**ABSTRACT**

**Background** Gastric cancer is the 2nd leading cause of cancer death worldwide. Malignant bowel obstruction (mbo) is a common complication in advanced gastric cancer because of peritoneal dissemination. A multicentre prospective study reported that patients with peritoneal dissemination of gastric origin survive for a median of 3.1 months. The aim of the present study was therefore to evaluate the efficacy and safety of metronomic combination chemotherapy with 5-fluorouracil and cisplatin in inoperable mbo from peritoneal dissemination in gastric cancer.

**Methods** Gastric cancer patients diagnosed with inoperable mbo because of peritoneal dissemination were treated with infusional 5-fluorouracil 300 mg/m² daily on days 1-5 and 8–12, and cisplatin 5 mg/m² daily on days 1–4 and 8–11 every 3 weeks. The primary endpoint was symptom control (remission of obstruction); the secondary endpoint was symptom control time and survival; the tertiary endpoint was adverse effects.

**Results** Between January 2013 and December 2014, 26 patients received the study treatment. Before treatment, 18 patients (69.2%) were nil per os, and 8 (30.8%) could consume liquids. After a mean of 3.3 cycles of the study treatment, just 4 patients (15.4%) was still nil per os. Of the remaining 22 patients, 3 (11.5%) could consume liquids, 7 (26.9%) could consume soft solids, and 12 (46.2%) ate a full diet. The improved ability to eat was statistically significant \( p < 0.0001 \). Median duration of remission from mbo was 105 days. Median survival was 182 days. The 3-month survival rate was 69.2%, and the 6-month survival rate was 53.8%. Treatment was well tolerated, with grade iii toxicities consisting of thrombocytopenia in 1 patient (3.84%) and mucositis in 2 patients (7.7%). No abnormalities in serum creatinine were observed.

**Conclusions** Metronomic combination chemotherapy with 5-fluorouracil and cisplatin is well tolerated and shows activity in inoperable mbo because of peritoneal dissemination in gastric cancer. Metronomic combination chemotherapy with 5-fluorouracil and cisplatin provides a rationale for exploring this medical problem in the future.

**Key Words** Gastric cancer, malignant bowel obstruction, chemotherapy, 5-fluorouracil

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**INTRODUCTION**

Gastric cancer is the 4th most commonly diagnosed cancer worldwide¹ and has a high incidence in some Asian countries (including China) and in Europe. Although its mortality rate has declined in recent years, gastric cancer remains the 2nd leading cause of cancer death worldwide. Most cases are detected at an advanced stage, which contributes to poor prognosis. The 5-year survival rate in such cases is approximately 20%.² Because of peritoneal dissemination, malignant bowel obstruction (mbo) is a common complication in patients with advanced gastric cancer. A multicentre prospective study reported that patients with peritoneal dissemination of gastric origin survive a median of 3.1 months³.

Although surgery should be considered the primary therapy for mbo, operative treatment might not be feasible in patients with a poor performance status or bulky peritoneal dissemination.
dissemination and massive ascites. A number of options are now available for inoperable patients. Generally, nasogastric drainage should be a temporary measure only. Self-expanding metallic stents are an option in malignant obstruction of the gastric outlet or proximal small bowel, and in colorectal obstruction6–4. Advances in the medical management of mbo can lead to improvement in symptom management and overall quality of life. Medical measures such as analgesics can be used to relieve continuous abdominal pain7. Vomiting can be controlled using anti-secretory drugs, antiemetics, or both8. Somatostatin analogues (for example, octreotide or lanreotide) block the release of vasoactive intestinal polypeptide, which rises in mbo9,10.

Most gastric cancer patients who are diagnosed with mbo from peritoneal dissemination are inoperable. Meanwhile, they can’t eat normally, and so conventional chemotherapy is not recommended. Metronomic chemotherapy is the frequent administration of cytotoxic drugs at doses that are low enough to avoid dose-limiting adverse effects that would otherwise require rest time11. This treatment modality targets tumour cells indirectly by continuously exposing the more slowly proliferating tumour endothelial cells to cytotoxic therapy, thus inhibiting angiogenesis and vasculogenesis12. Low-dose metronomic chemotherapy potentially offers several advantages, including low toxicity and treatment response regardless of the resistance profile of the tumour-cell population13. The fluoropyrimidine 5-fluorouracil is frequently used in the treatment of gastric cancer.

Based on the foregoing observations, we designed and conducted a study to test the activity of metronomic combination chemotherapy with 5-fluorouracil and cisplatin as an approach in patients with mbo. The aim was to evaluate the efficacy and safety of metronomic combination chemotherapy in inoperable mbo from peritoneal dissemination in gastric cancer. The primary endpoint was symptom control (mbo remission). The secondary endpoints were the time to symptom control and survival duration, and the tertiary endpoint was adverse events.

