randomized trials for AGC. Our results showed considerable inconsistency in the reporting of patient characteristics and the use of stratification factors in clinical trials for AGC. A similar finding was reported by Sorbye et al. [16], who analyzed metastatic colorectal cancer (MCRC) clinical trials and advocated that an urgent need exists for an international consensus on the reporting of patient characteristics and stratification in MCRC trials. Our data also revealed several differences in patient characteristics between trials conducted before and after 2004, and between Asian and non-Asian trials. It is possible that these differences may have contributed to the observed heterogeneity in the survival outcomes of each trial.

Several prognostic factors have been identified for patients with AGC who have undergone chemotherapy [10–14]. As described in the "Introduction", the GASTRIC project confirmed the impact of ECOG PS, disease status, number of metastatic organs, location of metastasis, and prior surgery on the survival of AGC patients, as determined by individual patient data analysis of previous randomized studies [10]. Notably, this project, which may have included the largest AGC patient set to date, identified that PS1 and PS2 were significantly associated with poor survival, with hazard ratios (HRs) of death of 1.36 and 2.17, respectively [10]. In the GASTRIC analysis, although most trials included PS among the reported patient characteristics, a number of studies classified PS0 and PS1 separately, and several studies used KPS rather than the ECOG scale. In addition, local recurrence and metastatic disease were reported to be associated with worse outcomes than locally advanced disease [10]. In our present analysis, approximately 50% of trials reported disease extension (locally advanced or metastatic disease), and only 30% of trials indicated disease status (advanced or recurrent disease).

Although the GASTRIC analysis did not evaluate the importance of specific metastatic organs on outcomes, another large prognostic analysis, by Chau et al. [11, 12], reported the impact of liver and peritoneal metastasis on AGC patient survival. Affected metastatic organs were reported in 64% of the trials in our analysis, but the number of metastatic organs, which has significant impact on survival according to the GASTRIC analysis, was only reported with a frequency of 39%. Although histology was not identified as prognostic in the GASTRIC analysis, several recent trials suggest that an interaction exists between histology and drug response [6, 7, 17, 18]. For example, a subset analysis of the First-line Advanced Gastric Cancer Study (FLAGS) trial has indicated that the oral fluoropyrimidine S-1 appears to be superior to fluorouracil in the treatment of diffuse-type gastric cancer [6]. This finding is consistent with the results of a subset analysis of the Japan Clinical Oncology Group (JCOG) 9912 study that also indicated S-1 is better than fluorouracil in patients with diffuse-type AGC or gastric cancer associated with high dihydropyrimidine dehydrogenase (DPD) activity, which is more commonly associated with diffuse-type than intestinal-type tumors [17]. This result was not unexpected, because S-1 is a potent competitive inhibitor of DPD. In contrast to DPD, human epidermal growth factor receptor 2 (HER2)-positive AGC, for which the anti-HER2 agent trastuzumab is effective [7], is reported to be higher among intestinal-type tumors [18]. The prognostic factors and tumor characteristics identified in these studies should be reported in all clinical trials of AGC, as they are necessary to adequately interpret trial data and treatment outcomes.

Our analysis also revealed that the types of second-line chemotherapy and proportions of patients who received such treatment were not routinely reported in AGC trials. As several recent reports have suggested that second-line chemotherapy has a significant impact on OS [19–21], we propose that second-line therapies should be diligently reported in future clinical trials of first-line AGC treatment, because second-line chemotherapy might influence the OS as the primary endpoint, as suggested by our previous analysis [22].

Additionally, the numerous prognostic factors identified for AGC may be important for the stratification of patients with respect to risk and treatment arms in randomized trials. To adequately analyze treatment effects on clinical outcomes, efforts should be undertaken to maximally decrease imbalance of prognostic factors between treatment arms in a clinical trial [23]. Although there is no definite consensus on the optimal method for stratification, stratification is recommended for superiority trials with fewer than 400 patients [24] and for non-inferiority trials with any number of patients [25]. In our analysis, stratification was conducted in only 60% of the examined trials, and was performed with quite variable stratifying factors. Based only on the present analysis, it is difficult to suggest a standardization approach for stratification factors in AGC trials, and further analysis and discussion are necessary.

In recent years, a trend of increased median OS in AGC patients has been observed concurrent with the development of new chemotherapeutic agents [2, 4, 7, 26]. It is also possible that second-line chemotherapy may have contributed to the improvement in OS [19–21]; however, our crude comparison of trials conducted prior to and after 2004 also showed significant differences in PS and disease extension. These differences may have also contributed to the improved survival reported in more recent trials, as well as survival differences between Asian and non-Asian trials. The exact impact of chemotherapy and patient characteristics on survival would be best addressed in well-designed randomized studies and meta-analyses of individual patient data.

In conclusion, our analyses of published clinical trials for AGC revealed inconsistencies in the reporting of

patient characteristics and use of stratification factors. An international consensus on the reported characteristics and stratification in AGC trials is necessary to improve the analysis of future clinical trials.

Conflict of interest None.

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PHASE II STUDIES

Phase II study of combination chemotherapy with biweekly cetuximab and irinotecan for wild-type *KRAS* metastatic colorectal cancer refractory to irinotecan, oxaliplatin, and fluoropyrimidines

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Summary The aim of this study is to prospectively evaluate the efficacy of combination chemotherapy with every second week cetuximab and irinotecan in patients with pretreated metastatic colorectal cancer harboring wild-type *KRAS*. Patients with wild-type *KRAS* metastatic colorectal cancer that had progressed after chemotherapy with irinotecan, oxaliplatin, and fluoropyrimidine were included. Cetuximab was administered at 500 mg/m^2 biweekly with irinotecan. The primary endpoint was response rate. The pharmacokinetics of cetuximab was also evaluated in 5 patients. From May 2009 to February 2010, a total of 31 patients were enrolled from five institutions. One patient was not eligible. Among the 30 patients who were treated with biweekly cetuximab plus irinotecan, partial response was observed in 9 patients. The objective response rate was 30.0% (95% confidence interval [CI], 14.7%–49.4%) and the disease control rate (complete response, partial response, or stable disease) was 76.7% (95% CI, 57.7%–90.0%). The median progression-free survival was 5.3 months and median overall survival was 10.8 months. Grade 3 skin toxicity was observed in 3 patients (10.0%) and one treatment related death due to pneumonia was observed. Combination chemotherapy with biweekly cetuximab and irinotecan was effective for

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pretreated metastatic colorectal cancer with wild-type *KRAS*.

Keywords Colorectal cancer · Chemotherapy · Cetuximab · Biweekly · Irinotecan

Introduction

Cetuximab, a recombinant, human/mouse chimeric monoclonal IgG1 antibody that specifically targets epidermal growth factor receptor (EGFR), has been shown to significantly improve the prognosis for metastatic colorectal cancer (MCRC) compared to best-supportive care alone in the third-line setting [1]. Furthermore, combining cetuximab with irinotecan results in a higher response rate than cetuximab alone, even in patients with irinotecan-refractory disease [2], suggesting that cetuximab may restore chemosensitivity in these patients. Because of these results, cetuximab plus irinotecan has become the standard chemotherapy in MCRC after failure with 5-fluorouracil (5-FU), oxaliplatin, and irinotecan. Following these two pivotal studies, several retrospective reports suggested that cetuximab is not efficacious in patients with cancers harboring *KRAS* mutations [3–7]. Therefore, the indications for cetuximab are considered to be limited to cancers bearing wild-type *KRAS* based on these retrospective studies [8]. We conducted a phase II study employing weekly cetuximab plus biweekly irinotecan for wild-type *KRAS* MCRC [9]. Objective response rate of 30.0% and disease control rate of 80.0% was shown in our previous study [10].

Based on past pivotal studies, the standard schedule for cetuximab is weekly administration [1, 2]. In principal, cetuximab is administered weekly with an initial intravenous infusion of 400 mg/m^2 on day 1 infused over 120 min, with subsequent weekly doses of 250 mg/m^2 infused over 60 min. This regimen was used in a Japanese phase II study [10] and in our prior study [9] with acceptable toxicity. However, in Japan, irinotecan has been commonly administered biweekly to patients with metastatic colorectal cancer. Therefore, if we could achieve similar efficacy and safety with biweekly administration of cetuximab, it would be more convenient both for the patient and for the treating institution. There are a few reports that evaluated efficacy and feasibility of biweekly administration of cetuximab [11–13]. Tabernero et al. conducted a phase I study of biweekly cetuximab. In their study, cetuximab could be safely administered biweekly at doses between 400 and 700 mg/m^2 [11]. They concluded that 500 mg/m^2 was the most convenient and feasible dose. Other two studies using biweekly cetuximab 500 mg/m^2 plus irinotecan showed a response rate of 22.5%–25% in pretreated MCRC with a similar toxicity compared with weekly cetuximab [12, 13]. However, to the best of our knowledge, no study using biweekly cetuximab evaluated *KRAS* status prospectively [11–13]. Therefore, we have planned a phase II study of combination chemotherapy with biweekly cetuximab and irinotecan for pretreated MCRC harboring wild-type *KRAS*.

