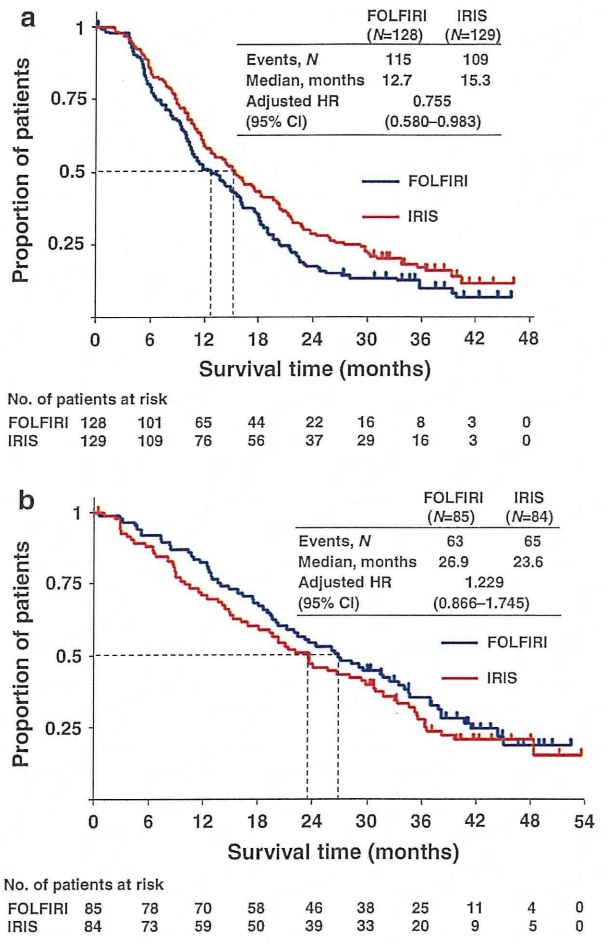

Fig. 4 Survival according to prior chemotherapy with oxaliplatin (**a**) or without oxaliplatin (**b**). *IRIS* irinotecan plus S-1, *FOLFIRI* infusional 5-fluorouracil, folinic acid, and irinotecan, *HR* hazard ratio, *CI* confidence interval

article to the memory of Prof. Hiroya Takiuchi, who contributed to the conception and design of this study. The senior academic authors designed the trial in cooperation with the study sponsors. The sponsors provided funding and organisational support, collected data, and performed analyses, but did not undertake any data interpretation. This report was written by the corresponding author (with additional input from the other authors), who had unrestricted access to the raw study data, gives assurance for the accuracy and completeness of the reported analyses, and had final responsibility for the decision to submit for publication. This work was funded by Taiho Pharmaceutical Co. Ltd., Japan, and Daiichi Sankyo Co. Ltd., Japan.

Conflict of interest The authors declare no conflict of interest.

Appendix (participating institutes): FIRIS Study Group

List of participating institutions in order of patient recruitment:

Shizuoka Cancer Center (Shizuoka, Japan); Aichi Cancer Center Hospital (Nagoya, Japan); National Cancer Center Hospital (Tokyo, Japan); Kochi Health Sciences Center (Kochi, Japan); Gunma Prefectural Cancer Center (Gunma, Japan); Kumamoto University Hospital (Kumamoto, Japan); Kinki University School of Medicine (Osaka, Japan); Chiba Cancer Center (Chiba, Japan); Nagoya Memorial Hospital (Nagoya, Japan); National Hospital Organization Shikoku Cancer Center (Matsuyama, Japan); Saitama Cancer Center (Saitama, Japan); Osaka Medical College Hospital (Takatsuki, Japan); National Kyushu Cancer Center (Fukuoka, Japan); Osaka City General Hospital (Osaka, Japan); Gunma University Graduate School of Medicine (Maebashi, Japan); Hokkaido University Hospital Cancer Center (Sapporo, Japan); National Hospital Organization Kyoto Medical Center (Kyoto, Japan); Keio University Hospital (Tokyo, Japan); Kansai Rosai Hospital (Hyogo, Japan); Tokyo Medical and Dental University (Tokyo, Japan); Osaka Medical Center for Cancer and Cardiovascular Diseases (Osaka, Japan); Aomori Prefectural Central Hospital (Aomori, Japan); Showa University Toyosu Hospital (Tokyo, Japan); Minoh City Hospital (Osaka, Japan); Saiseikai Kumamoto Hospital (Kumamoto, Japan); Toyama University Hospital (Toyama, Japan); National Hospital Organization Kagoshima Medical Center (Kagoshima, Japan); Tonan Hospital (Sapporo, Japan); Kanagawa Cancer Center (Yokohama, Japan); Niigata Cancer Center Hospital (Niigata, Japan); Saku Central Hospital (Nagano, Japan); Hyogo Cancer Center (Hyogo, Japan); Hiroshima University Hospital (Hiroshima, Japan); Tomakomai Nissho Hospital (Hokkaido, Japan); Aichi Cancer Center Aichi Hospital (Aichi, Japan); National Hospital Organization Nagoya Medical Center (Nagoya, Japan); Kobe University Hospital (Kobe, Japan); Yamagata Prefectural Central Hospital (Yamagata, Japan); Yokohama City University Hospital (Yokohama, Japan); and Kitasato University East Hospital (Kanagawa, Japan).

