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Conflict of Interest The authors have no conflict of interest.

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Clinical Significance of Cytological Status of Peritoneal Lavage Fluid During Intraperitoneal Chemotherapy for Gastric Cancer with Overt Peritoneal Dissemination

Shigenobu Emoto, MD, Joji Kitayama, MD, Hironori Ishigami, MD, Hironori Yamaguchi, MD, and Toshiaki Watanabe, MD

Department of Surgical Oncology, The University of Tokyo, Bunkyo-ku, Tokyo, Japan

ABSTRACT

Background. A positive cytology of peritoneal lavage fluid (CY1) is a poor prognostic factor in patients with gastric cancer (GC). We have recently reported that CY1 often changes to negative (CY0) following combination chemotherapy including intraperitoneal (IP) paclitaxel (PTX), which results in marked prolongation of survival in GC patients with peritoneal dissemination (P1).

Methods. A total of 95 P1 GC patients who received combination chemotherapy with S-1 and intravenous and IP PTX were enrolled. Peritoneal lavage fluid was periodically examined cytologically at the start of every cycle of chemotherapy, and the impact of CY status on patient outcome was retrospectively evaluated.

Results. Seventy-three (76.8 %) of 95 patients were diagnosed as CY1 before initial treatment. Median survival time (MST) of the CY1 group was significantly shorter than that of the CY0 group (19.1 vs. 32.5 months, $P = 0.033$). Cytological status changed from CY1 to CY0 in 68 (93.2 %) of 73 CY1 patients during the whole treatment period and MST of patients who showed a negative change was significantly longer than that of the unchanged group (20.0 vs. 13.0 months, $P = 0.0017$). In 64 patients who achieved CY0 by IP PTX regimen, the median time to achieve CY0 was 1.4 months, and patients who achieved a negative change within 1 month showed a particularly good outcome (MST = 26.1 months).

Conclusions. Periodic cytological examination of peritoneal lavage fluid is clinically useful to evaluate the efficacy of treatment as well as to predict the outcome of patients with P1 GC.

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J. Kitayama, MD
e-mail: kitayama-1su@h.u-tokyo.ac.jp

Peritoneal dissemination (P1) is the most common metastatic pattern in gastric cancer (GC) and has an extremely poor prognosis.[1,2] Thus far, most patients with P1 GC have only been treated palliatively. However, recent studies have demonstrated that intraperitoneal (IP) chemotherapy is safe and effective for patients with peritoneal metastasis, although the biomarkers to evaluate the response to this treatment and to predict the outcome of the patient has not been well known yet.[3–6]

A positive result of cytological examination of peritoneal lavage fluid (CY1) is considered to be a poor prognostic factor in GC.[7–9] Based on these results, CY1 is considered the same as distant metastasis (M1) regardless of the presence of peritoneal metastasis, both in the TNM classification and in the Japanese classification by the Japanese Gastric Cancer Association.[10,11] However, macroscopic peritoneal metastasis (P factor) is generally considered a stronger prognostic indicator than CY factor and a negative result of cytological examination of peritoneal lavage fluid (CY0) in patients with overt peritoneal dissemination tended to be considered a false negative result, and thus the clinical significance of CY status in P1 patients has not been studied extensively.

Recently, in Japan, repeated IP chemotherapy using an IP access port combined with systemic treatment has been introduced for the treatment of peritoneal carcinomatosis, which has resulted in a notable improvement in outcome of patients with P1 GC.[12–18] In these series, peritoneal fluid could be easily obtained from the subcutaneously placed port before every cycle of IP infusion of anticancer drugs, and CY status could be periodically examined during

treatment. In fact, the rate of reversion to negative cytology in CY1 patients has been reported as 56–97 % in these studies.[12–18] This is far higher than the rate in a previous study of systemic neoadjuvant chemotherapy in which only 7 (36.8 %) of 19 patients achieved a negative change in CY status.[19] However, the clinical significance of CY status before and after chemotherapy has not been studied extensively in P1 GC patients.

In this study, we retrospectively studied the CY status of patients with P1 GC who received intravenous (IV) and IP paclitaxel (PTX) combined with oral S1 and investigated the relationship between the change of CY status and clinicopathological factors/survival.