Patients and methods

Purpose

The aim of this study was to explore the effectiveness and safety of combination chemotherapy with biweekly cetuximab plus irinotecan for the treatment of patients with MCRC that had progressed after irinotecan-, oxaliplatin-, and fluoropyrimidine-based chemotherapy.

Study setting

A multi-institutional prospective phase II trial, where participating institutions included 5 specialized centers.

Endpoints

The primary endpoint was response rate. The tumor response was assessed objectively once every two weeks after each course according to the Response Evaluation Criteria in Solid Tumors (RECIST ver. 1.0), and the best overall response rate was taken as the antitumor effect for that patient. The secondary endpoints included adverse events defined by Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, progression-free survival time, and overall survival time. A pharmacokinetic (PK) study of cetuximab was evaluated in 5 patients.

Patients

Prior to enrollment in the study, patients must fulfill all of the following criteria: (i) Patients with histopathologically proven metastatic colorectal adenocarcinoma with wild-type *KRAS* were eligible for this study. EGFR positive staining was not required. *KRAS* status was evaluated in each institution using one of the following methods: cycleave PCR (Aichi Cancer Center Hospital) [14, 15] or direct sequence methods (BML, Tokyo, Japan). Wild-type *KRAS* meant patients without *KRAS* mutations in codons 12 and 13 regardless of the *KRAS* testing method. The remaining criteria were as follows: (ii) Eastern Cooperative Oncology Group performance status (PS) 0–2; (iii) presence of measurable metastatic disease as defined by the

RECIST criteria; (iii) presence of radiographically confirmed disease progression during previous chemotherapy using irinotecan or within 3 months after the last chemotherapy dose; (iv) treatment failure (defined as disease progression/discontinuation due to toxicity) within 6 months of the last dose of fluoropyrimidine- and oxaliplatin-based chemotherapy; (v) adequate bone marrow reserve (neutrophil count >1,000/mm^3, platelet count >100,000/mm^3); (vi) adequate hepatic function (aspartate aminotransferase and alanine aminotransferase <2.5 times the institutional upper normal limit [<5 times in patients with liver metastases] and total bilirubin <1.5 times the upper normal limit); and (vii) adequate renal function (serum creatinine <2.0 times the upper normal limit).

Patients were excluded if they met any of the following criteria: (i) uncontrollable ascites or pleural effusion and (ii) serious comorbidities, such as pulmonary fibrosis or interstitial pneumonia, uncontrollable diabetes mellitus, severe heart disease, other active malignancy, active inflammation, or other serious medical conditions.

The institutional review board of each participating center approved the study. This study was registered in the UMIN clinical trial registry (UMIN000001951). Written informed consent was obtained from each patient prior to treatment administration.

Treatment methods

The treatment schedule was based on the results of prior studies [10–12]. Cetuximab was administered initially at a dose of 500 mg/m^2 as a 2-hour infusion followed by biweekly administration of 500 mg/m^2 as a 1-hour infusion. Irinotecan was administered biweekly. The dose of irinotecan (100–150 mg/m^2) was selected by each physician according to each individual patient, based on prior toxicities experienced with irinotecan. Patients received premedication with antihistamine (e.g., 50 mg diphenhydramine hydrochloride intravenously [IV]) to minimize the risk of infusion-related reactions associated with cetuximab. The following anti-emetic treatments were administered on demand: dexamethasone 4 mg prior to cetuximab, and dexamethasone 8–16 mg plus granisetron 1 mg IV prior to irinotecan. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 3.0). Grade 3–4 hypersensitivity necessitated cetuximab discontinuation; infusion was slowed to 50% of the prior infusion rate for grade 1–2 allergic/hypersensitivity reactions. Cetuximab was withheld for grade 3 skin toxicity until resolution to ≤grade 2. Dose modification and treatment alterations were also performed for irinotecan-associated toxicities. For grade 4 thrombocytopenia or grade 3–4 neuropathy, irinotecan was discontinued. The irinotecan dose was reduced by 20 mg/m^2 in the case of grade 4 neutropenia, grade 2–3 thrombocytopenia, or grade 3–4 non-hematological toxicity. Other dose adjustments were made on an individual patient basis. Treatment was discontinued if the tumor progressed, severe toxicity occurred, or at the patient's request. There was no set maximum number of courses.

Evaluation of treatment and follow-up

Medical history, physical examination, and safety evaluation were performed prior to starting treatment and biweekly thereafter. Laboratory tests were also obtained biweekly or more frequent in the case of severe toxicities, and always prior to each irinotecan infusion. Toxicity was evaluated by CTCAE ver. 3.0. Tumor marker analysis (carcinoembryonic antigen [CEA]) was also performed every 4 weeks. Responses were evaluated using RECIST criteria every 8 weeks, or earlier if there were indications of treatment failure due to toxicity. All eligible subjects were included in the assessment of efficacy and safety. Non-evaluable subjects were only added into the efficacy assessment data set as "not evaluable." The following dates were recorded: (i) date of starting treatment, (ii) date achieving best tumor response, (iii) date of disease progression, (iv) final date assessing survival, and (v) date of death.

Statistical analysis

A 1-stage design employing binomial probability was used to determine sample size. A patient receiving at least 1 chemotherapy study dose was considered evaluable for response. The response rate threshold was defined as 5%, and the expected response rate was set at 25%, since the response rate in the BOND-1 study was 22.9% [2]. The sample size of this trial was 25 patients (α- and β-error probabilities, 0.05 and 0.2, respectively). Considering an approximately 10% dropout rate, 30 patients were required for this study. Progression-free survival was measured from the date of entry into the trial to the time when progression or death without evidence of progression occurred. The median survival time was estimated from the date of study entry to the date of death or last follow-up visit using Kaplan-Meier methodology.

Cetuximab pharmacokinetics (PK) analysis

Blood samples for PK analysis were taken in 5 patients at day 1 (end of infusion), day 15 (predose and end of infusion), and day 29 (predose). PK parameters were

calculated according to standard non-compartmental methods.

Results

Patient characteristics

A total of 31 patients were registered between May 2009 and February 2010. One patient was not eligible due to PS 3, and thirty eligible patients received more than one planned treatment with irinotecan and cetuximab and analyzed for efficacy and safety (Table 1). Most patients had a PS 0–1; 2 patients were PS 2. All patients had wild-type *KRAS* MCRC. All patients had received two or more prior chemotherapy regimens with a median interval from initiation of first-line chemotherapy to study entry of 17.7 months (range, 6.4–46.9 months). Prior oxaliplatin-containing regimens included FOLFOX (infusional and bolus 5-fluorouracil with oxaliplatin) in 29 patients and S-1 plus oxaliplatin in 1 patient. Prior irinotecan-containing regimens included FOLFIRI (infusional and bolus 5-fluorouracil with irinotecan) in 24 patients, irinotecan monotherapy in 2 patients, irinotecan plus hepatic arterial infusion chemotherapy of 5-FU in 3 patients, and S-1 plus irinotecan in 1 patient. Twenty-one patients received oxaliplatin-based therapy prior to irinotecan-based therapy, while the nine patients received these therapies in reverse sequence. Bevacizumab had been previously used in 19 patients prior to study entry. All patients discontinued prior irinotecan based chemotherapy due to disease progression. Prior oxaliplatin-based regimen was discontinued due to disease progression in 24 patients and toxicity in 6 patients (neuropathy in 5 patients and allergy in 1 patient). The median PFS of oxaliplatin-based therapy and irinotecan-based therapy was 6.3 months and 6.7 months, respectively. The most common site of metastasis was the lungs in 24 patients, followed by the liver in 23 patients. Increased CEA was observed in 26 patients (>2 times the upper normal range), with a median value of 194 U/mL (range, 11.6 to 6,050 U/mL).

