Complications in advanced or recurrent gastric cancer patients with peritoneal metastasis during and after palliative systemic chemotherapy

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Abstract. Peritoneal metastasis (PM) in gastric cancer (GC) is often the cause of several complications, including ascites and bowel obstruction. The prognosis of patients with extensive PM is poor. There are only limited data available on clinical characteristics regarding the period between the initiation of chemotherapy until the death of the patient. We conducted a retrospective study to determine the frequency of major events during and after palliative chemotherapy in advanced GC patients with PM. The records of patients who received first-line palliative chemotherapy at the Tochigi Cancer Center for locally advanced or metastatic disease were reviewed. The extracted information included treatments received and emerging complications. Overall survival was compared between patients with and those without PM. A total of 97 patients were reviewed and the prevalence of complications with or without concurrent PM were as follows: Bowel obstruction: PM, 37% (16/43) and non-PM, 20% (11/54) (P=0.0664); ascites: PM, 49% (21/43) and non-PM, 7% (4/54) (P<0.0001). The clinical characteristics of patients with PM from GC are unique. Therefore, it is crucial to consider PM as a predictive sign and an important factor when making clinical decisions and developing treatment strategies.

Introduction

The prognosis of patients with unresectable or metastatic gastric cancer (GC) is poor and the median survival time ranges between 6 and 12 months (1-12). Cisplatin (CDDP) and 5-fluoropyrimidine (5-FU) are the most frequently prescribed agents. Various chemotherapeutic agents have been used in an attempt to improve patient survival. Oral fluoropyrimidines (S-1 and capecitabine) plus CDDP were found to be non-infe-

rior to 5-FU plus CDDP (8,12). Furthermore, docetaxel and trastuzumab achieved additional results as first-line treatments in a phase III study (7,13). Although irinotecan failed to demonstrate results as a first-line treatment option in a TOP-003 trial (11), it was found to be non-inferior compared to standard treatment in a first-line setting (5,9).

Peritoneal metastasis (PM) in GC is often the cause of ascites and bowel obstruction. Chau *et al* (14) conducted a multivariate prognostic factor analysis and identified four independent poor prognostic factors, including PM; the patients were classified into good-, moderate- and poor-risk groups, with highly significant differences in survival among the groups.

In order to determine the association between PM and poor prognosis, it is crucial to elucidate the clinical course of the disease. It is, however, difficult to clearly define the patients' clinical characteristics from the pooled data alone. In addition, precise information associated with PM is seldom collected. One of the reasons may be the differences among individual doctors and other observers when classifying identical adverse events. Furthermore, the clinical course of PM varies widely between patients. Finally, following the termination of the protocol treatment, follow-up monitoring is also terminated, resulting in limited availability of information regarding events (i.e., whether the patient is deceased or alive). Therefore, in prospective trials, it is difficult to determine the clinical characteristics over the period between chemotherapy initiation and patient death.

We conducted a retrospective study to determine the frequency of major events during and after palliative chemotherapy in advanced GC patients with peritoneal dissemination.

Patients and methods

Inclusion criteria. The participants were recruited among patients who received first-line chemotherapy for locally advanced or metastatic disease at the Tochigi Cancer Center (TCC; Utsunomiya, Tochigi, Japan) and were selected according to the following criteria: i) Histologically confirmed gastric adenocarcinoma; ii) no history of prior chemotherapy; iii) adequate bone marrow, hepatic and renal function; and iv) absence of synchronous double cancer or other serious illness.

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Table I. Patient characteristics (n=97).

Characteristics	Patient no.	%
Age, years		
Median (range)	65 (33-83)	
Gender		
Male	67	69.0
Female	30	31.0
ECOG performance status		
0	28	29.0
1	54	56.0
2	12	12.0
3	3	3.0
Primary tumor		
Yes	44	45.0
No	53	55.0
Histological type		
Intestinal	37	38.0
Diffuse	51	53.0
Mixed	9	9.0
Metastatic site		
Lymph nodes	46	47.0
Peritoneum	43	44.0
Liver	26	27.0
Bone	4	4.0
Lung	3	3.0
Number of metastatic sites		
1	1	1.0
2	66	68.0
3	30	31.0

ECOG, Eastern Cooperative Oncology Group.

Table II. Treatment regimens.

