the remaining 11 patients (26.8%) achieving nPR. There were no mortalities associated with the procedure. At a median follow-up of 11.4 months, the mean survival time (MST) of all 41 patients enrolled in the present study was 8.5±0.7 months. MSTs in CR, PR and nPR groups were 15.4±5.6, 9.1±0.9 and 6.9±0.5 months, respectively (Table II), with significant differences among the 3 groups ($P<0.05$; Fig. 4). Kaplan-Meier analysis showed that the 1-year OS rate was 24.4% (Fig. 5).

Discussion

Peritoneal metastasis frequently occurs in patients with recurrent gastrointestinal malignancies (19). The most serious condition that may develop in peritoneal metastasis is PC, which has an extremely poor prognosis (6,20,21). PC has been estimated to be responsible for 60% of all gastric cancer-associated mortalities, with peritoneal metastases in these patients considered terminal (6,20,21). Therapy consists mainly of palliative chemotherapy; long-term survival is considered poor, since systemic chemotherapy agents are unlikely to reach cytotoxic concentrations in peritoneal nodules (22-27).

Although IP chemotherapy may deliver high-dose intensity treatment to the peritoneal cavity, drug penetration deep into the peritoneal surface is limited (28). Hyperthermia treatment may augment the penetration distance of anticancer drugs by up to 2,000 μm , as well as altering the permeability of tumor cell membranes to enhance uptake of chemotherapeutic drugs (28). In addition, the combination of hyperthermic treatment and chemotherapeutic drugs, including mitomycin C, etoposide and CDDP have shown synergistic cytotoxicity towards cancer cells (29). Thus, combinations of systemic and loco-regional chemotherapy may be considered in patients with carcinomatosis from gastric cancer. These combinations may be particularly effective for patients with small volumes

Table II. Effects of therapy on peritoneal dissemination.

Response	Patients, n (%)	Mean survival time (months)	95% confidence interval
Disappeared (complete response)	7 (17.07)	15.4±5.6	4.358-26.442
Decrease of ascites ≥50% (partial response)	23 (56.10)	9.1±0.9	7.263-10.937
Decrease of ascites <50% or increase (non-partial response)	11 (26.83)	6.9±0.5	5.929-7.871
Overall	41 (100.00)	8.5±0.7	7.175-9.825

CR, complete response; PR, partial response; nPR, non-partial response.

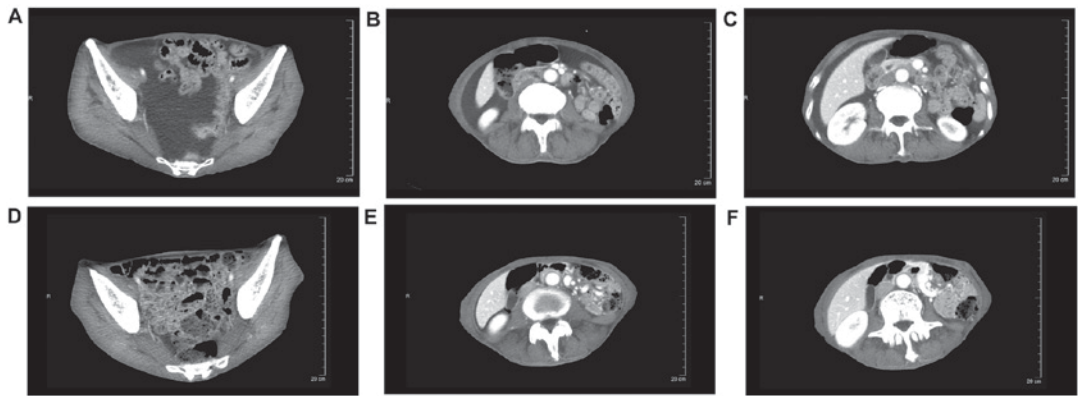


Figure 3. Typical peritoneal effusion response during therapy. CT images showing symptomatic ascites secondary to peritoneal metastasis prior to hyperthermic intraperitoneal perfusion chemotherapy: (A) pelvic region, (B) hepatorenal recess and (C) around the liver and kidney. Following 2 cycles of therapy, the patient was disease-free, as shown by the CT scans and was assessed as achieving complete response: (D) pelvic region, (E) hepatorenal recess, and (F) around the liver and kidney. CT, computed tomography.

