Acute toxicities were assessed weekly during CRT and every 2 weeks during additional chemotherapy for 90 days after the completion of CRT. Toxicities were evaluated based on the National Cancer Institute Common Toxicity Criteria (version 2.0). Late toxicity, which first occurred 90 days after CRT initiation, was assessed using the RTOG/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme.

Statistical methods

The primary endpoint was overall survival (OS), which was defined as the time from the date of registration to that of death resulting from any cause, and it was censored at the date of the last follow-up for survivors. Progression-free survival (PFS) was defined as the time from the date of registration to that of disease progression or death resulting from any cause, and it was censored at the date of the last visit for patients without progression. Based on the JCOG 9204 trial results (2), in which the 3-year survival rate was 61% for esophagectomy with adjuvant chemotherapy, we initially calculated the sample size expecting a 3-year survival rate of 60%, with a threshold of 45%. With the alpha and beta error levels set at 0.05 and 0.2, respectively, the required number of eligible patients was 68. We finally decided on a sample size of 76, including ineligible patients. The planned accrual and follow-up periods after registration was closed were 1 and 2 years, respectively. For early termination of this study, an interim analysis was planned once 50% of the patients were accrued. A CR point estimate of <60% at the interim analysis would result in early termination of the study.

The JCOG 9204 had enrolled patients based on the pathologic stage after surgery, whereas we enrolled patients based on the clinical stage diagnosed from CT scans. Therefore, this study might include patients with more advanced stages than those in the JCOG 9204. Thus, the protocol was amended to recalculate the sample size from the expected 50% 3-year survival rate and a threshold of 35% in December 2000. The required sample size was 67. The target sample size remained unchanged. The second amendment in February 2007 prolonged the follow-up period to 5 years after the last enrollment to evaluate late toxicity. These amendments were approved by the Data and Safety Monitoring Committee of JCOG.

Secondary endpoints included CR rate, PFS, and acute and late adverse events. Time-to-event distribution was estimated using the Kaplan-Meier method, and confidence intervals (CIs) were calculated using Greenwood's formula. All analyses were performed using SAS Version 9.1.3 software (SAS Institute, Cary, NC, USA) at the JCOG Data Center, with the final analysis conducted in March 2007.

RESULTS

Patient characteristics

Seventy-six patients, whose characteristics are summarized in Table 1, were accrued between April 2000 and March 2002. The median age was 61 years (range, 39–70). Fifty-nine (78%) and 17 (22%) patients showed ECOG PS of 0 and 1, respectively. Fifty-two patients had T3 disease, and 50 had N1 disease. The clinical stages (UICC-TNM) were IIA for 26 patients, IIB for 12 patients, and III for 38.

Table 1. Patient characteristics

Characteristic	Patients (n = 76)	(%)
Male	68	89.4
Female	8	10.6
Age (y)		
Range	39–70	
Median	61	
Performance status		
0	59	77.6
1	17	22.4
Tumor location		
Upper	3	3.9
Middle	44	57.9
Lower	29	38.2
T factor		
T1	8	10.5
T2	16	21.1
T3	52	68.4
N factor		
N0	26	34.2
N1	50	65.8
Stage		
IIA	26	34.2
IIB	12	15.8
III	38	50.0

Response

Two patients were excluded from the efficacy analysis because of inadequate liver function and T4 disease diagnosed after registration (Fig. 2). Of the 74 eligible patients, 46 achieved CR, resulting in a CR rate of 62.2% (95% CI, 50.1–73.2). The confirmed CR rate in 23 patients with T1–2 disease was 78.3% (95% CI, 56.3–92.5), and that in 51 patients with T3 disease was 54.9% (95% CI, 40.3–68.9).