Table 1 Patient characteristics

Characteristics		No.
Median age, years		61 (29–77)
Gender	Male/female	19/11
ECOG PS	0/1/2	12/16/2
Origin	Colon/rectum	15/15
Prior colorectomy	Yes	26
Prior Radiation	Yes	3
Prior Adjuvant CTx	Yes	5
Prior CTx for advance	FOLFOX/SOX	29/1
	FOLFIRI/irinotecan/IRIS	24/5/1
	Bevacizumab	21
Number of prior CTx	2/3 or more	21/9
Disease sites[a]	Liver	23
	Lung	24
	Lymph node	16
	Peritoneum	7
No. of disease sites	1 or 2/ 3 or more	10/20

[a] Some were overlapping

PS performance status; *ECOG* Eastern Cooperative Oncology Group; *CTx* chemotherapy, *FOLFOX* infusional and bolus 5-fluorouracil with oxaliplatin; *SOX* S-1 plus oxaliplatin; *FOLFIRI* infusional and bolus 5-fluorouracil with irinotecan; *IRIS* S-1 plus irinotecan

Treatment results

The median number of cetuximab and irinotecan administrations was 8 (range, 1 to 24) and 8 (range, 2 to 24), respectively. Irinotecan was administered at a dose of 100 mg/m^2, 120 mg/m^2, and 150 mg/m^2 in 7, 7, and 16 patients, respectively. Four patients continued protocol treatment as of the time of analysis, with a median follow-up of 12.0 months (range, 8.3–19.1 months). Two patients experienced cetuximab dose reductions due to skin toxicities, and 1 patient underwent a 50% infusion rate due to grade 2 infusion reaction. Seven patients required irinotecan dose reductions, primarily due to neutropenia and gastrointestinal toxicity. Protocol treatment was discontinued in 26 patients due to disease progression (n=24), dead by pneumonia (n=1), and lost follow up (n=1).

Efficacy

Among the 30 patients, no patient achieved a complete response, 9 patients experienced a confirmed partial response, and 14 had stable disease using RECIST criteria. Four patients had progressive disease, and three patients were not evaluable for treatment response due to symptomatic deterioration prior to radiological response evaluation in two patients and treatment withdrawal due to toxicity prior to response evaluation in one patient. The overall response rate was 30.0% (95% confidence interval [CI], 14.7%–49.4%) and the disease control rate (complete response, partial response, or stable disease) was 76.7% (95% CI, 57.7%–90.0%). Among the 14 patients with stable disease, 8 patients experienced tumor shrinkage of >10%; therefore a total of 17 of 30 patients (56.7%) achieved >10% tumor shrinkage (Fig. 1). A >50% decline in CEA was observed in 16 of 26 patients (61.6%) with abnormal values. The median progression-free survival was 5.3 months (95% CI; 3.6–7.1) and median overall

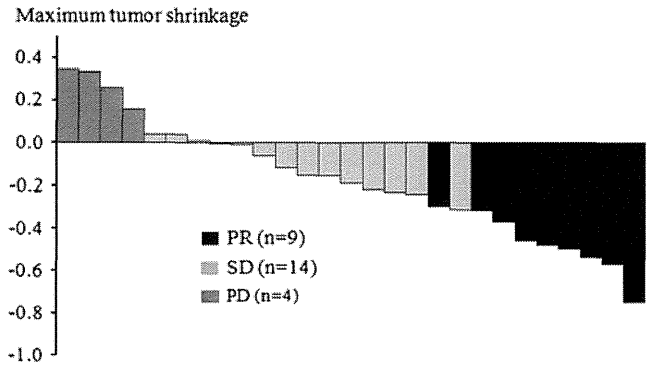

Fig. 1 Maximum tumor shrinkage from baseline. The objective response rate was 30.0%, and the disease control rate was 76.7%. Among the 14 patients with stable disease, 8 patients experienced >10% tumor shrinkage. Three patients were not evaluable for treatment response. Abbreviations: *PR* partial response; *SD* stable disease; *PD* progressive disease

survival was 10.8 months (95% CI; 6.8-not reached) with fourteen patients still alive (Fig. 2).

Toxicity

Grade 3–4 neutropenia was observed in 9 patients (30.0%), 3 patients experienced grade 3–4 anemia, and one patient experienced grade 3–4 thrombocytopenia (Table 2). Febrile neutropenia was observed in 2 patients (6.7%), which were successfully managed by treatment with granulocyte-colony stimulating factor and antibiotics. Skin toxicity including acne, rash, dry skin, pruritus, acneiform dermatitis, and papular rash, was observed in 27 patients (90.0%); the majority of these (n=15) were grade 2. Three patients (10.0%) experienced grade 3 skin toxicity. One patient died from pneumonia. This patient experienced fever and dyspnea 10 days after the fourth cycle of treatment. CT scan showed diffuse gland glass opacity with consolidations. Culture of blood and sputum was negative for any pathogen including *Pneumocystis jiroveci*. Although antibiotics and high doses of steroids were administered, the patient did not improve. Definitive cause of pneumonia could not be determined since autopsy was denied. Other grade 3–4 non-hematological toxicities included diarrhea (16.7%) and anorexia (10.0%).

Table 2 Toxicity

Toxicity	Grade 1–4 (%)	Grade 3–4 (%)
Leucopenia	15 (50)	5 (17)
Neutropenia	16 (53)	9 (30)
Febrile neutropenia	2 (7)	2 (7)
Anemia	14 (47)	3 (10)
Thrombocytopenia	2 (7)	1 (0.3)
Fever	7 (23)	0 (0)
Diarrhea	14 (47)	5 (17)
Skin toxicity	26 (87)	3 (10)
Nausea	15 (50)	1 (0.3)
Vomiting	7 (23)	1 (0.3)
Fatigue	14 (47)	3 (10)
Stomatitis	10 (33)	1 (0.3)
Anorexia	19 (63)	3 (10)
Hypomagnesia	16 (53)	1 (0.3)

Results of PK analysis

The mean of Cmax was 195.20 ug/mL on day 1 and 230.80 ug/mL on day 15, and the mean of trough concentrations was 22.14 ug/mL on Day 15 and 38.34 ug/mL on day 29 (Fig. 3). The both Cmax and trough were increasing. However; this was not shown in all the patients of multiple administrations due to the large variation in each case and the small patients number. The trough on day

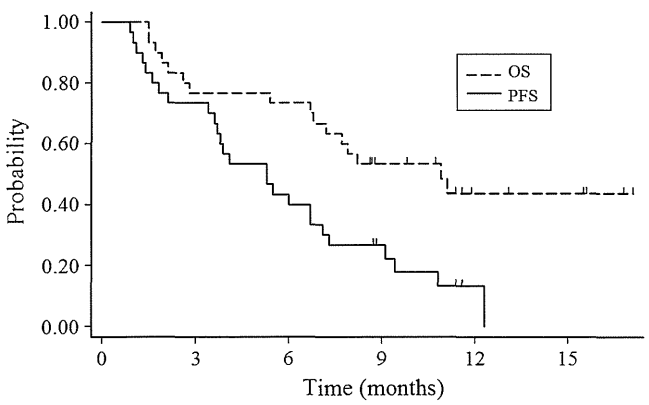

Fig. 2 Progression-free survival and overall survival time. The median progression-free survival was 5.3 months and median overall survival was 10.8 months. Abbreviations: *PFS* progression-free survival; *OS* overall survival

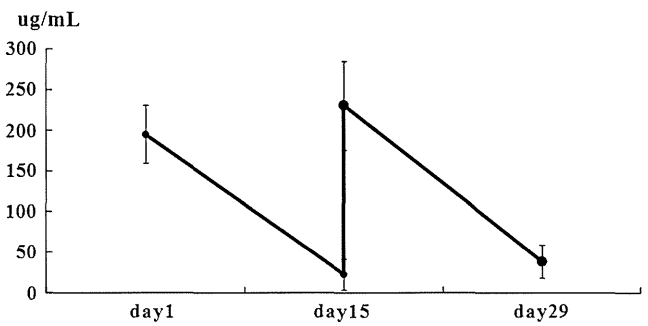

Fig. 3 Mean (±S.D.) peak and trough cetuximab serum concentrations day 1–day 29. The mean of Cmax was 195.20 ug/mL on day 1 and 230.80 ug/mL on day 15, and the mean of trough concentrations was 22.14 ug/mL on Day 15 and 38.34 ug/mL on day 29

15 and day 29 of Cetuximab 500 mg/m^2 administration were similar to the results from other studies [11, 12].

Discussion

In this study, we evaluated the efficacy and safety of combination chemotherapy with biweekly cetuximab plus irinotecan in patients with wild-type *KRAS* colorectal cancer who failed prior chemotherapy including irinotecan, oxaliplatin, and fluoropyrimidine. To our knowledge, this was the first report to evaluate biweekly cetuximab in prospectively recruit patients after assessing *KRAS* mutation status.

