Optimal Treatment Change Criteria for Advanced Gastric Cancer with Non-measurable Peritoneal Metastasis: Symptom/Tumor Marker-based *Versus* CT-based

HIROKO HASEGAWA[1], KAZUMASA FUJITANI[2], SHOICHI NAKAZURU[1], MOTOHIRO HIRAO[3], KAZUYOSHI YAMAMOTO[3], EIJI MITA[1] and TOSHIMASA TSUJINAKA[4]

Departments of [1]Gastroenterology and [3]Surgery, Osaka National Hospital, Osaka, Japan; [2]Department of Surgery, Osaka Prefectural General Medical Center, Osaka, Japan; [4]Department of Surgery, Kaizuka City Hospital, Kaizuka, Osaka, Japan

Abstract. *Background: For advanced gastric cancer (AGC) with peritoneal metastasis, decision-making regarding treatment change is often challenging because of the absence of measurable lesions. We attempted to clarify which criterion for treatment change contributes more to longer survival. Patients and Methods: We retrospectively reviewed 50 patients with non-measurable peritoneal metastasis in whom first-line chemotherapy for AGC was changed based on aggravated clinical symptoms or tumor markers (TMs), or radiologically-confirmed disease progression. Prognostic factors for overall survival (OS) were investigated. Results: Patients whose treatment was changed based on symptoms/TMs had significantly longer OS than patients with computed tomographic-based treatment change (p=0.04). On multivariate analysis, treatment change based on symptoms/TMs was identified as an independent prognostic factor for favorable OS (hazard ratio=0.321, 95% confidence interval=0.154–0.668, p=0.002). Conclusion: The present study suggests that aggravated clinical symptoms/elevated TMs could be a sensitive predictor for disease progression in patients with AGC with non-measurable peritoneal metastasis.*

Gastric cancer is the second most common cause of cancer-related death worldwide, although its global incidence has been declining for several decades (1-3). The current mainstay treatment for advanced gastric cancer (AGC) is systemic chemotherapy with fluoropyrimidine plus platinum, although the prognosis of patients with AGC remains poor, with a median survival time of 10-13 months (4-6).

Peritoneal metastasis, which commonly occurs along with diffuse-type adenocarcinoma, causes many serious complications such as uncontrollable ascites, intestinal obstruction, obstructive jaundice, and hydronephrosis. These complications usually result in complaints such as abdominal fullness, nausea, anorexia, and abdominal pain, and sometimes progress rapidly. Although two clinical trials have been conducted so far (7, 8), no standard treatment has been established for patients with AGC with peritoneal metastasis owing to the absence of measurable lesions that would otherwise enable treatment evaluation by the standard response evaluation criteria in solid tumors (RECIST) (9). In addition, a lack of measurable lesions makes it difficult to determine the optimal timing for treatment change. In these patients, clinical symptoms or tumor markers (TMs) instead of radiological findings are often used to evaluate disease progression. It remains uncertain whether long-term survival is better-achieved by basing treatment change on symptoms and TMs, or on radiological recognition of disease progression.

We attempted to clarify the appropriate criteria for treatment change and evaluated the prognostic significance of various clinicopathological parameters in patients with non-measurable peritoneal metastasis of AGC.

Patients and Methods

Study population. A total of 217 patients with primary unresectable or recurrent gastric cancer were treated at the Osaka National Hospital between April 2005 and March 2012. Out of these, 50 patients fulfilled the following criteria and were enrolled in this retrospective study: histologically proven unresectable or recurrent gastric adenocarcinoma with non-measurable lesions; histologically confirmed peritoneal metastasis or cancer cells on peritoneal lavage cytology without any bowel stenosis or ascites beyond the pelvic cavity; absence of other distant metastatic lesions such as in the liver, lung, bone, lymph nodes, or central nervous system;

Correspondence to: Kazumasa Fujitani, MD, Department of Surgery, Osaka Prefectural General Medical Center, 3-1-56 Bandaihigashi, Sumiyoshi-ku, Osaka, Japan. Zip Code: 558-8558, Tel: +81 666921201, Fax: +81 666067000, e-mail: fujitani@gh.opho.jp

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performance status (PS) of 2 or less on the Eastern Cooperative Oncology Group (ECOG) scale at the initiation of first-line chemotherapy; adequate oral intake; commencement of second-line chemotherapy after the failure of first-line chemotherapy; adequate bone marrow function (WBC count 3,000-12,000/mm^3, platelet count ≤100,000/mm^3, and hemoglobin ≥8.0 g/dl), hepatic function (total bilirubin ≤1.5 mg/dl, serum transaminases ≤100 U/l), and renal function (serum creatinine greater than the upper institutional limit) at the initiation of first-line chemotherapy; no other severe medical conditions; and no concurrent active malignancy.