Survival

There were 49 deaths in the final analysis, and all except 5 patients were followed up for >5 years. The median survival time was 2.4 years (Fig. 3); the 3- and 5-year survival rates were 44.7% (90% CI, 35.2–53.8) and 36.8% (95% CI, 26.1-47.5), respectively. The lower limit of 90% CI for the 3-year survival rate exceeded the threshold of 35%, and the

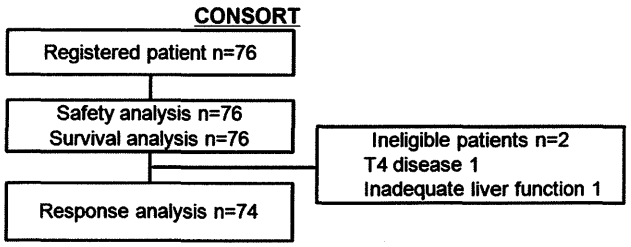

Fig. 2. Consolidated Standards of Reporting Trials diagram.

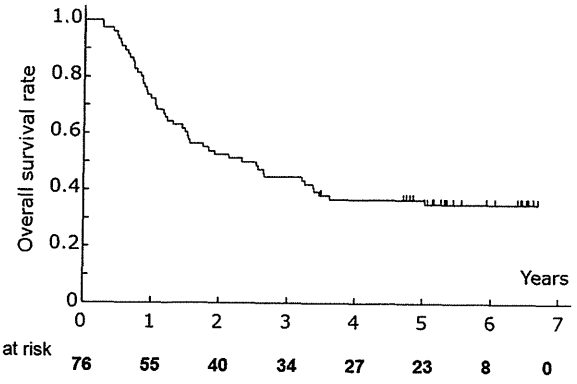

Fig. 3. Overall survival of the 76 patients enrolled in the study.

null hypothesis was rejected ($p = 0.019$). The median PFS was 1 year; the 3- and 5-year PFS rates were 32.9% and 25.6%, respectively (Fig. 4).

Acute toxicity

Data of adverse events for all 76 patients occurring within 90 days after CRT completion are shown in Table 2. Grade 4 leukopenia, neutropenia, anemia, and thrombocytopenia were observed in 1.3%, 1.3%, 2.6%, and 0% of the patients, respectively, whereas Grade 3/4 esophagitis, nausea, infection without neutropenia, and hyponatremia were observed in 17%, 17%, 12%, and 16% of the patients, respectively.

Fifty-three (69.7%) patients completed the 2-course CRT and 2-course additional chemotherapy. Seventy-two (95%) patients received the full dose (60 Gy) of radiation. The treatment protocol was terminated in 23 patients because of disease progression ($n = 10$), toxicity ($n = 11$), patient refusal ($n = 1$), and other reasons ($n = 1$). One early death occurred from esophageal perforation caused by disease progression 21 days after CRT completion. A relationship between early death and the treatment protocol was considered unlikely by the Data and Safety Monitoring Committee.

Late toxicity

Late toxicity data are shown in Table 3. Grade 3–4 late toxicities included pleural (9%) and pericardial (16%) effusion, stenosis, or esophageal fistula (13%), and radiation pneumonitis (4%). Four (5.3%) patients possibly died of treatment-related late toxicity at 3.1, 8.5, 21.3, and 27.8 months after registration. The cause of death were pneumonitis ($n = 2$), pericarditis ($n = 1$), and pleural effusion ($n = 1$). There was no evidence of residual or recurrent disease in these patients. The proportion of any Grade 3/4 late toxicity was 30.1% after 5 years from the initiation of chemoradiation.

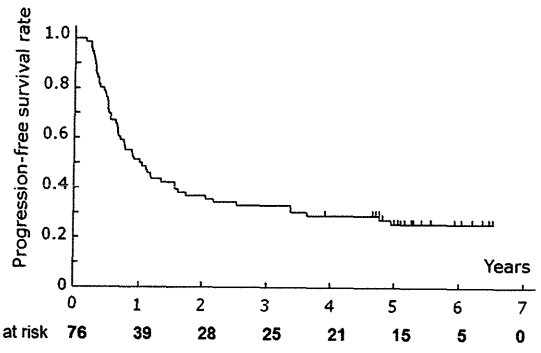

Fig. 4. Progression-free survival rate of the 76 patients enrolled in the study.