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Original Article

Clinicopathological Features and Outcomes of Gastric Cancer Patients with Pulmonary Lymphangitis Carcinomatosa

Taro Funakoshi[1,2,*], Hirofumi Yasui[1], Narikazu Boku[3], Akira Fukutomi[1], Kentaro Yamazaki[1], Nozomu Machida[1], Akiko Todaka[1], Takahiro Tsushima[1], Tomoya Yokota[1], Yusuke Onozawa[4], Hirotsugu Kenmotsu[5] and Masahiro Endo[6]

[1]Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Nagaizumi-tyo, [2]Department of Clinical Oncology, Kyoto University Hospital Cancer Center, Kyoto, [3]Department of Clinical Oncology, St. Marianna University School of Medicine, Kawasaki, [4]Division of Clinical Oncology, Shizuoka Cancer Center, Nagaizumi-tyo, [5]Division of Thoracic Oncology, Shizuoka Cancer Center, Nagaizumi-tyo and [6]Division of Diagnostic Radiology, Shizuoka Cancer Center, Nagaizumi-tyo, Japan

*For reprints and all correspondence: Taro Funakoshi, Kyoto University Hospital, 54, Kawaharacho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan. E-mail: tarofun@kuhp.kyoto-u.ac.jp

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Objective: Breast, gastric and lung cancers are the most common cancers that cause pulmonary lymphangitis carcinomatosa. However, little is known about the clinical features of pulmonary lymphangitis carcinomatosa in advanced gastric cancer.

Methods: We retrospectively reviewed the data throughout the clinical courses of 33 patients with gastric cancer who developed pulmonary lymphangitis carcinomatosa. Pulmonary lymphangitis carcinomatosa was confirmed by both a pulmonologist and a diagnostic radiologist on the basis of computed tomography findings of interstitial patterns such as thickening or irregularity of interlobular septa and bronchovascular bundles.

Results: The median age of the 33 patients was 55 years old (range, 25–73 years). The percentages of female patients, those with performance status 3 or 4, and those with respiratory symptoms at diagnosis were 70, 36 and 76%, respectively. The histologically diffuse type of gastric cancer accounted for 85% of cases. Mediastinal lymph node, peritoneal and bone metastases were found in 64, 61 and 39% of patients, respectively. Disseminated intravascular coagulation was noted in 21% of patients. The median survival time of the 18 chemotherapy-naïve patients treated with chemotherapy was 5.7 months (range, 0.4–37.0 months). Two patients obtained symptomatic relief, and one patient treated with S-1 + cisplatin + sunitinib survived >3 years.

Conclusions: Pulmonary lymphangitis carcinomatosa caused by gastric cancer has some specific clinicopathological features. While the prognosis of gastric cancer patients with pulmonary lymphangitis carcinomatosa is extremely poor, some patients may have survival benefit from chemotherapy.

Key words: lymphangitis – gastric cancer – chemotherapy – disseminated intravascular coagulation

INTRODUCTION

Gastric cancer is the fourth most common cancer and second leading cause of cancer death worldwide (1). In Japan, gastric cancer is the most common cancer and second leading cause of cancer death (2). The prognosis of unresectable or recurrent gastric cancer is very poor: the median survival time (MST) is ~4 months with best supportive care (BSC) (3–5). Since the late 1990s, several randomized trials testing new treatments

for advanced gastric cancer have shown a survival benefit of chemotherapy. Combination chemotherapy with fluoropyrimidine and platinum is used as the standard first-line treatment (6, 7). Furthermore, second-line chemotherapy with paclitaxel (PTX), docetaxel or irinotecan (CPT-11) prolongs survival, resulting in a MST from diagnosis of ~1 year (8, 9). However, the subjects of these clinical trials are generally limited to patients in good condition.