To our knowledge, there were three published reports that evaluated biweekly administration of cetuximab. Tabernero et al. conducted a phase I study of cetuximab monotherapy followed by a combination with a FOLFIRI regimen and reported that a cetuximab dose of 500 mg/m^2 every 2 weeks exhibited predictable pharmacokinetics, which were similar to those of the approved weekly dosing regimen [11]. Although most patients in the Tabernero study were chemo naïve patients, our results supported the assumption that 500 mg/m^2 might be optimal even in heavily pretreated patients with active serum concentrations of cetuximab maintained throughout the 2-week dosing period with this regimen. The other two reports in similarly pretreated settings showed almost consistent efficacy of biweekly use of cetuximab with irinotecan with a response rate of 22.5%–25% and 3.4–5.4 months [12, 13] , although these studies did not evaluate *KRAS* status (Table 3).

The response rate of 30% in the present study was relatively higher than those of previous prospective studies in a similarly pretreated setting, such as the BOND-1 study (22.9%, irinotecan plus cetuximab; 10.8%, cetuximab monotherapy) or the MABEL study, considering a study population with and without *KRAS* mutant tumors [2, 16]. The present disease control rate (76.7%) and progression free survival (5.3 months) was also relatively higher than that of the BOND-1 study (55.5% and 4.2 months in the combination arm) or the MABEL study (45.2% and 3.2 months) [2], although these indirect comparisons should be cautiously interpreted. The efficacy data in this study were almost similar to our previous phase II study using weekly cetuximab plus irinotecan for patients with *KRAS* wild-type metastatic colorectal cancer [9]. These results highlight the usefulness of biweekly administration of cetuximab.

Toxicity in our study and previous biweekly studies was almost compatible to those of weekly regimens (Table 3), although we experienced one possible treatment related death due to pneumonia. In this study, although 2 patients discontinued treatment due to toxicity, other toxicities were generally well tolerated and expected. Therefore biweekly administration may be a potentially convenient alternative to the approved weekly dosing regimen considering most chemotherapy regimens in colorectal cancer were based on biweekly administration, although cautions for toxicity are still required.

In conclusion, the results of this phase II study demonstrated that combination of biweekly cetuximab and irinotecan chemotherapy was active and tolerated in patients with wild-type *KRAS* colorectal cancer who failed prior chemotherapy including irinotecan, oxaliplatin, and fluoropyrimidine. Although the small number of patients in the single arm study was the major limitation to this study, our results suggested that the biweekly administration of cetuximab combined with irinotecan was feasible and active in patients heavily pretreated with MCRC. Further

Table 3 Results of prospective study of cetuximab plus irinotecan for MCRC refractory to irinotecan

Author	Weekly cetuximab plus irinotecan				Biweekly cetuximab plus irinotecan			
	Cunningham [2]	Wilke [16]	Pfeiffer [12]	Tahara [10]	Shitara [9]	Pfeiffer [12]	Martin-Martorell [13]	This study
Number of patients	329	1147	65	39	30	71	40	30
KRAS status	NR	NR	NR	NR	Wild	NR	NR	Wild
Previous oxaliplatin (%)	62.6	69	95	100	100	100	97.5	100
Response rate (%)	22.9	20.1	20	30.8	30	25	22.5	30
Disease control (%)	55.5	45.2	66	64.1	80	77	60	76.7
median PFS (months)	4.1	3.2	5.4	4.1	5.8	5.4	3.4	5.3
median OS (months)	8.6	9.2	10.4	8.8	12.5	8.9	8	10.8
Skin toxicity(G3-4)	9	13.3	11	5.1	0	5	7.5	10.0
Diarrhea (G3-4)	21	19	10	17.9	13.3	9	10	16.7
Neutropenia (G3-4)	9	9.9	4	23.1	33.3	7	7.5	30.0

NR not reported; *PFS* progression free survival; *OS* overall survival; *G* grade

randomized studies that compared biweekly administration of cetuximab with weekly administration might be warranted.

Acknowledgments None declared.

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Conflict of interest statement None declared.

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治療薬解説

大腸癌治療における分子標的治療薬の位置づけ

室　圭*

abstract

ここ数年進歩著しい分子標的治療薬が，大腸癌治療にも広く用いられるようになり，その標準的治療として組み入れられるようになった．現在，大腸癌領域において臨床導入されている分子標的治療薬は，抗血管内皮細胞増殖因子（vascular endothelial growth factor：VEGF）抗体薬のベバシズマブと抗上皮成長因子受容体（epidermal growth factor receptor：EGFR）抗体薬のセツキシマブ，パニツムマブである．これら有効性の証明された分子標的治療薬の臨床導入が，切除不能進行大腸癌の治療成績の向上に大きく寄与している．これらの薬剤を大腸癌治療経過中に，どのようにしてうまく使い切っていくかがきわめて重要なポイントである．今後，regorafenibなどの新規分子標的薬の上市も予定されている．ますます複雑化する大腸癌治療のレジメンを十分理解して，適切に毒性をマネジメントしていくことが望まれる．

1 はじめに

大腸癌化学療法において，3種類の抗癌剤，すなわちフルオロウラシル（5-FU）系薬剤〔5-FU＋ロイコボリン（LV）〕，イリノテカン（CPT-11），オキサリプラチン（L-OHP）がkey drugであり，これら3剤を化学療法の経過中にすべて使い切ることが生存期間延長に最も寄与することが明らかになった[1]．これらに加えて，ここ数年進歩著しい分子標的治療薬が，大腸癌治療にも広く用いられるようになり，その標準的治療として組み入れられるようになった．現在，大腸癌領域において臨床導入されている分子標的治療薬は2種類に分けられる．すなわち，angiogenesis系阻害の抗血管内皮細胞増殖因子（vascular endothelial growth factor：VEGF）抗体薬とシグナル伝達阻害の抗上皮成長因子受容体（epidermal growth factor receptor：EGFR）抗体薬である．前者の代表がベバシズマブ，後者の代表がセツキシマブ，パニツムマブである．*KRAS*遺伝子野生型であれば先に挙げた抗癌剤3剤に分子標的治療薬2剤を加えた5剤を，*KRAS*遺伝子変異型であれば抗癌剤3剤にベバシズマブを加えた4剤を，大腸癌治療経過中に，どのようにしてうまく使い切っていくかがきわめて重要なポイントである．最新のNational Comprehensive Cancer Network（NCCN）のPractice Guideline（Colon Cancer）や，わが国の大腸癌治療ガイドラインでは[2]，その治療アルゴリズムのなかで，上述の抗癌剤や分子標的治療薬は，いずれも1次治療や2次治療といった順番には関係なく，治療レジメンとして経過中にすべて使い切る形で複数の選択肢が提示されている．

図1A[3]は，米国の代表的な施設の1つであるMD Anderson Cancer CenterとMayo Clinicにおける大

＊ 愛知県がんセンター中央病院薬物療法部部長

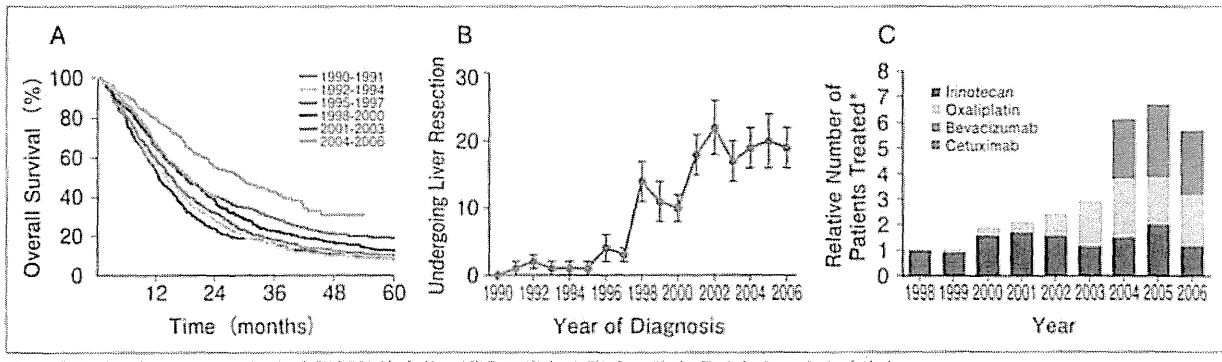

図1　肝切除（Conversion）と分子標的治療薬の導入が進行大腸癌の治療成績向上に大きく寄与
MDACC&Mayo Clinic　　〔参考文献3）より引用改変〕

腸癌化学療法症例の治療成績の年次推移を示したものである．1990年以降，年々治療成績の向上が認められており，特に2004年以降の治療成績が格段に良くなっているのがわかる．その理由として，切除不能の状況から切除可能となった，いわゆるconversion（肝切除）例が急速に増加している（図1B）[3]ことが挙げられる．その背景には，近年の化学療法の進歩と切除への意識が高まったことがあるのではないかと推察される．実際，図1C[3]に示されているように，2004年以降，従来の抗癌剤に加えて，ベバシズマブやセツキシマブといった分子標的治療薬が軒並み臨床導入され，化学療法における分子標的治療薬の役割が増していることが注目すべき点であろう．