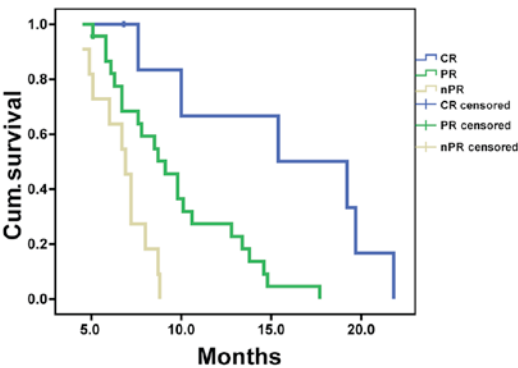


Figure 4. Kaplan-Meier overall survival curves for patients who achieved complete response, partial response and non-partial response. The mean survival time of the complete response group was 15.4±5.6 months, which was the longest of the groups. There were significant differences among the 3 groups ($P<0.05$).

of disease and symptomatic ascites. A phase I/II trial revealed that IP docetaxel plusS-1 was safe and effective in patients with gastric cancer with PC (30).

The present study analyzed the effectiveness of a combination of systemic chemotherapy (intravenous docetaxel) and loco-regional chemotherapy (IP CDDP), with the two administered on day 1 of every 3-week cycle. The present findings indicated that this therapeutic protocol was feasible and

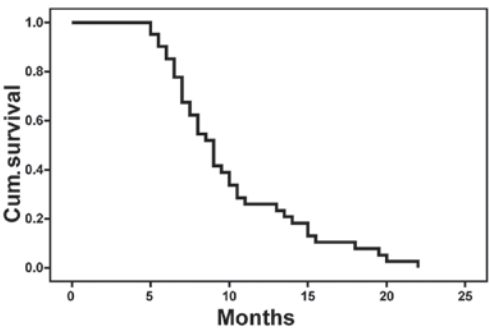


Figure 5. Kaplan-Meier analysis of overall survival for the 41 patients with peritoneal dissemination of gastric cancer enrolled in the present study. The median survival time was 8.6 months and the 1-year survival rate was 24.39%.

useful, and achieved satisfactory clinical outcomes. Another study reported that palliative treatment of ascites with IP instillation of mitoxantrone achieved an average decrease in ascites of ≥50% (31).

In daily clinical practice, CT was used to measure solid tumors, and the Response Evaluation Criteria in Solid Tumors 1.1 criteria (32) was used to determine the response to treatment. Malignant ascites were considered to be a non-evaluable lesion in the present study, since it is difficult to detect using conventional radiological examinations. Therefore, a simple

method of estimating residual peritoneal ascites was established, and new response criteria were developed using B-mode ultrasound examination above the bladder in the longitudinal section. Therapeutic outcomes were categorized as CR, PR and nPR, allowing its use in clinical settings.

The prognosis is poor for patients with macroscopic PC, which is responsible for ~60% of all gastric cancer-associated mortalities (33,34). Two prospective studies assessed outcomes in patients with PC from non-gynecologic malignancies: Gastric, colorectal and pancreatic cancer (6,35). The presence of ascites was associated with poor survival of patients with gastric or pancreatic carcinoma. Analyses of factors prognostic for survival showed that differentiation of the primary tumor did not affect the prognosis of patients with PC. Mean and median OS times in these patients with PC from non-gynecologic malignancies were 6.0 and 3.1 months, respectively (6,35).

In contrast to these earlier studies, which analyzed factors associated with survival in untreated patients, the patients in the present study received HIPC and intravenous chemotherapy. MST in all treated patients was 8.5 ± 0.7 months, being 15.4 ± 5.6 months in the CR group, 9.1 ± 0.9 months in the PR group and 6.9 ± 0.5 months in the nPR group, with significant differences between each pair of groups. These results provided evidence that the presence of ascites was associated with poor survival.

In conclusion, the present study indicated that B-mode ultrasound was effective and feasible in evaluating malignant ascites in patients with gastric cancer, as well as in determining response to treatment. The present study also demonstrated that the combination of HIPC and intravenous chemotherapy was effective and safe in patients with gastric cancer with malignant ascites. The overall response rate was 73.2%, and patients who achieved CR exhibited significantly longer survival compared with those who achieved PR or nPR. Additional studies in larger populations are required to evaluate the efficacy and safety of this combination in carefully selected patients with gastric cancer with peritoneal metastases.

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