Pulmonary lymphangitis carcinomatosa (LC) is one of the specific patterns of lung metastasis characterized by extensive lymphatic permeation and embolism in lymph capillary by tumor cells. This condition is characterized by respiratory symptoms such as cough and dyspnea, and is associated with a poor prognosis. Bruce et al. (10) reviewed 374 case reports in 1996 and found that breast, gastric and lung cancers are the most common tumor types that cause LC; moreover, half of the patients died within 3 months after the first appearance of respiratory symptoms. Thus, the development of effective treatments for patients with LC is urgently required. However, patients with LC are generally excluded from clinical trials because of their poor condition.

Data about the clinical features and outcomes of patients complicated with LC, especially the efficacy of systemic chemotherapy, are limited even though advanced gastric cancer sometimes causes LC.

In this study, we retrospectively investigated the clinicopathological features and outcomes of gastric cancer patients with LC.

PATIENTS AND METHODS

Patient Selection

The electric medical charts throughout the clinical courses of all patients in the Shizuoka Cancer Center from its establishment in September 2002 to December 2011 were screened using the search terms, 'lymphangitis carcinomatosa' and 'gastric cancer', in both Japanese and English. The computed tomography (CT) findings of the candidates for this study were independently reviewed by two doctors: a pulmonologist and a diagnostic radiologist. LC was diagnosed on the basis of CT findings showing interstitial patterns such as thickening or irregularity of interlobular septa and bronchovascular bundles (Fig. 1a). Subjects were selected if they met the following criteria: (i) histologically proven adenocarcinoma, (ii) diagnosis of LC confirmed on at least one CT examination and (iii) medication and follow-up by the physicians of the Shizuoka Cancer Center. Histological confirmation of LC was not mandatory. Patients with suspected infection or pulmonary edema and interstitial pneumonitis because of other reasons were excluded. We retrospectively obtained the clinical data of all subjects from medical records. Cough and dyspnea persisting >1 week were specified as the respiratory symptoms caused by LC. This study was approved by the ethical committee of Shizuoka Cancer Center.

Treatments

The choice of treatment—BSC or chemotherapy—was at the physician's discretion. The chemotherapy regimens were as follows: methotrexate (100 mg/m^2, intravenous bolus) and fluorouracil (5-FU, 600 mg/m^2, intravenous bolus) weekly (MF), a combination of S-1 (40 mg/m^2, orally twice daily, Days 1–21) and cisplatin (CDDP, 60 mg/m^2, intravenously, Day 8) every 5 weeks (SP), SP plus sunitinib (clinical trial (11)), S-1 monotherapy (40 mg/m^2, orally twice daily, Days 1–28) every 6 weeks, CPT-11 (60 mg/m^2, intravenously) plus CDDP (30 mg/m^2, intravenously) biweekly and PTX (80 mg/m^2, intravenously, Days 1, 8 and 15) every 4 weeks. The chemotherapy regimen for each patient was selected by the physician, who modified the dose of each agent according to adverse events and the patient's general condition. Chemotherapy was initiated after obtaining written informed consent from each patient.