Regimens	Patient no.	%
First-line (n=97)		
S-1	30	31.0
CPT/CDDP	21	22.0
MTX/5-FU	19	20.0
5-FU continuous infusion	16	16.0
Others	11	11.0
Multiple-line (n=59, 120 regimens)		
Paclitaxel (weekly)	26	21.5
Docetaxel (tri-weekly)	20	17.0
S-1	18	15.0
CPT/CDDP	15	12.5
MTX/5-FU	12	10.0
CPT	12	10.0
Others	17	14.0

CPT, irinotecan; CDDP, cisplatin; 5-FU, 5-fluorouracil; MTX, methotrexate.
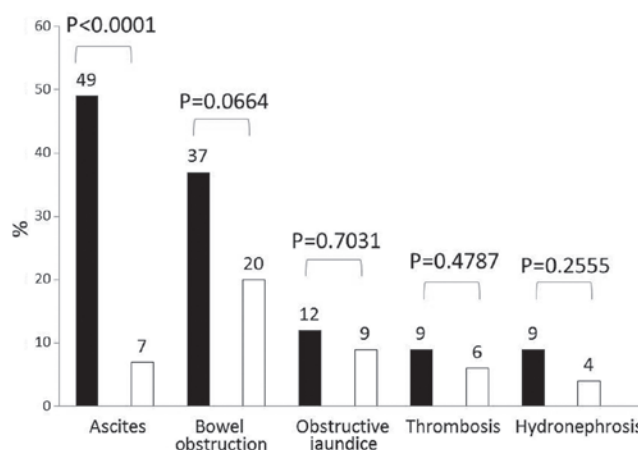

Figure 1. Developed complications in relation to peritoneal metastasis. Black bar, patients with peritoneal metastasis. White bar, patients without peritoneal metastasis.

Diagnositc criteria of complications. The patient records were reviewed and the extracted information included metastatic sites, treatments received, developed complications and overall survival. The complications were determined according to the following criteria: i) Bowel obstruction, diagnostic imaging (air-fluid level formation) and/or decompression tube insertion; ii) ascitic fluid collection, a large amount of ascites and/or therapeutic drain insertion for ascites; iii) obstructive jaundice, biliary drainage and/or jaundice with imaging findings of biliary tree dilatation; iv) hydronephrosis, diagnostic imaging and/or therapeutic insertion of ureteral catheter(s); and v) thrombosis, recorded thrombotic event with abnormal blood tests.

Results

Patient characteristics. A total of 140 patients at TCC received first-line chemotherapy. Of those patients, 43 were excluded as they matched our exclusion criteria and the remaining 97 patients were reviewed and included this analysis (Fig. 2).

The patient characteristics are summarized in Table I. The patients included 67 men and 30 women, with a median age of 65 years (range, 33-83 years). A total of 43 patients had PM prior to chemotherapy, whereas the remaining 54 patients did not have PM (non-PM).

Treatment regimens. The treatment regimens are outlined in Table II. The JCOG9912 and JCOG0106 trials were conducted during the period of our analysis and 30% of the patients at TCC were also enrolled in those trials. The median survival time was 11.7 months and the median follow-up period of the survivors was 17.5 months (range, 1.4-43 months).

Complications. As determined by our diagnostic criteria, the following coexisting illnesses developed in our patients: Bowel obstruction, 28% (27/97), ascites, 26% (25/97), obstructive jaundice, 10% (10/97), thrombosis, 7% (7/97) and hydronephrosis, 6% (6/97) (Table III).
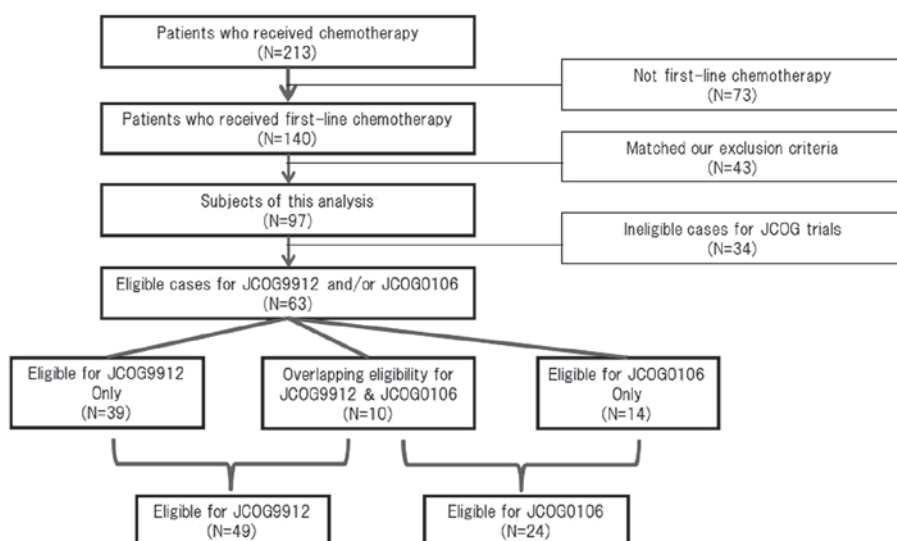
Figure 2. Diagram of this analysis and patient eligibility for the JCOG9912 and JCOG0106 trials at the Tochigi Cancer Center.

Table III. Developed complications.