以上から，肝切除と分子標的治療薬の導入が近年の進行大腸癌の治療成績向上に大きく寄与しているものと判断される．

以下の項では，それぞれの分子標的治療薬における重要な臨床試験結果や注意すべき副作用を示す．

Ⅱ　ベバシズマブ

ベバシズマブは，血管新生に必須のVEGFに特異的なヒト化IgG1モノクローナル抗体である．抗VEGF-A抗体として血液中のVEGF-Aに結合することで，VEGFR-1とVEGFR-2受容体への結合をブロックし，それ以下のシグナルを遮断する働きがある．それによって，腫瘍部位での腫瘍血管新生を阻害するとともに，密生して複雑化した腫瘍血管を整備することで腫瘍内の組織間圧を軽減させ，抗癌剤の腫瘍への到達（delivery）を改善する作用機序が推測されている．

ベバシズマブの臨床的効果を示す結果が最初にHurwitzらにより報告された（AVF2107g試験）[4]．本試験では，進行大腸癌における1次治療としてイリノテカン＋5-FU＋LV（IFL）＋ベバシズマブ群（5mg/kg/2週）とIFL＋プラセボ群の無作為化比較試験（RCT）が，全生存期間（overall survival：OS）をプライマリーエンドポイントとして行われ，ベバシズマブ群の生存期間中央値（median survival time：MST）が20.3カ月，プラセボ群が15.6カ月であり，ベバシズマブによる明らかな生存期間延長が確認された（HR＝0.66，p＜0.001）[4]．その後，5-FU，CPT-11（IFL）治療後の2次治療として本剤とFOLFOX4併用療法のOSにおける有用性も明らかになった（ECOG 3200試験：FOLFOX4＋ベバシズマブ群のMSTが12.9カ月，FOLFOX4単独群のMSTが10.8カ月）[5]．さらに，現在1次治療の化学療法として全世界で最も広く行われているFOLFOX（FOLFOX4）療法またはカペシタビン＋L-OHP（CapeOX）療法にベバシズマブのon/offを比較するRCT（NO16966試験）が行われ，プライマリーエンドポイントの無増悪生存期間（progression free survival：PFS）は，ベバシズマブ併用群がプラセボ群に比較して有意に延長していた（9.4カ月vs. 8.0カ月，HR＝0.83，p＝0.0023）[6]．上記試験ではいずれもベバシズマブ群の忍容性は十分良好であったが，

本剤に特徴的な毒性である血栓塞栓症・出血・高血圧・タンパク尿・消化管穿孔が認められた．時に致死的となるこれらの毒性には，十分な留意と予測に基づいた臨床的配慮が必要となる．

以上のように，ベバシズマブは化学療法剤との併用により，1次治療と2次治療での有用性が報告され，本剤が大腸癌化学療法のkey drugの1つであるという認識を確固たるものにした．

米国で行われた市販後研究（BRiTE試験）から，ベバシズマブの維持療法の有用性が認められた．すなわち，ベバシズマブを用いた1次治療の増悪（progressive disease：PD）後，2次治療以降にもベバシズマブを継続していく有用性が示唆されたのである（bevacizumab beyond first progression：BBP）[7]．BBPに関しては，ドイツのAIOグループが第Ⅲ相比較試験（ML18147試験）を行っており，2012年1月でプライマリーエンドポイントであるOSにおける優越性が検証されたことがプレスリリースされた．同年の米国臨床腫瘍学会（ASCO）で詳細な結果が報告される予定であり，その内容が注目される．

Ⅲ セツキシマブ

EGFRはレセプタープロテインチロシンキナーゼの代表格であり，HERファミリーのHER1としても知られている．EGFRは正常組織にも発現しているが，大腸癌をはじめとする多くの上皮性腫瘍において過剰発現している．EGFRがEGFやtransforming growth factor α（TGF-α）などのリガンドと結合することで，レセプターの二量化が起こり，レセプターの細胞内チロシンキナーゼドメインが活性化され，これにより，細胞内シグナル伝達が活性化される．細胞内シグナル伝達の代表的な経路はRAS/RAF/MEK/MAPK pathway とPI3K/PTEN/AKT pathwayであり，これらの経路を通ったシグナルは最終的に核内に伝達され，細胞増殖，アポトーシスの抑制，血管新生などが引き起こされる．セツキシマブはIgG1ヒト－マウスキメラモノクローナル抗体であり，EGFRに特異的に結合することにより，シグナル伝達を阻害し，細胞死を誘導する．また，IgG1抗体であることより抗体依存性細胞障害（antibody-dependent cell-mediated cytotoxicity：ADCC）活性を有することが期待されている．

大腸癌では当初2次，3次治療としてCPT-11との併用ならびに単剤で有効性が報告され，その後1次治療としての有用性が明らかとなった．具体的には，1次治療例としてFOLFIRI＋セツキシマブのFOLFIRIに対するPFSの優越性が証明された（CRYSTAL試験）[8]．2次治療としてCPT-11＋セツキシマブはCPT-11に対してOSでの優越性を示せなかったがPFSでの優越性は明らかであった（EPIC試験）[9]．さらに，5-FU，L-OHP，CPT-11抵抗性の3次治療として，セツキシマブ vs. best supportive care（BSC）の比較試験（NCIC CTG CO.17）が報告され，セツキシマブ群がOS，PFSのいずれも有意に優れていた[10]．こうした試験の後解析の結果，本剤と腫瘍組織の*KRAS*遺伝子変異との治療効果における密接な関係，すなわち*KRAS*遺伝子のstatusがセツキシマブのバイオマーカーとなることが明らかとなってきた．KRAS遺伝子変異症例ではセツキシマブの効果は期待できないので，*KRAS*遺伝子野生型での投与が推奨される．

毒性に関して，ざ瘡様皮疹，皮膚乾燥，皮膚掻痒，爪囲炎，裂創などの皮膚障害が必発であることから，本剤投与に当たり，皮膚症状に対するマネジメントが非常に重要である．また，キメラ型抗体であることより，infusion reactionへの配慮も必要となる．

Ⅳ パニツムマブ

パニツムマブはセツキシマブとほぼ同様の機序をもつ抗EGFR抗体薬であるが，IgG2抗体であり，完全ヒト化抗体薬であることから，セツキシマブと比べて，ADCC活性を有さず，infusion reactionの頻度が少ないことが知られている．わが国では2010年に承認され，1次～3次治療まで，すべての治療ラインでの使用が可能となっている．重要な試験としては，1次治療FOLFOX4療法との併用のPRIME試験[11]，

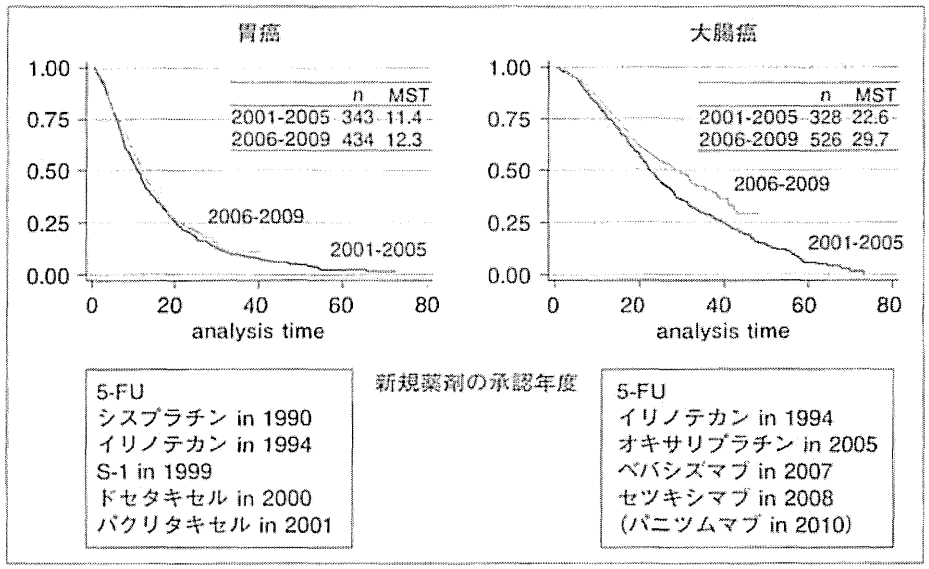

図2
愛知県がんセンター中央病院のデータ
〔参考文献14)より引用改変〕

2次治療FOLFIRI療法との併用の20050181試験[12]，3次治療単剤とBSCとの比較試験（20020408試験）[13]の3つがあり，いずれもプライマリーエンドポイントであるPFSの優越性が検証された．本剤においても*KRAS*遺伝子変異型での効果は認められず，実地臨床においてはセツキシマブと同様に，*KRAS*遺伝子野生型に限定して使用されるべき状況となっている．皮膚毒性に関してもセツキシマブと同等以上に出現するので留意が必要である．