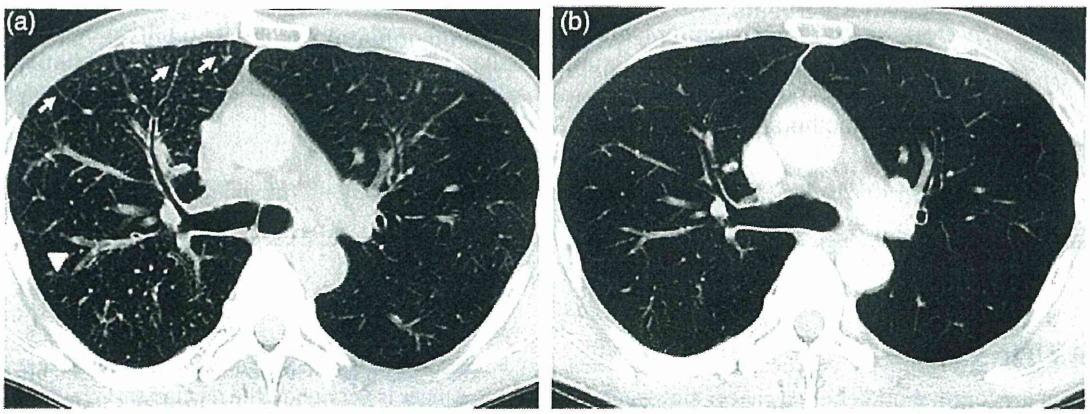

Figure 1. (a) High resolution computed tomography (HRCT) at diagnosis of lymphangitis carcinomatosa: Arrows represent thickening and irregularity of interlobular septa and arrow head represents thickening of bronchovascular bundles. (b) HRCT after two courses of chemotherapy (SP) The thickening and irregularity of interlobular septa and bronchovascular bundles improved remarkably, and respiratory symptoms disappeared.

We divided patients into three groups according to the number of chemotherapy regimens administered before and after the diagnosis of LC: Group A, no prior chemotherapy before the diagnosis of LC followed by chemotherapy; Group B, one or more prior chemotherapy regimen before the diagnosis of LC followed by chemotherapy; Group C, BSC after the diagnosis of LC regardless of prior chemotherapy.

Response and Toxicity Evaluation

We repeated physical examinations and laboratory tests at least once every 2 weeks. Objective response was assessed according to the Response Evaluation Criteria in Solid Tumors, version 1.1, and toxicity was evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Statistical Analysis

Overall survival (OS) was calculated from the first diagnosis of LC to the date of death from any cause. Survival curves were calculated by the Kaplan–Meier method using StatView, version 5.0 (Abacus Concepts, Berkeley, CA, USA).

RESULTS

Subjects

According to medical records, from September 2002 to December 2011, 1208 patients with unresectable gastric adenocarcinoma were treated at the Shizuoka Cancer Center, and 52 patients (4.3%) were picked up by screening as candidates complicated with LC. Eight patients were excluded because chest CT scans were unavailable, and 5 were lost to follow-up. Finally, 33 out of the remaining 39 patients (2.7% of the total sample) who were confirmed to have LC according to CT findings by both a pulmonologist and a diagnostic radiologist were enrolled in this study (Fig. 2). Infection, pulmonary edema and interstitial pneumonitis, which exhibit similar patterns to LC on CT, were ruled out by the physician according to the clinical findings such as vital signs and physical examination, and the radiographic, CT, echocardiographic and bacterial culture findings.

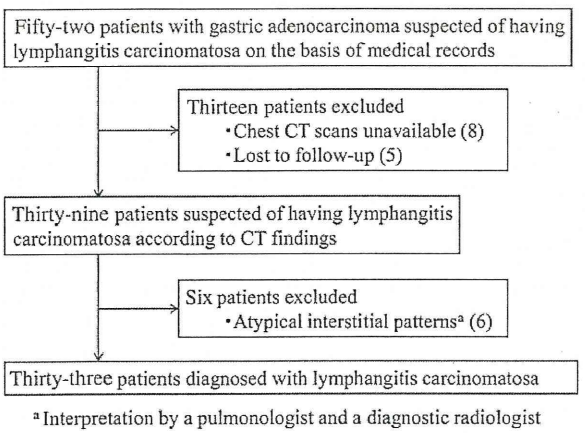

Figure 2. Subject selection process.

Patient Characteristics

The baseline characteristics of the patients at the diagnosis of LC are shown in Table 1. The median age was 55 years (range, 25–73 years), and 70% of patients were women ($n = 23$). Twelve patients (36%) exhibited performance status 3–4, 25 (76%) had respiratory symptoms, and 8 (24%) required

Table 1. Patient characteristics at diagnosis

	All ($n = 33$)	Group A ($n = 18$)	Group B ($n = 7$)	Group C ($n = 8$)
Age				
Median (range)	55 (25–73) years	56 (25–71) years	51 (26–67) years	54 (25–73) years
Sex				
Male	10	7	2	1
Female	23	11	5	7
Eastern Cooperative Oncology Group performance status				
1	12	10	2	0
2	9	5	3	1
3	9	3	1	5
4	3	0	1	2
Disease status				
Metastatic	24	13	6	5
Recurrent	9	5	1	3
Respiratory symptoms				
Yes	25	13	6	6
No	8	5	1	2
Histology				
Diffuse type	28	14	6	8
Intestinal type	5	4	1	0
Site of metastasis				
Mediastinal lymph node	21	11	5	5
Peritoneum	20	8	6	6
Bone	13	9	2	2
Liver	6	4	1	1
Pleural effusion				
Yes	13	8	2	3
No	20	10	5	5
Disseminated intravascular coagulation				
Yes	7	3	2	2
No	26	15	5	6