METHODS

Patients
The study included patients 18 years of age and older who were treated at our institution between 1 January 2013 and 31 December 2014 because of a diagnosis of mbo (based on computed tomography imaging) from peritoneal dissemination of gastric cancer, abdominal symptoms arising from mbo (any of nausea or vomiting, abdominal pain, or distention), and no indication for surgery. Inclusion criteria were an Eastern Cooperative Oncology Group performance status of 0–3, adequate bone marrow reserve (white blood cell count > 3.5 × 10^9/L, platelets > 100 × 10^9/L, hemoglobin > 10 g/dL), adequate hepatic and renal function (hepatic enzymes and bilirubin less than twice the upper limit of normal, serum creatinine < 1.4 mg/dL). Patients were ineligible if they had a cognitive disturbance, esophageal obstruction, symptomatic cerebral metastasis, or meningeal dissemination. Patients were also excluded if they had received chemotherapy or radiotherapy within the preceding 28 days or if they had other conditions judged by the investigators to be unsuitable. Written informed consent was obtained from all patients. This study was approved by the institutional review board and the ethics committee of the institution and was conducted in accordance with the Declaration of Helsinki.

Patient Evaluations
Pre-chemotherapy evaluations included documentation of the complete medical oncologic history, physical examination, assessment of performance status, routine chemistry, electrocardiography, and CT imaging of the abdomen. Patients were assessed daily to determine number of vomiting episodes, severity of their nausea, and (if relevant) volume of fluid draining from the nasogastric tube, intensity of pain, and ability for oral intake. A scoring system similar to that used for the assessment of swallowing in patients with mbo was constructed to assess the level of oral intake before and after the procedure14 (Table 1). Adverse events (limited to grade 3 or higher) judged by each investigator to be related to chemotherapy were evaluated according to the U.S. National Cancer Institute’s Common Terminology Criteria for Adverse Events, version 4.

Treatment Plan
The planned administration of 5-fluorouracil consisted of 300 mg/m^2 daily delivered in a continuous intravenous infusion on days 1–5 and 8–12 every 21 days. The 5-fluorouracil was accompanied by a protracted intravenous infusion of cisplatin 5 mg/m^2 daily on days 1–4 and 8–11 every 21 days. During chemotherapy, other medications were continued when necessary. Antiemetics (promethazine), anti-secretory drugs (atropine or raceanisodamine), steroids, octreotide, and rescue opioids (morphine or fentanyl) were allowed, and their use was documented.

Statistical Methods
The primary endpoint was symptom control (mbo remission); secondary endpoints were time to symptom control and survival duration; the tertiary endpoint was adverse effects. Associations between clinical variables were analyzed using the chi-square or Fisher exact test. Survival curves were estimated using the Kaplan–Meier method, and p values were generated using the log-rank test. Numeric data are presented as mean ± standard error. The difference between means was analyzed using the Student t-test. All statistical analyses were performed using the SPSS software application (version 16.0: SPSS, Chicago, IL, U.S.A.). Differences were considered significant at p < 0.05.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Malignant bowel obstruction scoring system</th>
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<tbody>
<tr>
<td><strong>Oral intake</strong></td>
<td><strong>Score</strong></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Liquids only</td>
<td>1</td>
</tr>
<tr>
<td>Soft solids</td>
<td>2</td>
</tr>
<tr>
<td>Full diet</td>
<td>3</td>
</tr>
</tbody>
</table>
RESULTS

Patient Characteristics
The 26 patients presenting with mbo during the study period (January 2013 to December 2014) were all eligible and were enrolled into the study. Table II shows the characteristics of the patients. Median age was 62 years (range: 38–85 years), and the group included 19 men and 7 women.

Dietary Outcome
The patient cohort received a median of 3 cycles of 5-fluorouracil (range: 1–7 cycles; Table III). Before metronomic combination chemotherapy, 18 patients were unable to tolerate any oral intake, and 8 patients were tolerating only liquids. No patients tolerated a diet of soft solids or a full diet. After metronomic combination chemotherapy, only 4 of the 26 patients (15.4%) were still nil per os; 3 (11.5%) could consume liquids, 7 (26.9%) could consume soft solids, and 12 (46.2%) could eat a full diet. The 12 patients who could eat a full diet then underwent conventional chemotherapy with 5-fluorouracil and cisplatin. Overall, 21 of the 26 patients (80.8%) experienced an improvement in their dietary intake. In 5 patients (19.2%), the original dietary intake level did not change, and no patient experienced a worsening of dietary intake level (Table III). Comparing the pre- and post-procedure overall intake scores, we observed a statistically significant improvement ($p < 0.0001$, Table IV). Median time to the start of food consumption was 5.0 days.

Before metronomic combination chemotherapy, almost all the patients complained of nausea, intermittent vomiting, abdominal pain, and bloating. After metronomic combination chemotherapy, 5 patients complained of persistent nausea, intermittent vomiting, abdominal pain, and bloating. Median duration of mbo remission was 105 days (Figure 1).