PATIENTS AND METHODS

Patients

The clinical records of 95 patients who were primarily diagnosed as GC with peritoneal metastasis (P1) and received combination chemotherapy, including IP PTX, at The University of Tokyo Hospital from 2005 through 2012 were retrospectively analyzed. Among them, 39 patients had received systemic chemotherapy in other hospitals before receiving the IP PTX regimen, whereas the other 56 patients had not received previous chemotherapy. All patients provided written, informed consent for their records to be used in the clinical study before receiving treatment. This study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the University of Tokyo. The degree of peritoneal metastasis was evaluated according to the first English edition and the 12th edition of the Japanese Classification of Gastric Carcinoma (P0: no peritoneal metastases; P1: adjacent peritoneal involvement; P2: a few scattered metastases to distant peritoneum; P3: many distant peritoneal metastases).[20] The eligibility criteria for initiation of IP chemotherapy were previously described.[21] In brief, inclusion criteria were as follows: histologically proven unresectable gastric adenocarcinoma; peritoneal metastasis; over 20 years of age; Eastern Cooperative Oncology Group performance status of 0–2; adequate bone marrow, liver, and renal function; and an expected survival period of more than 3 months.

Chemotherapy, Cytological Examination of Peritoneal Lavage Fluid, and Conversion Surgery

Staging laparoscopy was performed at the start of treatment in all patients, and a peritoneal access port was implanted in the subcutaneous space of the lower abdomen, with a catheter placed in the pelvic cavity.[22] The chemotherapy regimen consisted of S-1 and IV and IP PTX as described previously.[15] In brief, S-1 was administered orally twice a day at a dose of 80 mg/m^2/day for 14 consecutive days, followed by 7 days' rest. PTX was administered IV at a dose of 50 mg/m^2 and IP at 20 mg/m^2 on days 1 and 8. PTX was diluted in 1 liter of normal saline and administered through the implanted peritoneal access port over 1 h concurrently with IV infusion after standard premedication. The combination chemotherapy was repeated until disease progression or intolerable toxicity.

Peritoneal lavage fluid was collected via the implanted peritoneal access port just before PTX administration, with minimal invasiveness for patients, and cytological examination was performed with Papanicolaou staining during every cycle of IP chemotherapy. The relations between clinicopathological features and CY status were evaluated. Survival analyses according to CY status and change in CY status were performed. We defined negative change of CY status in CY1 patients as three consecutive negative cytological examinations during IP treatment. We also defined positive change of CY status in CY0 patients as three consecutive positive cytological examinations during IP treatment except within 3 months before stopping IP chemotherapy or death.

All patients who achieved a negative change in cytological status underwent second-look staging laparoscopy, and conversion gastrectomy was considered when peritoneal metastasis had disappeared or was markedly reduced without the appearance of other metastatic lesions, and general condition of the patients is tolerable for gastrectomy.

Statistical Analyses

The relations between clinicopathological features and CY status were evaluated using Chi squared test and Fisher's exact test. Survival rates were calculated according to the Kaplan–Meier method, and differences were evaluated using the log-rank test. All statistical analyses were performed using the JMP program version 9.0 (SAS Institute, Cary, NC).

RESULTS

CY Status before Treatment and Survival Analysis

In the 95 patients, 73 (76.8 %) patients were diagnosed as CY1 before treatment. The relationships between clinicopathological features and the CY status before treatment are shown in Table 1. The degree of peritoneal metastasis

TABLE 1 Clinicopathological factors and peritoneal lavage cytological status

	N	CY0	CY1 (%)	Univariate analysis			Multivariate analysis		
				OR	95 % CI	*P*	OR	95 % CI	*P*
Total	95	22	73 (76.8)						
Age (year)									
>57	46	10	36 (78.3)	1.17	0.45–3.04	0.81			
≤57	49	12	37 (75.5)						
Sex									
Male	54	9	45 (83.3)	2.32	0.88–6.14	0.094	2.49	0.85–7.69	0.096
Female	41	13	28 (68.3)						
Performance status									
0	70	20	50 (71.4)	0.22	0.047–1.01	0.052	0.24	0.03–1.01	0.052
1, 2	25	2	23 (92.0)						
Macroscopic type									
Type 4	61	12	49 (80.3)	1.70	0.64–4.49	0.32			
Other	34	10	24 (70.6)						
Histological type									
Diffuse	76	16	60 (79.0)	1.73	0.57–5.27	0.37			
Other	19	6	13 (68.4)						
Peritoneal metastasis									
P1, P2	30	11	19 (63.3)	0.35	0.13–0.94	0.041	0.49	0.16–1.53	0.22
P3	65	11	54 (83.1)						
Ascites									
Absent	33	12	21 (63.6)	0.34	0.13–0.90	0.040	0.49	0.14–1.70	0.26
Present	62	10	52 (83.9)						
CEA									
Normal	80	19	61 (76.3)	1.25	0.32–4.88	1.00			
Elevated	15	3	12 (80.0)						
CA19-9									
Normal	63	13	50 (79.4)	0.66	0.25–1.78	0.45			
Elevated	32	9	23 (71.9)						
CA125									
Normal	47	15	32 (68.1)	0.37	0.17–1.00	0.054	0.83	0.24–2.88	0.77
Elevated	48	7	41 (85.4)						