oxygen inhalation because of hypoxemia. Ten patients (30%) required intravenous fluid infusion or nutrition support because of insufficient oral intake. Eighteen patients (55%) did not have a history of prior chemotherapy. Twenty-eight patients (85%) had histologically confirmed diffuse-type gastric cancer, and 8 (24%) had macroscopically confirmed scirrhous-type gastric cancer. Metastatic diseases were detected in the mediastinal lymph nodes, peritoneum, bone and liver in 21 (64%), 20 (61%), 13 (39%) and 6 patients (18%), respectively. Thirteen patients (39%) had pleural effusion, and 2 (6%) required drainage because of dyspnea and hypoxemia. Furthermore, seven patients (21%) were complicated with disseminated intravascular coagulation (DIC).

Exposure to Treatment

After the diagnosis of LC, 25 patients were treated with systemic chemotherapy (Groups A and B) and 8 patients received BSC (Group C). In Group A ($n = 18$), 10, 6, 1 and 1 patient received MF, SP, SP plus sunitinib and S-1 monotherapy, respectively. In Group B ($n = 7$), 6 and 1 patient received PTX and CPT-11 plus CDDP, respectively.

Response and Survival

The MST of the total subjects was 2.5 months (range, 0.1–37.0 months). In Group A, 2 of 6 patients (33%) who had target lesions obtained partial response, and their MST was 5.7 months (range, 0.4–37.0 months). Two patients treated by MF and SP exhibited remarkable improvement in both respiratory symptoms and chest CT findings (Fig. 1a and b), and achieved OS of 7.9 months and 11.8 months, respectively. A 30-year-old woman with LC and pleural dissemination due to gastric signet ring-cell carcinoma treated with SP plus sunitinib (in a clinical trial) followed by SP exhibited remarkable improvement in chest CT findings and tumor shrinkage, and lived for 37 months. However, she ultimately died due to disease progression of LC and new metastases in the peritoneum and bone. On the other hand, none of the patients in Group B responded to chemotherapy; MST was 1.5 months (range, 0.5–3.5 months). The MST in Group C was as short as 0.3 months (range, 0.1–1.6 months) (Fig. 3).

Adverse Events

The total numbers of patients with the respective major adverse events, including hematological and non-hematological toxicity, in Groups A and B were as follows: Grade 3 or higher anorexia, 11 patients; Grade 3 febrile neutropenia, 1 patient; and Grade 2 or higher DIC, 7 patients (6 had DIC at the initiation of chemotherapy). Two patients, one with Grade 2 urticaria and the other with Grade 3 anorexia, discontinued treatment because of adverse events or refusal to continue treatment due to toxicity. No treatment-related deaths was observed, but two patients in Group A and one patient in Group B died within 30 days after the initiation of chemotherapy; 2 of these patients had DIC at diagnosis, and all 3 early deaths were judged to be due to disease progression.

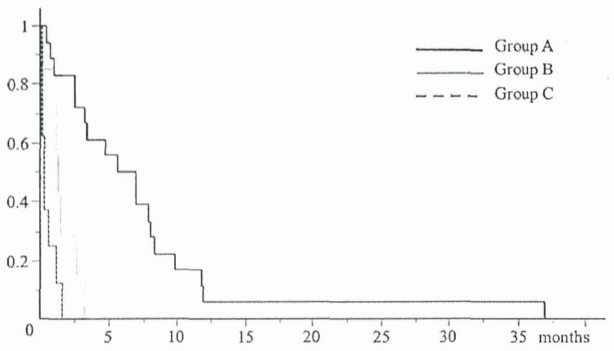

Figure 3. The median overall survival times in Groups A, B and C were 5.7 months (range, 0.43–37.0 months), 1.5 months (range, 0.5–3.5 months) and 0.3 months (range, 0.1–1.6 months), respectively.