Criteria for disease progression. While receiving first-line chemotherapy, patients underwent physiological assessments that included digital rectal examination and measurements of three TMs namely carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9, and CA125, every month, and abdominal computed tomographic (CT) scans every 2-3 months. The cut-off values for CEA, CA19-9, and CA125 were 5 ng/ml, 37 U/ml, and 35 U/ml, respectively.

Chemotherapy regimens were changed if progressive disease (PD) developed, as defined by either of the following criteria: aggravated clinical symptoms or elevated TMs, or radiologically confirmed disease progression.

In terms of clinical symptoms, abdominal pain and abdominal distension were assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (10). Disease progression was defined as the appearance of abdominal pain or distension of grade 2 or more, or a growing mass in Douglas' pouch by digital rectal examination.

For TMs, a rise of more than 50% in the initial value of any of the evaluated TMs was defined as disease progression.

Radiological disease progression was defined as peritoneal or mesenteric thickening, new-onset bowel wall thickening, a significant increase in ascites, or the appearance of one or more new lesions.

Statistics. Overall survival (OS) was defined as the time from initiation of first-line chemotherapy to the date of death from any cause or the last follow-up. Time-to-treatment failure (TTF) was defined as the interval between initiation of first-line chemotherapy and treatment discontinuation for any reason, including disease progression, treatment toxicity, patient preference, or death. Both OS and TTF were calculated using the Kaplan–Meier method and compared with the log-rank test. Differences in proportions were evaluated with the Chi-square test, and the significance of age differences was estimated by the Mann–Whitney test. Univariate and multivariate analyses were performed using the Cox proportional hazards model to identify variables independently associated with OS. Statistical results with a *p*-value of less than 0.05 were considered significant.

Results

Patients' characteristics. Clinicopathological characteristics of the 50 patients at the initiation of first-line chemotherapy are shown in Table I. There were 20 males and 30 females with a median age of 62 (range=5-78) years. Forty-five patients had a PS of 0 or 1, and the remaining 5 patients had a PS of 2. Primary gastric cancer was intestinal-type adenocarcinoma in two patients and diffuse-type adenocarcinoma in the remaining 48. Ascites limited to the pelvic cavity was confirmed in 21 patients by CT scan. While 14 patients showed no elevation in pre-treatment serum levels of TMs, the remaining patients demonstrated TM elevations as follows: CEA in 19 patients with a median value of 20.0 (range=0.4-317.0) ng/ml, CA19-9 in 16 patients with a median value of 70.0 (range=1.0-1299.0) U/ml, and CA125 in 11 patients with a median value of 47.3 (range=21.0-412.0) U/ml. In terms of clinical signs or symptoms, abdominal pain of grade 1 occurred in five patients and abdominal distension of grade 1 was observed in seven, whereas the remaining 38 patients had no abdominal findings prior to the initiation of first-line chemotherapy.

Chemotherapeutic regimens. Table II summarizes the chemotherapy regimens administered. As first-line treatment, 34 patients received S-1 combined doublet/triplet chemotherapy (6, 11-15), while 16 patients received S-1 monotherapy (11). The majority of patients were participants in clinical trials and were treated according to trial protocols. For non-trial participants, chemotherapy regimens were chosen at their physicians' discretion. As second-line treatment, an S-1 based regimen (6, 11-14, 16) was administered to 15 patients, taxane monotherapy (17, 18) to 23, and irinotecan-based therapy (17, 19) to 12, which was partly in accordance with the recent global consensus identifying taxanes and irinotecan as standard second-line treatments (20, 21).

Treatment change. As shown in Table III, 24 patients underwent treatment changes based only on aggravated symptoms or elevated TMs, while treatment changes were made in 26 patients after confirmed PD on CT scan. In the 24 patients in the first group, aggravated symptoms included abdominal pain in nine, abdominal distension in five and a growing mass in Douglas' pouch in four, with symptoms overlapped in 2 patients. Of note, only five out of these 24 patients were confirmed as having PD on CT scan even after the decision to change treatments. In contrast, in the 26 patients whose treatments were changed based on CT scan findings, elevated TMs and aggravated symptoms were observed in 14 and 20 patients, respectively, but none underwent treatment change before confirmed PD on CT scan.

Survival according to treatment change criteria. The median OS of all patients was 16.8 months with a median follow-up time of 18.5 months (18.1 months in 41 patients who died and 28.5 months in nine living patients). Twenty-four patients undergoing treatment change based on symptoms or TMs had significantly longer OS than the 26 patients with treatment change based on CT (25.5 months *vs.* 14.3 months, $p=0.04$) (Figure 1). Median TTF for first-line chemotherapy did not differ between these two cohorts (7.8 months in the former 24 patients, and 6.4 months in the latter 26 patients, $p=0.48$) (Figure 2).