Salvage treatment

Twenty-six (34.2%) patients had residual disease or locoregional recurrence without distant metastasis after CRT. Because of inadequate conditions or patient refusal, 7 and 5 patients received chemotherapy and the best supportive care, respectively; the remaining 14 patients received unplanned curative-intent salvage therapy. Eleven patients underwent salvage esophagectomy for residual ($n = 4$) and recurrent ($n = 7$) disease, and the remaining 3 patients underwent endoscopic treatment such as endoscopic mucosal resection (EMR) or argon plasma coagulation. The characteristics of the patients who underwent salvage surgery are described in Table 4.

The median time to salvage surgery after CRT initiation was 13.9 months (range, 4.0–22.7). Six patients underwent esophagectomy with two- or three-field lymph node dissection, 3 patients underwent simple esophagectomy, and 1 underwent only lymphadenectomy; 1 patient could not undergo any resection because of extensive lymph nodes metastasis detected at thoracotomy. Reconstruction was performed using a gastric tube in 7 patients who had R0 resection. There was no operative mortality or hospital death. The median survival time and 3-year survival rate for these 10 patients who received salvage esophagectomy was 16.7 months and 40% (95%C.I: 12.3%–67.0%), respectively.

Of the 3 patients who underwent endoscopic treatment, 1 had mediastinal lymph node metastasis 3 months after argon plasma coagulation, 1 died of surgery-related complication of the pharynx detected 1 year after EMR, and 1 survived for >5 years with no evidence of disease.

DISCUSSION

From the results, CRT for Stage II–III ESCC showed a CR rate of 62.2% (95% CI, 50.1–73.2), a 3-year survival rate of 44.7% (90% CI, 35.2–53.8), and a 5-year survival rate of 36.8% (95% CI, 26.1–47.5). The 3-year survival rate, which is the primary endpoint of this study, met the decision criteria.

Clinically, it is very important to know whether definitive CRT can achieve survival comparable with surgery plus postoperative adjuvant chemotherapy. In this regard, there were several differences in the background between the present study and JCOG 9204 (2) described in Statistical Methods. The study conducted after JCOG 9204, which compared preoperative and postoperative adjuvant chemotherapy comprising the administration of 5-FU and CDDP to Stage II–III esophageal cancer patients (JCOG 9907) (10), could be a reference for this study, because the patients were registered before surgery based on the clinical stage. In the recently

Table 2. Toxicity (n = 76)

	NCI-CTC Version 2.0				
Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	≥Grade 3 (%)
Leukocytes	5	34	32	1	43
Neutrophils	17	31	19	1	26
Hemoglobin	13	35	15	2	22
Platelets	15	13	4	0	5
Dysphagia, esophagitis	29	14	13	0	17
Nausea	25	20	13	–	17
Vomiting	16	6	0	0	0
Diarrhea	10	5	1	0	1.3
Stomatitis/pharyngitis	15	9	6	0	8
Radiation dermatitis	18	4	0	0	0
Febrile neutropenia	–	–	1	0	1.3
Infection without neutropenia	7	8	8	1	12
Hyponatremia	40	–	11	1	16
AST	35	4	3	0	3.9
ALT	43	7	2	1	3.9
Creatinine	15	13	1	0	1.3

Abbreviations: NCI-CTC Version 2.0 = National Cancer Institute Common Toxicity Criteria Version 2.0; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

published results of JCOG 9907, the preoperative chemotherapy arm was highly superior to the postoperative chemotherapy arm in terms of OS. The 5-year survival rate of the postoperative chemotherapy arm in JCOG 9907 did not differ significantly from that in the present study, that is, 38.4% and 36.8%, respectively (10). By contrast, the 5-year survival rate of the preoperative chemotherapy arm in JCOG 9907 was 60.1%, although further follow-up is needed to verify the data. CRT may produce comparable outcomes with surgery plus postoperative adjuvant chemotherapy; however, surgery after preoperative chemotherapy is considered to be superior to CRT. Nevertheless, CRT is one of the treatment options for patients with Stage II and III ESCC because of its apparent advantage of preserving the esophagus, which may provide better quality of life.