DISCUSSION

LC is a metastatic pattern characterized by the diffuse spreading of malignant cells into the pulmonary lymph vessels. While the pathological features of this condition were first reported by Andral in 1829 (10, 12), the first case of LC caused by gastric cancer was reported by Troisier in 1873 (10, 13). Before the 1990s, most literature on LC consisted of case reports focusing on the diagnosis by pathological examination and/or CT (14–18). Although several cases of LC have been reported since then, the etiology and detailed clinicopathological features of LC remain unknown. A review article of LC published in 1996 included various kinds of cancers. Breast, gastric, lung, pancreatic, prostate, cervical and colorectal cancers are the most common tumors that cause LC (10), and adenocarcinoma is the major histological type associated with LC (19, 20).

Given the limited number of published reports, the actual incidence of LC in gastric cancer remains unknown. Our database indicates 4.3% of unresectable gastric adenocarcinoma patients were suspected of having LC, and 2.7% were retrospectively diagnosed with LC mainly on the basis of CT findings. Thus, it appears LC is not very rare among patients with advanced gastric cancer.

Although lung metastases form nodules via hematogenous metastasis in most cases, 6–8% of patients with lung metastasis are classified as having LC (10, 21). There are several hypotheses to explain the occurrence of this condition. First, hematogenous metastasis from tumors may initially cause obliterative endarteritis; cells may subsequently emerge through the vascular walls into the perivascular lymphatic vessels (19). Second, direct lymphatic invasion from retrograde lymphatic infiltration from the mediastinal or hilar lymph nodes may result in LC (20). Another hypothesis is that the lymphogenous permeation of tumor cells metastasizes to the pleura (22). Nevertheless, the pathogenic mechanism of LC remains

unknown. In this study, 64% of the subjects had mediastinal lymph node metastases, supporting the hypothesis of direct lymphatic invasion from retrograde lymphatic infiltration. In terms of metastatic pattern, diffuse-type gastric cancer has been reported to exhibit a higher incidence of lymphatic permeation than hematogeneous metastasis, generally exhibiting a higher incidence of peritoneal metastasis and fewer liver metastases than the intestinal type (23); this could explain the high proportion of diffuse-type tumors (85%) as well as the low incidence of liver metastasis (18%) and high incidence of peritoneal metastasis (61%) in this study. Interestingly, the incidence of bone metastasis in the present study is extremely high relative to that of advanced gastric cancer in the general population. It is speculated that LC and bone metastasis of gastric cancer might share a common mechanism of metastasis, such as adhesion molecules that may cause obliterative endarteritis.

The major clinical symptoms of LC are cough and dyspnea (10). It is hypothesized that severe lymphatic permeation and the presence of an intralymphatic pool of tumor cells obstruct the lymphatic ducts, causing edema in the stroma of the respiratory tract. As the disease progresses, the tumor cells leak out of the lymphatic duct and cause diffuse fibrosis. Restrictive pulmonary dysfunctions such as interstitial pneumonia consequently occur. In this study, 76% of patients had respiratory symptoms such as cough and/or dyspnea; 24% of patients required oxygen inhalation. In particular, 36% of the patients exhibited performance Status 3–4 at diagnosis. This further indicates LC often deteriorates patients' condition.

The prognosis of patients with LC is extremely poor; approximately half of patients with LC die within 3 months after presenting with their first respiratory symptoms (10). The data regarding the effects of chemotherapy are very contradictory, and no standard treatment has been established so far. In clinical practice, the chemotherapy recommended for primary tumors is also generally adopted as the main treatment of patients with LC. Several case reports of gastric cancer associated with LC mainly from Japan report that the efficacy of chemotherapy is limited; none of the reported patients survived >1 year (Table 2) (24–34). In this study, 10 of the 18 patients in Group A was treated with MF, while SP has been the standard treatment in the first-line chemotherapy for advanced gastric cancer since 2007 in Japan. The reasons for this high prevalence of MF are as follows: (i) this study included patients treated between 2002 and 2011, (ii) some patients had ascites and/or could not take oral agents, (iii) the MF regimen was commonly used for patients with severe peritoneal metastasis, mainly diffuse type histologically, before the results of the JCOG0106 trial were published (35), (iv) three patients in Group A had DIC at diagnosis and MF was reported to be effective for patients with DIC (36). As a result, the MST of chemotherapy-naïve patients (Group A) was 5.7 months and only one patient survived >1 year. In addition, chemotherapy in the second or later lines was ineffective, as all patients in Group B died within 4 months. It is important to recognize that most patients with LC are in poor medical condition and that the indication and choice of chemotherapy regimens, particularly for patients with a history of prior chemotherapy, should be determined carefully. However, in this study, first-line chemotherapy resulted in the resolution of the respiratory symptoms and improvement of CT findings in two patients (one case is presented in Fig. 1), and another patient survived >3 years. Therefore, effective chemotherapy may provide a chance of symptom relief and long survival even for patients with LC.