Table I. *Patient characteristics at the initiation of first-line chemotherapy*

		n=50
Gender	Male/Female	20/30
Age (years)	60>/60≤	24/26
	Median (range)	62 (25-78)
ECOG PS	0-1/2	45/5
Disease status	Primary/Recurrent	28/22
Histology (Lauren's)	Intestinal/Diffuse	2/48
Ascites	Present/Absent	21/29
Alb (g/dl)	3.5>/3.5≤	21/29
Hb (g/dl)	10>/10≤	21/29
Pretreatment elevated TMs	CEA/CA19-9/CA125	19/16/11
Pretreatment symptoms abdominal pain/abdominal distension/ palpable mass in Douglas' pouch	5/7/0	

ECOG, Eastern Cooperative Oncology Group; PS, performance status; Alb, albumin; Hb, hemoglobin; TMs, tumor markers.

Table II. *Chemotherapy regimens*.

First-line	n=50
S-1 alone	16
S-1 + cisplatin	20
S-1 + irinotecan	2
S-1 + paclitaxel	5
S-1 + docetaxel	4
S-1 + cisplatin + paclitaxel	2
S-1 + cisplatin+ docetaxel	1
Second-line	**n=50**
S-1 alone	8
S-1 + irinotecan	2
S-1 + paclitaxel	2
S-1 + docetaxel	3
Paclitaxel	19
Docetaxel	4
Irinotecan alone	10
Irinotecan + cisplatin	2

Table III. *Reasons for treatment change*.

Based on	n
Symptoms/TMs	24
Elevated TMs (50%)	18
Aggravated symptoms	16
Both elevated TMs and aggravated symptoms	10
CT scan	26

CT: Computed tomography; TMs: tumor markers.

Table IV. *Univariate analysis of prognostic factors for overall survival*.

Prognostic factor	MST (months)	*p*-Value
Gender		
Male	18.4	0.3170
Female	22.3	
PS		
1	19.8	0.2282
2	10.3	
Age (years)		
≤60	18.4	0.4331
>60	17.7	
Histology		
Intestinal	18.4	0.5266
Diffuse	15.7	
Disease status		
Primary	18.4	0.7211
Recurrent	21.8	
Ascites		
Absent	22.3	0.1800
Present	17.7	
Hemoglobin		
<10 g/dl	17.7	0.8936
≥10 g/dl	22.6	
Albumin		
<3.5 g/dl	25.5	0.0275
≥3.5 g/dl	14.3	
Treatment change criteria		
Based on symptoms/TMs	25.5	0.0396
Based on CT scan	14.3	

CT: Computed tomography; MST: median survival time; PS: performance status;
TMs: tumor markers.

Prognostic factors. The results of univariate and multivariate analyses on the impact on OS of various factors such as gender, PS, age, histology, presence of primary tumor and ascites, serum albumin levels, and hemoglobin levels at the initiation of first-line chemotherapy, as well as the treatment change criteria are summarized in Tables IV and V, respectively. When incorporating the potential prognosticators with *p*-values ≤0.15 in univariate analysis, multivariate analysis identified treatment change, based on symptoms or TMs [hazard ratio (HR)=0.321, 95% confidence interval (CI)=0.154-0.668, p=0.002), as an independent prognostic factor for favorable OS.

Discussion

Peritoneal metastasis presents a diagnostic and treatment challenge in patients with AGC. It is often noted initially based on clinical symptoms such as ascites, bowel hypomotility, and bowel obstruction, because radiological tests cannot always detect the spread of malignant cells within the

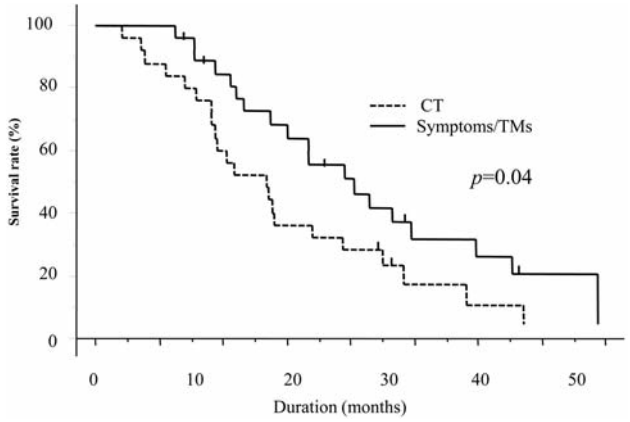

Figure 1. *Overall survival (OS) in patients undergoing treatment change based on symptoms or tumor markers (TMs) compared with that based on computed tomography (CT).*