Chemoradiotherapy achieves prolonged survival with possibly more late toxicity. Late toxicity after thoracic radiotherapy has been reported in patients with esophageal cancer, lung cancer, and Hodgkin's lymphoma (11–13). Some reports have described that long-term toxicity after CRT results in serious, life-threatening complications. In a previous study, 2 of 78 patients with CR after CRT died of myocardial infarction, and 8 (10.2%) died of pericardial or pleural effusion (14) Late toxicity after CRT against ESCC has not yet been investigated in detail, and early reports of trial outcomes generally seem to underestimate the risk of late toxicity in long-term survivors (15). In the present study, the incidence of ≥Grade 3 late toxicity was similar to that reported in a previous study (14). Most of these events occurred several years after CRT. It is considered that reduction in radiation dose, careful observation, and control of late toxicity may improve post-CRT survival. RTOG 94-05 demonstrated that a higher irradiation dose (64.8 Gy) in CRT was not advantageous with regard to survival and local control, compared with the standard dose (50.4 Gy) (16). One of the reasons was the low tolerability of the high-dose arm because of toxicity. Whereas decreasing the irradiation dose in radiotherapy is essential for reducing late toxicity, the radiation volume is also

Table 3. Late toxicity (n = 76)

	RTOG/EORTC late radiation morbidity scoring scheme					
Late toxicity	Grade 1	Grade 2	Grade 3	Grade 4	≥Grade 3 (%)	≥Grade 4 (%)
Pleural effusion (nonmalignant)	24	5	7	0	9	0
Esophagus-related (dysphagia, stenosis, fistula)	11	4	4	6	13	8
Pericardial effusion	6	5	9	3	16	4
Radiation pneumonitis	33	6	2	1	4	1.3
Skin-related	3	0	0	0	0	0
Spinal cord—related	3	0	0	0	0	0

Abbreviation: RTOG/EORTC: radiation therapy oncology group/european organization for research and treatment of cancer.
Four (5.3%) patients possibly died of treatment-related late toxicity: pericarditis (n = 1), pleural effusion (n = 1), and pneumonitis (n = 2).

Table 4. Characteristics and outcomes in patients who underwent salvage surgery

Characteristic	Patients (n = 11)	Characteristic	Patients (n = 11)
Male	11	Residual/Recurrent	4 /7
Female	0		
Age (y)		Surgical curability	
Range	46–70	R0	7
Median	59	R1 + R2	4
Tumor location			
Upper	0	Operative mortality or hospital death	0
Middle	6		
Lower	5	Relapse after surgery	8
Clinical stage*		No relapse	3
IIA	5		
IIB	0		
III	6		

* Clinical stage at the time of registration.

important. In this study, late toxicity might have been caused by the extended volume of irradiation, which corresponds to the dissected area in extended surgery. In the near future, three-dimensional conformal radiotherapy, which was not mandatory in this study, or other methods based on advanced technology such as intensity-modulated radiotherapy and proton therapy, may have potential advantages over conventional two-dimensional radiotherapy in terms of reduced doses for the heart. A clinical trial with these latest radiotherapy techniques is required (17).

Salvage treatment—*e.g.*, salvage surgery (18–20) or salvage EMR (21)—has recently been reported to have therapeutic potential for patients with local failure of CRT. In our study, one-third of the patients did not achieve CR, and 50% of the remaining patients had recurrence after achieving CR. For the latter, salvage treatment should be indicated, if applicable. Mucosal disease can be removed by EMR, and locoregional residual or recurrent disease can be curatively resected by surgery. It has been reported that 6–34% of patients undergo salvage esophagectomy after definitive CRT (22, 23). Although a high rate of hospital deaths (6–33%) is observed compared with that after surgery without preoperative therapy, some patients achieve long-term survival with a 5-year survival rate of 25–35% (24–26). In the present study, 11 (14.5%) patients underwent salvage esophagectomy and 7 had R0 resection. There was no operative mortality or hospital death. The limitations of salvage surgery include patient tolerance, capability of medical staff, and early detection of residual or recurrent disease; however, salvage esophagectomy can achieve long-term survival. Some patients benefit from salvage surgery after definitive CRT; therefore, this procedure is worth further investigation.