This study has some limitations. First, this is a retrospective study at single institution, and the diagnosis of LC was based on CT findings; it was not confirmed histologically in all

Table 2. Case reports of chemotherapy for gastric cancer with pulmonary lymphangitis carcinomatosa from Japan

Year (reference)	Age	Sex	Histology (type)	Number of prior chemotherapy regimens	Symptom	Diagnosis	Chemotherapy	Prognosis (month)
1999 (23)	50	M	Diffuse	0	Cough	CT	CDDP + mitomycinC + fluorouracil (5-FU) + etoposide	3
2004 (24)	51	M	Diffuse	0	Cough	CT	S-1	10
2005 (25)	51	F	Diffuse	0	Dyspnea	CT+TBLB	S-1 + docetaxel	2
2005 (26)	40	F	Diffuse	2	NA	CT	S-1 + CPT-11	7
2008 (27)	78	F	NA	0	Dyspnea	CT	S-1 + CDDP	10
2008 (28)	70	F	Diffuse	0	NA	CT	S-1 + CPT-11	2
2008 (29)	31	F	Intestinal	1	Dyspnea	CT	Docetaxel + CDDP + S-1	2
2009 (30)	28	F	Diffuse	0	Dyspnea	CT	S-1 + paclitaxel	1
2010 (31)	63	M	Diffuse	0	Dyspnea	CT	5-FU + leucovorin	9
2011 (32)	38	M	Diffuse	0	Cough	CT	S-1 + docetaxel	8
2011 (33)	60	F	Diffuse	1	Dyspnea	CT	CPT-11	4

NA, not available; TBLB, transbronchial lung biopsy.

patients because most patients with LC are in poor condition and require rapid treatment before histological confirmation. Moreover, it is difficult to rule out the complication of pulmonary tumor thrombotic microangiopathy, which exhibits similar clinicopathological features to LC, although different CT findings between these two diseases are reported (15, 16, 37, 38). Second, although the objective of this study was to investigate the clinicopathological features and outcomes of gastric cancer patients with LC, this study included only gastric cancer patients with LC and did not compare the results to those in patients who did not develop LC. Lastly, the subjects were treated with various kinds of chemotherapy regimens not only in the first line, but in subsequent lines as well. Therefore, it is rather difficult to evaluate the efficacy of a specific chemotherapy regimen for LC. However, this study is one of the largest case series of LC caused by gastric cancer. Therefore, the present findings may facilitate clinical decision making and future advancements in the treatment of LC.

In conclusion, LC caused by gastric cancer has distinct specific characteristics including the predominance of female patients, diffuse-type gastric cancer, metastases to the mediastinal lymph nodes and peritoneum, and association with bone metastasis and DIC. While the prognosis of gastric cancer patients with LC is extremely poor even after systemic chemotherapy, some patients may have survival benefit from chemotherapy. The development of new drugs for LC, including molecular-targeting agent, is urgently required.

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Conflict of interest statement

None declared.

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Phase II trial of nanoparticle albumin-bound paclitaxel as second-line chemotherapy for unresectable or recurrent gastric cancer

Yasutsuna Sasaki,[1,2] Tomohiro Nishina,[3] Hirofumi Yasui,[4] Masahiro Goto,[5] Kei Muro,[6] Akihito Tsuji,[7] Wasaburo Koizumi,[8] Yasushi Toh,[9] Takuo Hara[10] and Yoshinori Miyata[11]

[1]Department of Medical Oncology, Saitama Medical University International Medical Center, Hidaka-shi; [2]Division of Medical Oncology, Department of Medicine, Showa University Hospital, Tokyo; [3]Department of Gastrointestinal Medical Oncology, National Hospital Organization Shikoku Cancer Center, Matsuyama-shi; [4]Department of Gastrointestinal Oncology, Shizuoka Cancer Center, Nagaizumi-cho; [5]Cancer Chemotherapy Center, Osaka Medical College, Osaka; [6]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya; [7]Department of Clinical Oncology, Kochi Health Sciences Center, Kochi; [8]Department of Gastroenterology, Kitasato University, Sagamihara-shi; [9]Department of Gastroenterological Surgery, National Kyushu Cancer Center, Fukuoka; [10]Department of Surgery, Kouseiren Takaoka Hospital, Takaoka-shi; [11]Deparment of Gastroenterology, Saku Central Hospital, Nagano, Japan