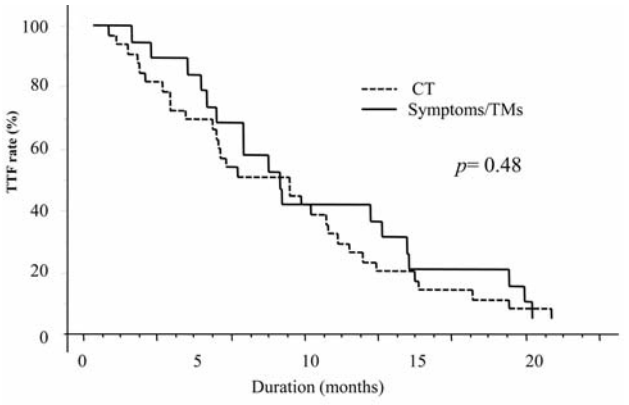

Figure 2. *Time to treatment failure (TTF) on first-line chemotherapy in patients undergoing treatment change based on symptoms or tumor markers (TMs) compared with that based on computed tomography (CT).*

Table V. *Multivariate analysis of prognostic factors for overall survival.*

Prognostic factor	HR	95% CI	*p*-Value
Albumin			
<3.5 g/dl	1.134	0.578-2.225	0.715
≥3.5 g/dl	1		
Treatment change criteria			
Based on symptoms/TMs	0.321	0.154-0.668	0.002
Based on CT scan	1		

HR, Hazard ratio; CI, confidence interval.

peritoneal cavity and no radiological methods have demonstrated a high predictive value for this condition. Therefore, exploratory laparoscopic examination plays a key role in the diagnosis of peritoneal metastasis by direct observation of the peritoneal cavity (22). Chemotherapy is the mainstay of treatment for alleviating symptoms and improving survival in these patients. However, these patients do not usually have measurable lesions according to the RECIST criteria, which makes it difficult to assess the efficacy of chemotherapy based on radiological findings. Therefore, some delay in the diagnosis of PD is unavoidable in patients with only non-measurable lesions and physicians often have to evaluate disease progression by integrating clinical symptoms and changes in TMs.

With respect to the relationship between clinical symptoms and survival, asymptomatic patients generally have a favorable prognosis because those with a higher tumor burden experience symptoms caused by tumor growth (23, 24). However, in this study, OS was better in patients undergoing treatment changes based on symptoms or TMs than in those receiving treatment alterations after PD was proven on CT scan. In cases of peritoneal metastasis, especially non-measurable peritoneal metastasis alone, aggravated clinical symptoms could become a more sensitive predictor for disease progression, while PD detected by CT scan might reflect a comparatively higher tumor burden. Similarly, symptom alleviation was able to sensitively predict disease control by systemic chemotherapy in patients with advanced pancreatic cancer (25).

Among 18 patients in whom elevated TMs led to treatment change (Table III), a rise of more than 50% in the initial values of CEA, CA19-9, and CA125 was observed in 12, 10, and 5 patients, respectively (data not shown). A previous study found that an increase in initial values of TMs greater than 50% correlated well with disease progression in patients with AGC under first-line chemotherapy (26). CEA and CA19-9 have been shown to be the most useful markers for monitoring PD in gastric cancer (27-29), and the biological relevance of CA125 in the progression or reduction of peritoneal metastasis from AGC has been recently demonstrated (30, 31). In the present study, a more than 50% rise in initial values of TMs showed promise for detecting PD in patients with non-measurable peritoneal metastasis. For other TMs, CA72-4 or the combination of CA72-4 and CA125 are expected to be highly specific for peritoneal metastasis from AGC (31-35), thereby sensitively reflecting disease progression (27, 30).

When comparing the OS and TTF shown in Figures 1 and 2, post-progression survival, defined as the time from recognition of disease progression on first-line chemotherapy to death from any cause or last follow-up, was shorter in patients undergoing treatment change after confirmed PD on CT scan, which suggests a higher tumor burden in these patients at the point when the decision is made to switch to second-line treatment.

Regarding other modalities for diagnosing progression of non-measurable peritoneal metastasis, ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) would be unreliable because of its low sensitivity for diffuse-type gastric adenocarcinoma (36).

Although the prognostic factors shown in Tables IV and V have been identified for patients with AGC undergoing first-line chemotherapy (37-41), treatment change based on symptoms or TMs was chosen as an independent prognostic factor in our patient cohort with non-measurable peritoneal metastasis. This was partly due to our unique approach of noting treatment change irrespectively of the presence of radiologically-confirmed PD.

The limitations of this study, which include its retrospective, single-Institution nature, and the relatively small sample size of 50 patients, need to be taken into account before generalizing the results to daily clinical practice until prospective, multi-center validation is available. However, we believe that our findings will help physicians prognosticate disease course and facilitate decision making on switching to second-line treatments.

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