V わが国（当院）の実態

先述したように，米国のMD Anderson Cancer CenterとMayo Clinicにおける近年の分子標的治療薬導入による大腸癌化学療法の治療成績向上のデータを示した．では，わが国ではどのような状況であろうか．図2[14]は当院における化学療法例について年代別の胃癌，大腸癌の治療成績を比較したものである．大腸癌に関して，当院の2001～2005年と2006年以降の2つの年代で生存成績を比較したところ，2006年以降の年代で明らかな生存成績向上が確認された．これは，2005年以降にオキサリプラチンや分子標的薬であるベバシズマブ，セツキシマブの新規薬剤が導入されたことが大きい．一方，胃癌においては，2001～2005年と2006年以降で全く差を認めず，この10年間で進歩がない現状が浮き彫りになった．これは胃癌で有効な抗癌剤として，5-FU系，シスプラチン（CDDP），CPT-11，taxane系とactive drugこそ多く，テガフール・ギメラシル・オテラシルカリウム（S-1）＋CDDP療法という標準的治療も確立されたものの，2001年パクリタキセル承認以降，新規薬剤の導入が進んでいないことが主要因であると思われる．2011年にHER2陽性胃癌に対するトラスツズマブが承認された．胃癌全体の約15%と一部の胃癌ではあるが，明らかな生存期間の延長が認められたトラスツズマブの臨床導入により，今後胃癌全体の治療成績向上が図られることに期待したい．

以上から，新規薬剤，特に最近では有効性の証明された分子標的治療薬の臨床導入が，切除不能進行癌の治療成績向上にとってきわめて重要であるということを強く認識すべきであろう．

VI 今後臨床導入が期待される分子標的治療薬

2012年のAmerican Society of Clinical Oncology-Gastrointestinal Tract Cancer（ASCO-GI）においてCORRECT試験の結果が報告され，regorafenib

の有用性が証明された．Regorafenibは経口マルチキナーゼ阻害薬であり低分子化合物である．血管新生にかかわる受容体型チロシンキナーゼ（VEGFR 1-3，TIE2）および間質系にかかわる受容体型チロシンキナーゼ（PDGFR-β，FGFR），発癌に関与する受容体型チロシンキナーゼ（KIT，PDGFR，RET）に対する阻害作用を有する．CORRECT試験は，プライマリーエンドポイントをOSにおき，標準的化学療法に不応の切除不能進行・再発大腸癌（いわゆるサルベージライン）に対するregorafenibの有用性を評価する多施設共同プラセボ対照二重盲検無作為化比較第Ⅲ相国際共同試験である．本試験では日本からも100例の患者が短期間で登録され，症例集積に大きく貢献した点が注目される．これまでに，切除不能進行・再発大腸癌に対して多数の低分子化合物の開発がなされてきたが，OSの延長には結びつかなかった．多くの試験が初回化学療法における化学療法への上乗せ効果を検証するものであったが，マルチターゲットの低分子化合物の毒性が比較的強く，多岐にわたることから，併用により従来の化学療法剤のdose intensityを下げてしまうことが問題となっていた．本剤は，大腸癌で初めて有効性を示した低分子化合物となったが，単剤でかつサルベージラインでの開発が成功に結びついた主要因であると考えられる．今後の承認，実臨床への応用に期待がかかる．

Ⅶ おわりに

大腸癌化学療法は，5-FU，CPT-11，L-OHPの抗癌剤とベバシズマブ，セツキシマブ，パニツムマブの分子標的治療薬の導入により明らかなOSの延長を獲得し，個別化治療の第一歩を踏み始めた．わが国は長らく欧米で構築されたエビデンスに追従せざるを得ない状況であったが，ここにきて少なくとも薬剤環境に関してはようやく欧米並になった．しかし，まだまだ日本全国のすべての医師が高度に複雑化した大腸癌化学療法を十分に使いこなせているわけではない．1，2年後に承認されるであろうregorafenibではgrade 3以上の手足症候群，倦怠感，高血圧，下痢，皮疹が少なからず認められ，これらの毒性を適切にマネジメントする臨床力が求められる．どんな立場の医療者であろうとも，大腸癌化学療法に携わっている限り，up-to dateの知識の整理と最新の情報収集を怠らず行い，多くの臨床経験を積んでいくことが必要となる．適正な大腸癌化学療法を実践していくために，われわれ臨床家がなすべき課題はますます重く，多くなってきている．

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Trastuzumab for a Patient With Heavily Pretreated Gastric Cancer Plus Massive Ascites and Ovarian Metastasis

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CASE REPORT

A 42-year-old female with a chief complaint of anorexia and abdominal fullness was diagnosed with gastric cancer and referred to our hospital in September 2008. Her oral intake was decreased to one-third of her normal intake. She was the mother of three children and had no significant past medical history. On physical examination, her abdomen was distended with fluid. Her ECOG performance status was 2. Gastroduodenoscopy revealed diffuse infiltration of gastric cancer with the appearance of linitis plastica. Pathological examination showed poorly differentiated adenocarcinoma (Figure 1A) with a signet-ring-cell carcinoma component. Computed tomography (CT) scan revealed massive ascites, thickened gastric wall, and bilateral ovarian metastases.

Beginning in October 2008, chemotherapy with weekly 5-fluorouracil, and methotrexate was administered as first-line chemotherapy. After three chemotherapy cycles, her abdominal distension and oral intake improved. Although the same regimen was continued for one additional month on an outpatient basis, the patient was again admitted in December 2008 with anorexia and abdominal distension due to increased ascites, which necessitated routine twice weekly paracentesis. She refused peritoneovenous shunt placement.

Second-line chemotherapy using paclitaxel was administered four times, with no tumor or ascites response. However, following chemotherapy with docetaxel and intraperitoneal cisplatin injection, there was a decrease in her ascites, and the patient could be discharged.

In April 2009, she was readmitted with fatigue, anorexia, and increased ascites. Paracentesis showed hemorrhagic ascites, which required twice weekly drainage, and she also required weekly transfusions. After two cycles of chemotherapy with triweekly pemetrexed, there was transient response, with a decrease in ascites that changed from hemorrhagic to serous.

In June, the patient's general status worsened, with frequent vomiting caused by gastrointestinal stenosis, massive ascites, and enlarged ovarian metastases (Figures 2A–B). Additionally, she also developed dyspnea with dry cough, and lymphangitic pulmonary metastases of the right lower lung were suspected (Figure 3A). Since she and her family strongly desired additional chemotherapy, the HER2 status of her gastric cancer biopsy specimen was evaluated by immunohistochemistry (IHC: HercepTest™, DAKO, Copenhagen, Denmark) and was found to be strongly positive (3+) (Figure 1B) in accordance with high gene amplification of *HER2* (red signal, Figure 1C).

Because of her deteriorated performance status, trastuzumab monotherapy was initiated (4 mg/kg first dose, then 2 mg/kg weekly). A percutaneous transesophageal gastrostomy was also performed. After three cycles, her dyspnea improved (Figure 3A). After six administrations of trastuzumab, the volume of ascites was

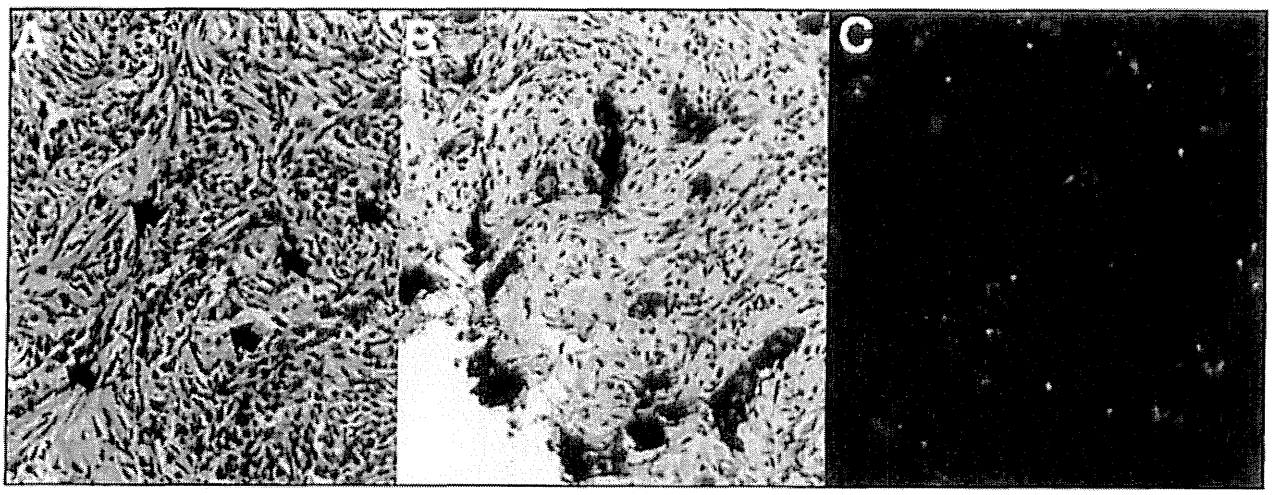

Figure 1. Pathological specimen of the primary gastric cancer. (A) Endoscopic biopsy specimen showed poorly-differentiated adenocarcinoma cells (arrows). (B) HER2 status was evaluated by IHC (HercepTest), and was found to be strongly positive (3+). (C) High gene amplification of HER2 was also seen by FISH (red signal).