Key words

Gastric cancer, *nab*-paclitaxel, phase II, second-line chemotherapy, triweekly

Yasutsuna Sasaki, Division of Medical Oncology, Department of Internal Medicine, Showa University School of Medicine, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8666, Japan.
Tel/Fax: +81-3-3783-8661
E-mail: yasutsuna@med.showa-u.ac.jp

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This multicenter phase II study first investigated the efficacy and safety of nanoparticle albumin-bound paclitaxel (*nab*-paclitaxel) when given every 3 weeks to patients with unresectable or recurrent gastric cancer who had received a prior round of fluoropyrimidine-containing chemotherapy. Patients with unresectable or recurrent gastric cancer who experienced progression despite fluoropyrimidine-containing treatment were studied. *Nab*-paclitaxel was given i.v. at 260 mg/m^2 on day 1 of each 21-day cycle without anti-allergic premedication until disease progression or study discontinuation. The primary endpoint was the overall response rate. The secondary endpoints were the disease control rate, progression-free survival, overall survival, and safety. From April 2008 to July 2010, 56 patients were enrolled, 55 patients received the study treatment, and 54 patients were evaluable for responses. According to an independent review committee, the overall response rate was 27.8% (15/54; 95% confidence interval [CI], 16.5–41.6) and the disease control rate was 59.3% (32/54; 95% CI, 45.0–72.4). One patient had a complete response. The median progression-free survival and overall survival were 2.9 months (95% CI, 2.4–3.6) and 9.2 months (95% CI, 6.9–11.4), respectively. The most common grade 3/4 toxicities were neutropenia (49.1%), leucopenia (20.0%), lymphopenia (10.9%), and peripheral sensory neuropathy (23.6%). There were no treatment-related deaths. *Nab*-paclitaxel, given every 3 weeks, showed promising activity against previously treated unresectable or recurrent gastric cancers, with well-tolerated toxicities. (Trial registration, ClinicalTrials.gov: NCT00661167).

Gastric cancer remains the second leading cause of cancer-related deaths worldwide[1] and is especially frequent in East Asia, including Japan.[2] Although surgical resection is the only curative treatment for gastric cancer, approximately 60% of patients eventually experience relapses after curative surgeries.[3] Globally, fluoropyrimidine-based combination chemotherapy regimens, including fluorouracil or its oral derivatives, taxanes, irinotecan, and platinum compounds, have yielded median progression-free survival (PFS) times of 2–7 months and median overall survival (OS) times of less than 1 year in first-line settings.[4–9] In Japan, the combination of S-1 (tegafur plus gimeracil plus oteracil potassium) and cisplatin is the most frequently prescribed first-line therapeutic regimen for patients with advanced/metastatic and recurrent gastric cancer. Recently, several phase III trials reported improved median OS times of more than 1 year.[10–12] Additionally, in a randomized European trial, irinotecan showed survival benefits, compared to best supportive care (BSC), as second-line treatment in gastric cancer patients after the failure of first-line chemotherapy.[13] A Korean study showed that docetaxel or irinotecan could also significantly prolong OS, compared with BSC, after one or two chemotherapeutic regimens that consisted of fluoropyrimidine and platinum.[14]

In Japan, paclitaxel (PTX) is commonly used as second-line chemotherapy for gastric cancer patients in practice, based on experiences with breast cancer and non-small-cell lung cancer (NSCLC). Paclitaxel yielded overall response rates (ORR) that ranged from 16 to 27%, overall OS times of 5–11 months, and modest toxicity in several phase II trials.[15–18]

The 130-nm nanoparticle albumin-bound paclitaxel (*nab*-paclitaxel) is a novel, solvent polyoxyethylated castor oil (Cremophor)-free, biologically interactive form of PTX. *Nab*-paclitaxel is among the first of a new class of anticancer agents to incorporate albumin particle technology and exploit the unique properties of albumin, a natural carrier of lipophilic molecules in humans. *Nab*-paclitaxel allows the safe infusion of significantly higher doses of PTX than those used in standard PTX therapy, with shorter infusion schedules (30 min *vs* 3 h,