P1 adjacent peritoneal involvement, *P2* a few scattered metastases to distant peritoneum, *P3* many distant peritoneal metastases

and presence of ascites were correlated with CY status in univariate analysis, but no factor was independently correlated with CY status in multivariate analysis.

Median follow-up time was 21.6 months. Overall survival curves constructed with respect to the CY status before treatment are shown in Fig. 1. Median survival time (MST) of P1CY0 group was 32.5 months, which was significantly longer than that of P1CY1 group (19.1 months) ($P = 0.033$). In univariate analysis, CY1 as well as PS1/2, presence of ascites, elevated CA125 were significantly correlated with poor outcome in those patients. In multivariate analysis, however, CA125, but not CY1, was determined to be an independent poor prognostic factor (data not shown).

Change of CY Status during Treatment

Changes in CY status during chemotherapy are shown in Fig. 2. Thirty-nine patients had received systemic chemotherapy before receiving the combination chemotherapy including IP PTX, whereas the other 56 patients had not received previous chemotherapy before the IP PTX regimen. In the former 39 patients, 27 were CY1 before the initial treatment. Four of the 27 (14.8 %) cases changed to CY0 with systemic chemotherapy, whereas the other 23 cases remained CY1. Of these 23 patients, 22 (95.7 %) patients reverted to CY0 with the IP PTX regimen. In the latter 56 patients, 46 patients were diagnosed as CY1, and 42 (91.3 %) of the 46 patients achieved CY0 with the IP

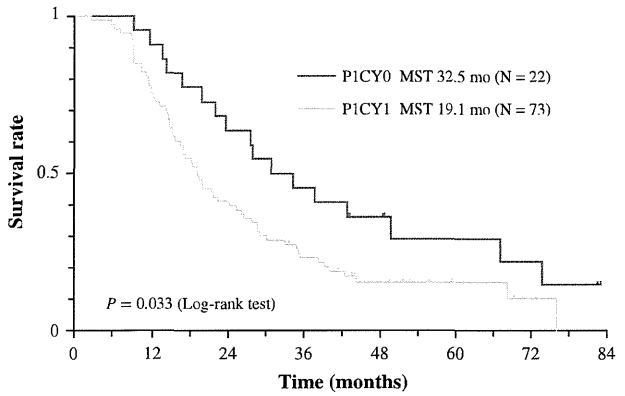

FIG. 1 Overall survival curves constructed with respect to CY status before treatment. Median survival time (MST) of P1CY0 group was significantly longer than that of P1CY1 group (32.5 vs. 19.1 months, $P = 0.033$)

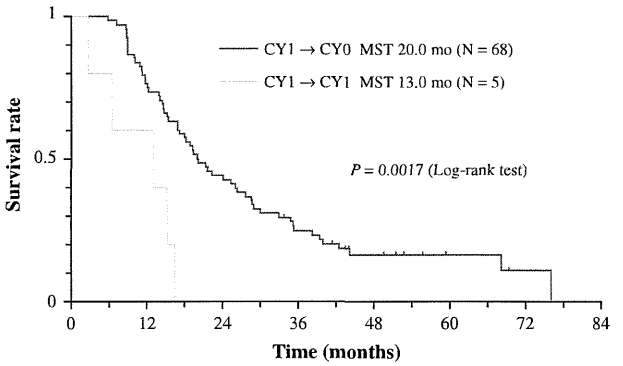

FIG. 3 Overall survival curves constructed with respect to change in CY status during treatment. MST of those who achieved a negative change in CY status was 20.0 months, whereas that of those who did not achieve a negative change in CY status was 13.0 months ($P = 0.0017$)

PTX regimen. All 22 patients who were CY0 before treatment remained CY0 throughout the observation period. In total, 68 (93.2 %) of 73 patients who were CY1 before treatment achieved CY0 during the whole treatment period, and 64 (92.7 %) of 69 CY1 patients reverted to CY0 with the IP PTX regimen.