Neoadjuvant CRT has recently been recognized as a standard therapy for resectable esophageal cancer in Western countries. According to CALGB 9781, CRT followed by surgery prolonged survival (median survival time, 4.48 vs. 1.79 years) compared with surgery alone in the treatment of esophageal cancer (27). However, most participants in CALGB 9781 had esophageal adenocarcinoma. Meta-analysis has revealed the survival benefit of neoadjuvant CRT in patients with esophageal adenocarcinoma (28). According to FFCD 9102, which included 90% patients with squamous cell carcinoma, surgery after neoadjuvant CRT (40 Gy) and continuation of CRT to 60 Gy without surgery had the same impact on survival and quality of life for responders as induction CRT (29). The results of a randomized trial from Germany, in which 172 ESCC patients randomly received CRT with or without additional surgery, indicated equal efficacy of surgery and CRT. The median survival times were 16.4 months and 14.9 months, respectively, and the 2-year survival rates were 39.9% and 35.4% with and without surgery, respectively (30). This suggests that CRT, which can preserve organ function, is equally effective as surgery for responders. For nonresponders, salvage surgery can be a therapeutic option. Importantly, which types of patients are benefited by salvage surgery or how the surgical procedure is performed after CRT should be prospectively evaluated. We are planning a Phase II trial of CRT for resectable ESCC, followed by salvage surgery for residual or recurrent disease.

CONCLUSION

Chemoradiotherapy is effective for Stage II–III ESCC with manageable acute toxicities and can provide a noninvasive treatment option. However, further improvement is required for reduction in late toxicity.

REFERENCES

1. The Editorial Board of the Cancer Statistics in Japan. Cancer Statistics in Japan 2007 Foundation for Promotion of Cancer Research.
2. Ando N, Iizuka T, Ide H, *et al.* Surgery plus chemotherapy compared with surgery alone for localized squamous cell carcinoma of the thoracic esophagus: A Japan Clinical Oncology Group Study—JCOG9204. *J Clin Oncol* 2003;21:4592–4596.
3. Kato H, Tachimori Y, Watanabe H, *et al.* Recurrent esophageal carcinoma after esophagectomy with three-field lymph node dissection. *J Surg Oncol* 1996;61:267–272.
4. Ando N, Ozawa S, Kitagawa Y, *et al.* Improvement in the results of surgical treatment of advanced squamous esophageal carcinoma during 15 consecutive years. *Ann Surg* 2000;232: 225–232.
5. Herskovic A, Martz K, al-Sarraf M, *et al.* Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med* 1992;326: 1593–1598.
6. Cooper JS, Guo MD, Herskovic A, *et al.* Chemoradiotherapy of locally advanced esophageal cancer: Long-term follow-up of