Adverse Events and Survival
Overall, the chemotherapy regimen was well-tolerated. Grade 3 thrombocytopenia was observed in 1 patient, and 1 patient experienced grade 3 mucositis. In 2 patients, chemotherapy was delayed for 1 week, with thrombocytopenia and mucositis being the cause for the delays. No abnormalities in serum creatinine were observed. From the date of the initial chemotherapy cycle, the overall survival duration was 182 days. The 3-month survival rate was 69.2%, and the 6-month survival rate was 53.8% (Figure 2).

DISCUSSION
Gastric cancer ranks as the 2nd leading cause of cancer death worldwide. In advanced gastric cancer patients, mbo is a common complication because of peritoneal dissemination. The survival rate for gastric carcinoma patients with peritoneal dissemination remains poor because of a lack of effective treatments. A multicentre prospective study reported that patients with peritoneal dissemination of gastric origin survive a median of 3.1 months. From a clinical viewpoint, the main indicators of peritoneal dissemination from cancer are bowel obstruction and ascites. Obstruction gives rise to a vicious cycle of increased intestinal secretions and fluid accumulation, distension, and peristaltic activity. The resultant damage to the intestinal epithelia elicits an inflammatory response. The symptoms—principally continuous abdominal pain,
colic, nausea, and vomiting—typically have a slow onset. Once established, however, symptoms are severe. By impeding oral intake and inducing gastrointestinal symptoms, mbo can have a large negative effect on quality of life. The management of patients with mbo is therefore a significant issue for oncologists.

Because of multiple sites of obstruction and the poor general condition of patients with mbo, surgical treatment and conventional chemotherapy are generally not recommended. Management is likely to require intravenous hydration and parenteral nutrition together with pharmaceutical interventions. In the inoperable patient, the latter include corticosteroids, antiemetics, anti-secretory drugs, analgesics, and somatostatin analogues as symptomatic treatments. If drug therapy has not controlled symptoms, a temporary nasogastric tube might be needed to drain stomach contents and reduce vomiting. Although nasogastric tube placement can result in symptomatic relief for some patients with mbo, complications including mucosal erosion and hemorrhage, esophagitis, and aspiration pneumonia are common.

Metronomic chemotherapy is the regular administration of conventional chemotherapeutic drugs at low, minimally toxic doses, with no prolonged drug-free breaks. This approach is attractive in clinical practice for patients with residual toxicity from earlier treatment and those whose age or frailty mean that they are not considered fit enough for conventional chemotherapy. Metronomic chemotherapy directed against tumour, endothelial or immune cells alters the tumour microenvironment and suppresses innate features supporting tumour growth.

In the present study, we evaluated 26 patients with inoperable mbo resulting from peritoneal dissemination by gastric cancer, demonstrating that metronomic combination chemotherapy with 5-fluorouracil and cisplatin improved subjective symptoms such as nausea, vomiting, and abdominal pain in 80.8% of patients. Before treatment, 18 of 26 patients (69.2%) were nil per os. After metronomic combination chemotherapy, 84.6% of patients (22 of 26) could sustain some oral intake. Median time to mbo remission was 105 days. Median survival duration was 182 days. The 3-month survival rate was 69.2%, and the 6-month survival rate was 53.8%. Treatment was well tolerated,

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dietary status [n (%)]</th>
<th>Mean</th>
<th>Median</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No oral intake</td>
<td>Liquids only</td>
<td>Soft solids</td>
<td>Full diet</td>
</tr>
<tr>
<td>Before treatment</td>
<td>18 (69.2)</td>
<td>8 (30.8)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>After treatment</td>
<td>4 (15.4)</td>
<td>3 (11.5)</td>
<td>7 (26.9)</td>
<td>12 (46.2)</td>
</tr>
<tr>
<td>Dietary status [n (%)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>21/26 (80.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unchanged</td>
<td>5/26 (19.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsened</td>
<td>0</td>
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with the only grade 3 toxicities being thrombocytopenia (1 patient, 3.8%) and mucositis (2 patients, 7.7%; grade 3 in 1 patient, and grade 2 in the other).

Our results show that metronomic combination chemotherapy with 5-fluorouracil and cisplatin is well tolerated and shows activity in MBO resulting from peritoneal dissemination by gastric cancer, providing a rationale for exploring this treatment in the future.

Although this single-arm study is limited with respect to an efficacy evaluation, it is the first such study conducted in this palliative setting. Among its other limitations, the changes in co-treatments during the study period might seem to strongly influence the assessment of the results obtained.

CONCLUSIONS

A high rate of improvement in abdominal symptoms suggests the efficacy of metronomic combination chemotherapy with 5-fluorouracil and cisplatin in inoperable MBO resulting from peritoneal dissemination by gastric cancer. This metronomic combination chemotherapy was well tolerated, and no serious adverse events were reported. Further studies of 5-fluorouracil infusion in patients MBO are needed to determine the best evaluation tools and the most effective combination therapy.

ACKNOWLEDGMENTS

We thank all the participating investigators.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood Current Oncology's policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

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REFERENCES