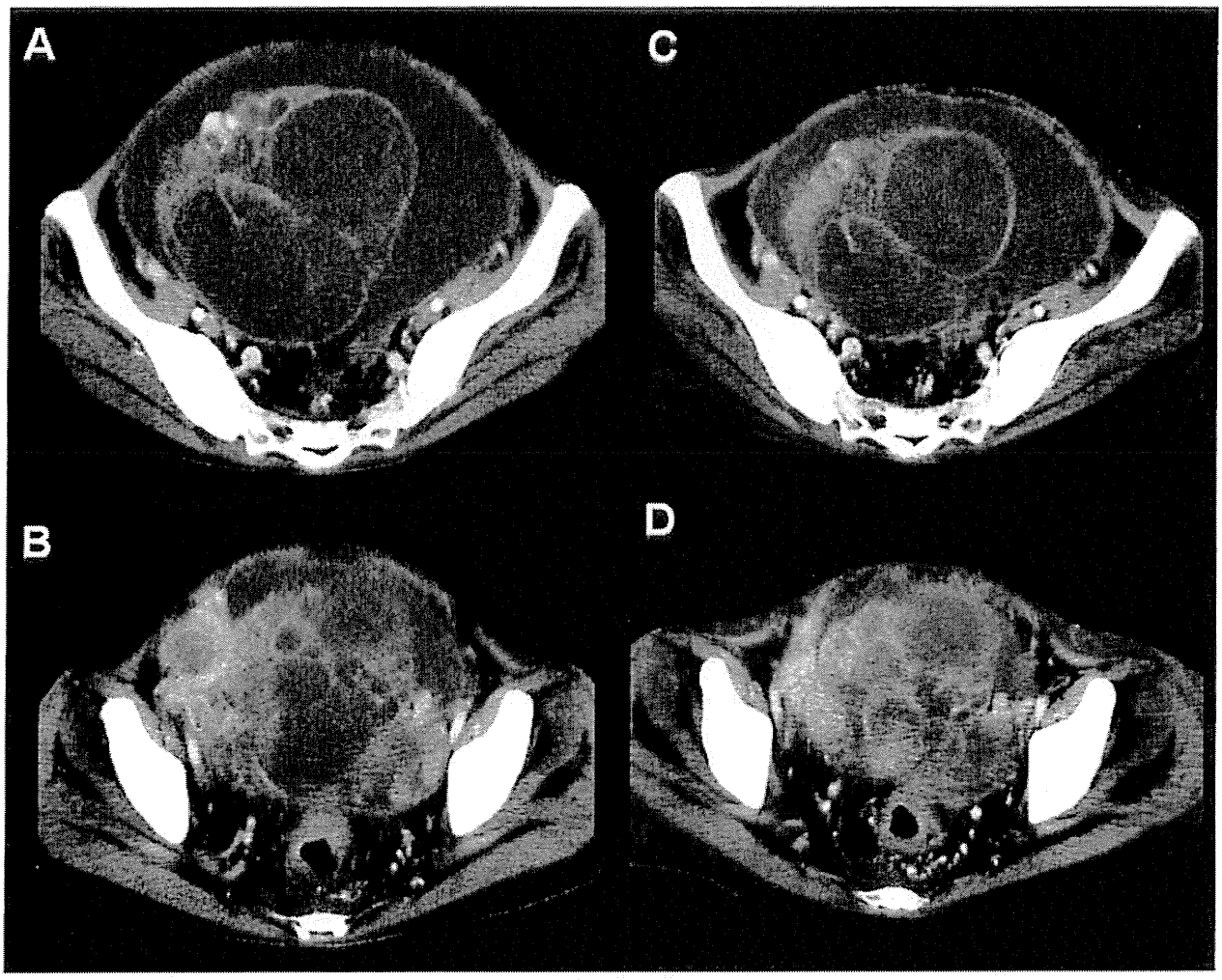

Figure 2. CT scan before and on trastuzumab monotherapy. (A–B) CT scans before treatment showed large ovarian metastasis with ascites. (C–D) CT scans after 6 administrations of trastuzumab showed that her ovarian tumors were slightly reduced.

decreased, and the frequency of paracentesis was reduced from twice to once weekly. A CT scan showed that her ovarian tumors were slightly reduced (Figures 2C–D). No apparent trastuzumab toxicity was observed, and her performance status was maintained for two and a half months. Trastuzumab monotherapy was continued for 3 months until the patient became icteric in September 2009, 11 months after the first admission and 9 months since routine paracentesis was begun. Best supportive care was offered thereafter.

DISCUSSION

Trastuzumab, a recombinant, human–mouse chimeric monoclonal IgG1k antibody that specifically targets HER2 protein, has improved survival in HER2-positive breast cancer patients. In the first pivotal trial of breast cancer, trastuzumab plus paclitaxel or an anthracycline improved overall survival by a hazard ratio of 0.80 (95% confidence interval [CI], 0.64–1.0, $P = .046$) compared with chemotherapy alone.[1] In another trial, trastuzumab plus docetaxel also improved breast cancer survival compared with chemotherapy alone.[2] After these results, trastuzumab-containing chemotherapy became the standard of care for breast cancer patients with HER2 overexpression.[3]

Because HER2-positive gastric cancers have been reported, the efficacy of trastuzumab for HER2-positive gastric cancer has also been anticipated. The ToGA study[4] comparing 5-fluorouracil plus cisplatin with or without trastuzumab showed improved survival in the trastuzumab arm with a hazard ratio for death of 0.74 (95% CI, 0.60–0.91, $P = .0,046$). In contrast to breast cancer, HER2 amplification revealed by fluorescence in situ hybridization (FISH) was seen in gastric cancers with IHC results of 0 or 1+ by modified HercepTest. Therefore, when survival analysis in the TOGA study was limited to HER2 cancers that were 2–3+ by IHC and FISH-positive, the reduction in risk of death became more apparent (HR 0.65; 95% CI, 0.51–0.83). No apparent increase in toxicity was seen in the trastuzumab arm[4]; therefore combination chemotherapy using trastuzumab may become the standard of care for HER2-positive gastric cancer and has been approved in the United States for this indication.

In the TOGA study screening data,[5] the HER2-positive rate was higher in gastroesophageal junction cancer (33.2%) than in gastric cancer (20.9%). In addition, the diffuse type had a lower positive rate (6%) than the intestinal type (34%) of gastric cancer. However,