a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. *JAMA* 1999;281:1623–1627.
7. Ohtsu A, Boku N, Muro K, *et al.* Definitive chemoradiotherapy for T4 and/or M1 lymph node squamous cell carcinoma of the esophagus. *J Clin Oncol* 1999;17:2915–2921.
8. Hironaka S, Ohtsu A, Boku N, *et al.* Nonrandomized comparison between definitive chemoradiotherapy and radical surgery in patients with T2-3NanyM0 squamous cell carcinoma of the esophagus. *Int J Radiat Oncol Biol Phys* 2003;57:425–433.
9. Japanese Society for Esophageal Diseases. Guidelines for the clinical and pathologic studies on carcinoma of the esophagus. 8th ed. Tokyo: Kanehara Shuppan; 1992.
10. Igaki H, Ando N, Kato H, *et al.* A randomized trial of postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus neoadjuvant chemotherapy for clinical stage II/III squamous cell carcinoma of the thoracic esophagus (JCOG 9907) [Abstract]. *J Clin Oncol* 2008;26(Suppl 15):4510.
11. Carver JR, Shapiro CL, Ng A, *et al.* American Society of Clinical Oncology clinical evidence review on the ongoing care of adult cancer survivors: Cardiac and pulmonary late effects. *J Clin Oncol* 2007;25:3991–4008.
12. Friedman DL, Constine LS. Late effects of treatment for Hodgkin lymphoma. *J Natl Compr Canc Netw* 2006;4:249–257.
13. López RM, Cerezo PL. Toxicity associated to radiotherapy treatment in lung cancer patients. *Clin Transl Oncol* 2007;9: 506–512.
14. Ishikura S, Nihei K, Ohtsu A, *et al.* Long-term toxicity after definitive chemoradiotherapy for squamous cell carcinoma of the thoracic esophagus. *J Clin Oncol* 2003;21:2697–2702.
15. Bentzen SM, Trotti A. Evaluation of early and late toxicities in chemoradiation trials. *J Clin Oncol* 2007;25:4096–4103.
16. Minsky BD, Pajak TF, Ginsberg RJ, *et al.* INT 0123 (Radiation Therapy Oncology Group 94-05) Phase III trial of combined-modality therapy for esophageal cancer: High-dose versus standard-dose radiation therapy. *J Clin Oncol* 2002;20:1167–1174.
17. Zhang X, Zhao KL, Guerrero TM, *et al.* Four-dimensional computed tomography-based treatment planning for intensity-modulated radiation therapy and proton therapy for distal esophageal cancer. *Int J Radiat Oncol Biol Phys* 2008;72:278–287.
18. Nakamura T, Hayashi K, Ota M, *et al.* Salvage esophagectomy after definitive chemotherapy and radiotherapy for advanced esophageal cancer. *Am J Surg* 2004;188:261–266.
19. Hennequin C, Gayet B, Sauvanet A, *et al.* Impact on survival of surgery after concomitant chemoradiotherapy for locally advanced cancers of the esophagus. *Int J Radiat Oncol Biol Phys* 2001;49:657–664.
20. Tomimaru Y, Yano M, Takachi K, *et al.* Factors affecting the prognosis of patients with esophageal cancer undergoing salvage surgery after definitive chemoradiotherapy. *J Surg Oncol* 2006;93:422–428.
21. Hattori S, Muto M, Ohtsu A, *et al.* EMR as salvage treatment for patients with locoregional failure of definitive chemoradiotherapy for esophageal cancer. *Gastrointest Endosc* 2003;58:65–70.
22. Wilson KS, Lim JT. Primary chemo-radiotherapy and selective oesophagectomy for oesophageal cancer: Goal of cure with organ preservation. *Radiother Oncol* 2000;54:129–134.
23. Murakami M, Kuroda Y, Okamoto Y, *et al.* Neoadjuvant concurrent chemoradiotherapy followed by definitive high-dose radiotherapy or surgery for operable thoracic esophageal carcinoma. *Int J Radiat Oncol Biol Phys* 1998;40:1049–1059.
24. Swisher SG, Wynn P, Putnam JB, *et al.* Salvage esophagectomy for recurrent tumors after definitive chemotherapy and radiotherapy. *J Thorac Cardiovasc Surg* 2002;123:175–183.
25. Meunier B, Raoul J, Le Prise E, *et al.* Salvage esophagectomy after unsuccessful curative chemoradiotherapy for squamous cell cancer of the esophagus. *Dig Surg* 1998;15:224–226.
26. Tachimori Y, Kanamori N, Uemura N, *et al.* Salvage esophagectomy after high-dose chemoradiotherapy for esophageal squamous cell carcinoma. *J Thorac Cardiovasc Surg* 2009; 137:49–54.
27. Tepper J, Krasna MJ, Niedzwiecki D, *et al.* Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. *J Clin Oncol* 2008;26:1086–1092.
28. Gebski V, Burmeister B, Smithers BM, *et al.* Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: A meta-analysis. *Lancet Oncol* 2007;8: 226–234.
29. Bedenne L, Michel P, Bouché O, *et al.* Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. *J Clin Oncol* 2007; 25:1160–1168.
30. Stahl M, Stuschke M, Lehmann N, *et al.* Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. *J Clin Oncol* 2005;23:2310–2317.