All patients who achieved a negative change in cytological status underwent second-look staging laparoscopy, and conversion gastrectomy was performed in 53 (55.8 %) of the 95 patients in whom peritoneal metastasis had disappeared or was markedly reduced without the appearance of other metastatic lesions. The rate of conversion in each subgroup was shown with their outcome in Fig. 2. In those patients who received conversion surgery, patients with CY0 before treatment appears have better outcome than those who changed to CY0 from CY1, although it should be evaluated in the study with more sample number. In P1CY1 patients, MST of those who achieved a negative change in CY status was significantly longer than that of those who did not achieve a negative change in CY status (20.0 vs. 13.0 months, $P = 0.0017$; Fig. 3).

Impact of Time to Negative Change in CY Status with IP-PTX Regimen

In the 69 patients who were diagnosed as CY1 before the combination chemotherapy, including IP PTX, 64 patients achieved CY0 after the IP PTX regimen. However, the time to a negative change in CY status varied among patients. Fifty-four (79.4 %) of 69 patients achieved a

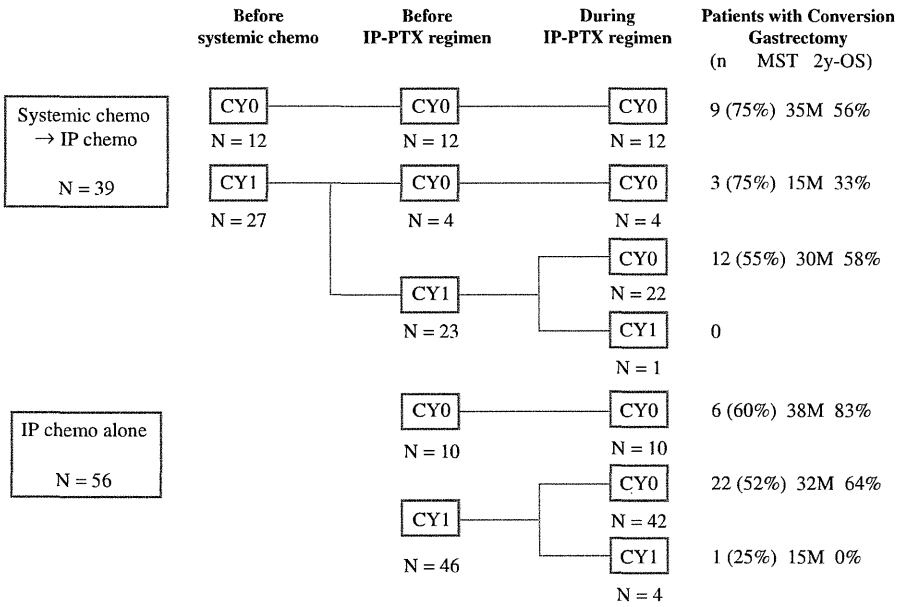

FIG. 2 Changes in CY status during IP chemotherapy. The changes of CY status and the number (rate) of the patients who received conversion gastrectomy and their MST and 2-year survival rate were expressed in each subgroup. Conversion gastrectomy was totally performed in 52 patients with CY0 status and in 1 patient with P1CY1 status due to the strong desire of the patient

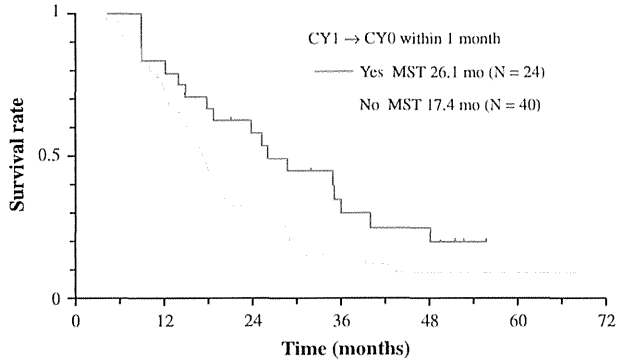

FIG. 4 Survival from start of IP chemotherapy with respect to time to negative change in CY status during treatment. Patients who achieved a negative change in CY status within 30 days showed excellent survival compared with others

negative change within 6 months, and the median time to a negative change was 1.4 months. In particular, 24 (37.5 %) patients showed a negative change in CY status within 1 month (the first cycle of IP PTX regimen) from the introduction of IP PTX. MST of these patients was 26.1 months, which tended to be longer compared with the other 40 patients in whom the achievement of CY0 took more than 1 month (MST = 17.4 M; Fig. 4).