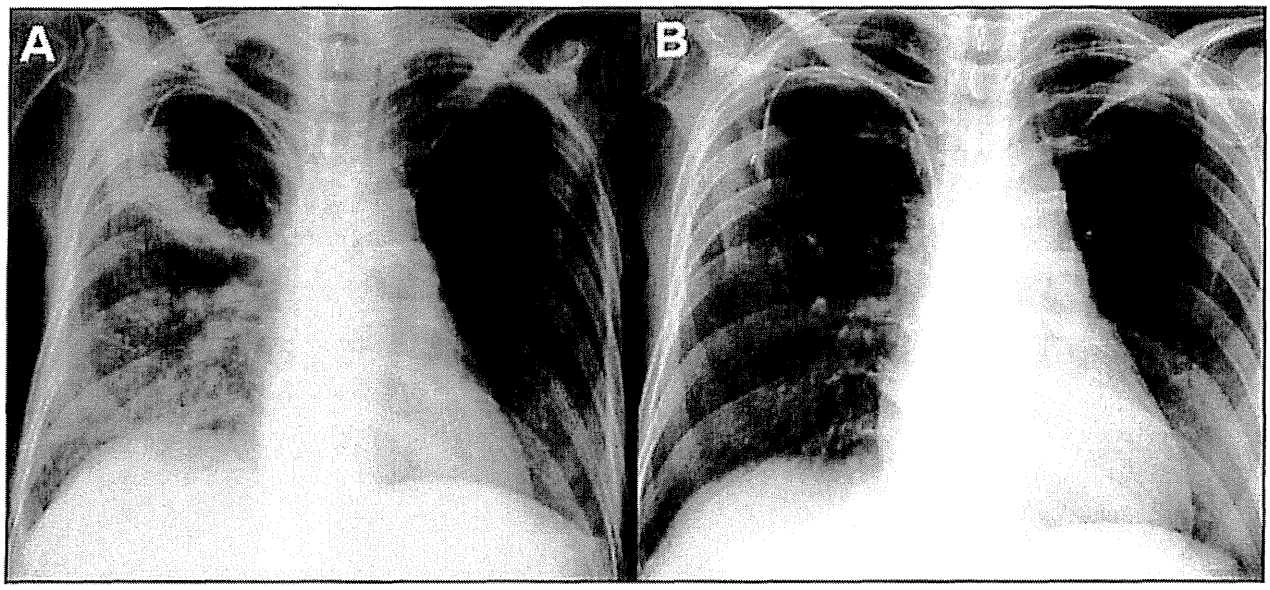

Figure 3. Chest x-ray before and on trastuzumab monotherapy. (A) Lymphangitic pulmonary metastases of right lower lung were suspected. (B) Abnormal finding improved with trastuzumab.

as confirmed by experience with our patient, although patients with diffuse-type gastric cancer are frequently HER2 negative, HER2 status of all gastric cancer types should be evaluated.

Because the ToGA study included chemonaive patients with gastric cancer, the benefit or efficacy of chemotherapy using trastuzumab for patients pretreated with chemotherapy is not currently known. In addition, the antitumor effect of trastuzumab monotherapy is not known. However, trastuzumab monotherapy has been shown to be active with a response rate of 15% in pretreated breast cancer (18% for 3+ IHC),[5] although this is a slightly lower response rate than for monotherapy in chemonaive breast cancer (35% in 3+ IHC),[7] and trastuzumab monotherapy has been adopted for patients who are not considered suitable for cytotoxic chemotherapy.[3]

In summary, this case was instructive for the following reasons: (1) trastuzumab monotherapy was feasible in this heavily pretreated patient with gastric cancer plus massive ascites, (2) trastuzumab and sufficient supportive care were effective in improving the cancer-related symptoms in this patient, (3) although chemotherapy using trastuzumab may become standard first-line chemotherapy for patients with HER2-positive gastric cancer, trastuzumab may even be effective in the salvage setting.

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Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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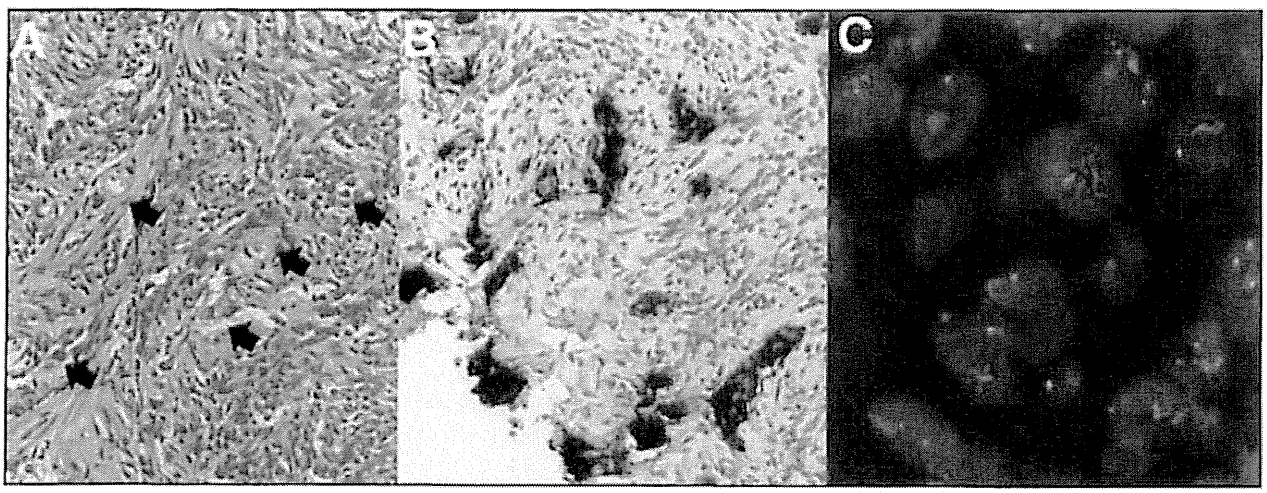

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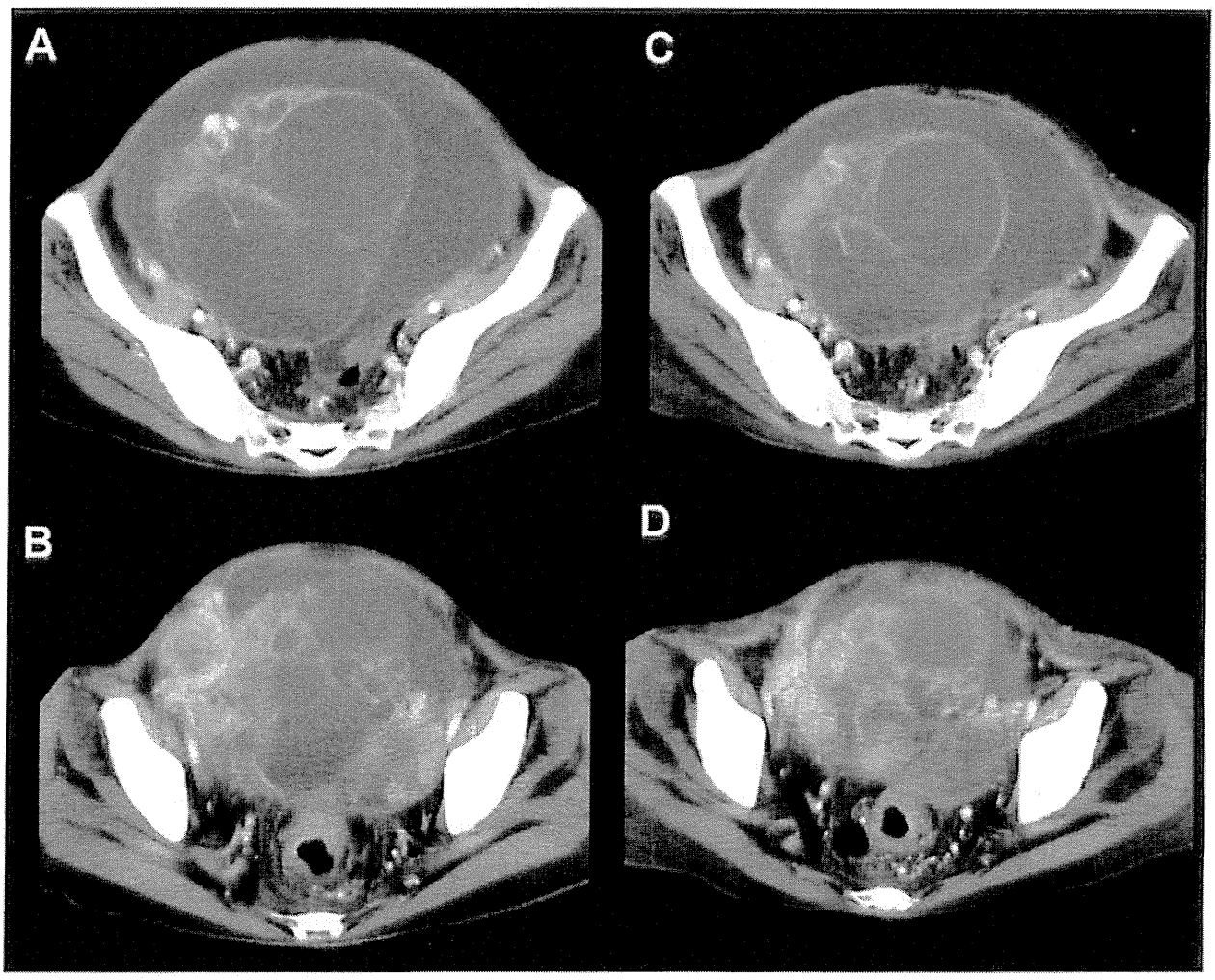

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