Complications	Patient no. (n=97)	%
Bowel obstruction	27	28
Ascites	25	26
Obstructive jaundice	10	10
Thrombosis	7	7
Hydronephrosis	6	6

In total, 43 (44%) of our patients had GC with PM (Fig. 1). Of these patients, 16 (37%) developed bowel obstruction, whereas the prevalence of this condition in non-PM patients was only 20% (P=0.0664). There was a statistically significant difference between the two groups regarding the development of ascites, with 21 (49%) of the PM patients compared to only 4 (7%) of the non-PM patients (P=0.0001). Obstructive jaundice (n=5, 12%), thrombosis (n=4, 9%) and hydronephrosis (n=4, 9%) were also encountered more frequently among patients with PM compared to those without PM.

Discussion

The findings of this retrospective study demonstrated that <1/3 of the patients with advanced or recurrent GC developed ascites or bowel obstruction, with a higher frequency among patients with PM. However, development of obstructive jaundice, thrombosis and hydronephrosis was observed in <10% of the patients. There were no differences with regards to metastatic sites.

In phase III trials of metastatic GC, the frequency of patients with PM is ~20-30%. Although the rate of PM is very similar between Western countries and Japan, there is a difference in the frequency of non-target lesions according to the Response Evaluation Criteria In Solid Tumors (RECIST) criteria (15). It is generally considered that the majority of the patients with non-target lesions are patients with PM. The rates of non-target lesions in Japanese trials are higher compared to those in Western trials. One of the reasons for this difference is the eligibility criteria; Japanese trials tend to allow enrollment of patients with vey small metastases that cannot be detected by imaging techniques, but are detectable only by laparotomy. This may provide an explanation as to why patients with PM in the JCOG9912 trial had a better outcome compared to the patients enrolled in Western trials (1-16).

Although several other studies have described PM as a prognostic factor for survival (16-18), the Japanese Clinical Oncology Group (JCOG) indicated in the JCOG9912 trial that PM was not a significant factor (19). The JCOG0106 clinical trial, a phase III, non-platinum comparison trial with eligibility limited only to patients with PM (20), was conducted during the same period by JCOG; patients with extensive PM were not enrolled in this trial due to poor prognosis and the severe toxicity. It is possible that certain investigators preferred to enroll patients with moderate PM in the less toxic JCOG0106 trial.

The JCOG trials assigned patients with PM into two different studies. However, 16% (10/63) of the eligible cases included in the two JCOG trials overlapped (Fig. 2). Selection bias is one reason why the prognostic index of JCOG differed from those of other analyses and any evaluation of their results of a prognostic index should be performed with caution.

Our data suggest unique trends of PM and the present treatment strategy for PM appears to be reasonable. However, there is currently no widely accepted specific treatment for PM; JCOG failed to demonstrate a clear strategy in two trials limited only to patients with PM (JCOG0106 and JCOG0407). Japanese investigators are attempting to establish a PM limited strategy in one of two manners: one group of investigators intends to achieve a survival benefit by intraperitoneal direct infusional chemotherapy (21), similar to the treatment of ovarian cancer, whereas another group is investigating non-platinum systemic treatment with a paclitaxel-based regimen for PM-limited disease (22).

An ongoing trial in cooperation with the West Japan Oncology Group (WJOG) has already completed enrollment and is partly considering the unique clinical course of PM.

The WJOG4007 trial, comparing second-line treatment with irinotecan or paclitaxel, is not limited to PM patients. Even if the prevalence of PM is not extensive at the time of enrollment, it is expected that ~1/3 of the patients will develop PM during cancer progression. A proportion of the PM patients are likely to develop bowel obstruction and would in turn lose their opportunity to receive irinotecan, due to its poor elimination from the intestine and liver. The majority of oncologists tend to avoid selecting irinotecan as a first-line treatment for patients with PM due to its characteristic excretion mechanism. However, certain experienced gastrointestinal oncologists predict disease progression and the development of PM and, therefore, prefer to use irinotecan as early as possible, suggesting that, by using all active chemotherapeutic agents, including irinotecan, patients may achieve a survival benefit.

Our data did not elucidate at which timepoint the complications occur. It is considered that disease progression in cases with PM is closely associated with bowel obstruction and ascites. In general, bowel obstruction and ascites represent typical symptoms and clinical evidence of disease progression in GC patients with PM. It is difficult to assess disease progression in patients with small PM. Japanese investigators recently reported that progression-free survival does not directly reflect on overall survival in GC (23). There may be several reasons for this and we hypothesized that one of the possible explanations is the unique clinical characteristics of PM in GC. The majority of the patients with PM do not have RECIST target lesions; thus, it is very difficult to define a distinct point of disease progression. When conducting control trials by using progression-free survival as a primary endpoint in GC, we must consider enrolling only patients who have target lesions, while indirectly considering bowel obstruction and ascites as progression events.

Our data also suggests that we should consider a change of active regimens in patients with PM when there are clinical symptoms of bowel obstruction and ascites without any definitive progression of metastases on imaging. In the presence of bowel obstruction and massive ascites, it is impossible to continue with anticancer treatment, unless the patient's clinical condition is reversed. The clinical characteristics of patients with PM of GC are unique and it is crucial to consider PM as a predictive sign and an important factor when making clinical decisions and developing treatment strategies.

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