DISCUSSION

Recently, we and others have developed a new treatment strategy—neoadjuvant intraperitoneal and systemic chemotherapy (NIPS)—for P1 GC, which appears to produce significant survival benefits for those patients.[12,13, 15,16] The key point of this treatment method is that anticancer drugs can be repeatedly administered into the abdominal cavity via an IP access port, together with systemic chemotherapy. In particular, PTX can be successfully used for IP chemotherapy through its pharmacokinetic advantages, which results in MST of more than 20 months and 1-year survival of greater than 70 % in patients with P1 GC.[15,18,23] In these patients, we periodically examined the CY status during the course of chemotherapy and examined the impact of CY status on the outcome of patients who received combination chemotherapy using IP PTX.

The first finding in this study is that the P1CY0 group showed significantly better survival compared with the P1CY1 group in univariate analysis, although this was not an independent prognostic factor in multivariate analysis. Previous studies have shown similar results in patients with GC who did not have IP chemotherapy, whereas others have suggested that CY status is not an independent prognostic factor and thus a more accurate system to detect IP free cancer cells is needed.[7,8,24–26] Our results indicate that CY1 before treatment is somehow related to the outcome even in patients with overt peritoneal metastasis who were treated with IP chemotherapy.

In our series, however, 93.2 % of CY1 patients changed to CY0 after the combination chemotherapy, including IP PTX, and a negative change in CY status was significantly correlated with better outcome. Only one previous study showed that a negative change in CY status in the course of neoadjuvant systemic chemotherapy was an independent good prognostic factor, although the rate of negative change in cytological status was much lower than ours.[19] Our results, together with theirs, suggest that CY status during cyclical IP chemotherapy well reflects the efficacy of IP as well as systemic chemotherapy, and thus could be a powerful predictive indicator of the outcome of patients with P1 GC.

An important advantage of our treatment strategy is that peritoneal fluid can be repeatedly obtained from the access port, which enables the close monitoring of peritoneal cytological status during the course of IP chemotherapy. Because peritoneal lesions are usually too tiny to be evaluated by conventional CT imaging (with a RECIST system), CY status is useful information for evaluating the real efficacy of chemotherapy for peritoneal lesions. Indeed, we could accurately evaluate the time taken to revert to CY0 in those patients, which revealed that the time to a negative change of peritoneal cytological status is fairly variable. In fact, CY reverted to negative within 1 cycle of the combination chemotherapy in 24 cases, and, interestingly, survival of those patients tended to be better than that of others in whom it took more than several courses to achieve CY0.

In our series, patients who achieved CY0 usually underwent second-look staging laparoscopy, and if peritoneal metastasis had disappeared or were markedly reduced, we performed gastrectomy in a salvage setting. Therefore, the prolonged survival of the negative change group might be attributable to gastrectomy. However, the benefit of the gastrectomy is undefined yet. In fact, we performed the combination chemotherapy for 2–12 cycles with median value of 3 before conversion surgery and continued the same regimen as long as possible after surgery, which resulted in an excellent outcome in 52 patients with CY0 status, but not in one patient with remaining CY1. This suggests that the CY status could be a useful biomarker to determine the indication for salvage gastrectomy during IP chemotherapy. The real contribution of gastrectomy to the outcome of P1 GC should be examined by a controlled study in the future.

In summary, cytological examination of peritoneal lavage fluid is the most common and easiest way to evaluate the tumor volume of peritoneal metastasis at present, and thus it should be periodically performed to evaluate the response of peritoneal lesions to treatment. The sensitivity

of conventional cytological examination of peritoneal lavage fluid in detecting IP free cancer cells is lower than that of other new methods such as RT-PCR of CEA-mRNA and immunocytochemical detection using flow cytometry.[6,27] More accurate quantification of tumor cells in the peritoneal cavity using these methods should be used as a reliable biomarker to determine the treatment strategy in patients with P1 GC.

CONCLUSIONS

Periodic cytological examination of peritoneal lavage fluid in the course of IP chemotherapy is useful to evaluate the efficacy of treatment and a negative change of the cytological status is a predictive indicator of the outcome in GC with peritoneal dissemination.

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