Invest New Drugs (2012) 30:787–793
DOI 10.1007/s10637-010-9615-z

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

Kohei Shitara · Satoshi Yuki · Motoki Yoshida · Daisuke Takahari · Setsuo Utsunomiya · Tomoya Yokota · Yozo Sato · Yoshitaka Inaba · Masahiro Tajika · Hiroki Kawai · Hidekazu Yamaura · Mina Kato · Kentaro Yamazaki · Yoshito Komatsu · Kei Muro

Received: 5 November 2010 / Accepted: 30 November 2010 / Published online: 22 December 2010

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

K. Shitara (✉) · D. Takahari · T. Yokota · K. Muro
Department of Clinical Oncology, Aichi Cancer Center Hospital,
1-1 Kanokoden, Chikusa-ku,
Nagoya, Aichi Prefecture 464-8681, Japan
e-mail: Kouheis0824@yahoo.co.jp

S. Yuki
Department of Gastroenterology, Hokkaido University Graduate School of Medicine,
Sapporo, Japan

M. Yoshida
Cancer Chemotherapy Center, Osaka Medical College,
Osaka, Japan

S. Utsunomiya
Department of Gastroenterology, Nagoya Kyoritsu Hospital,
Nagoya, Japan

Y. Sato · Y. Inaba · H. Yamaura · M. Kato
Department of Diagnostic and Interventional Radiology,
Aichi Cancer Center Hospital,
Nagoya, Japan

M. Tajika · H. Kawai
Department of Gastroenterology, Aichi Cancer Center Hospital,
Nagoya, Japan

K. Yamazaki
Department of Gastroenterology, Shizuoka Cancer Center,
Shizuoka, Japan

Y. Komatsu
Department of Cancer Chemotherapy, Hokkaido University Hospital Cancer Center,
Sapporo, Japan

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

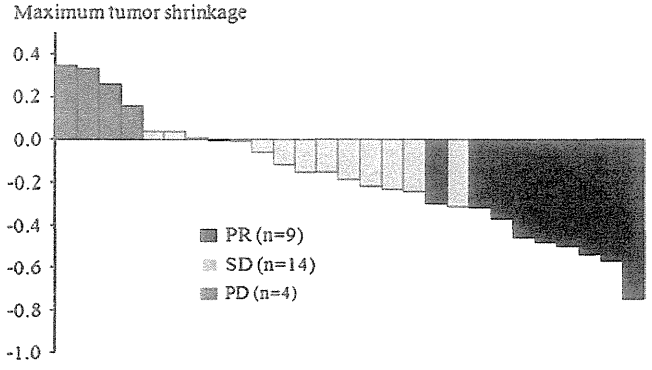

Fig. 1 Maximum tumor shrinkage from baseline. The objective response rate was 30.0%, and the disease control rate was 76.7%. Among the 14 patients with stable disease, 8 patients experienced >10% tumor shrinkage. Three patients were not evaluable for treatment response. Abbreviations: *PR* partial response;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

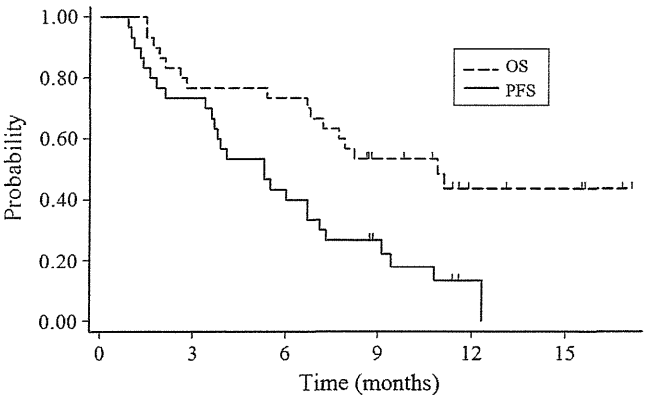

Fig. 2 Progression-free survival and overall survival time. The median progression-free survival was 5.3 months and median overall survival was 10.8 months. Abbreviations: *PFS* progression-free survival; *OS* overall survival

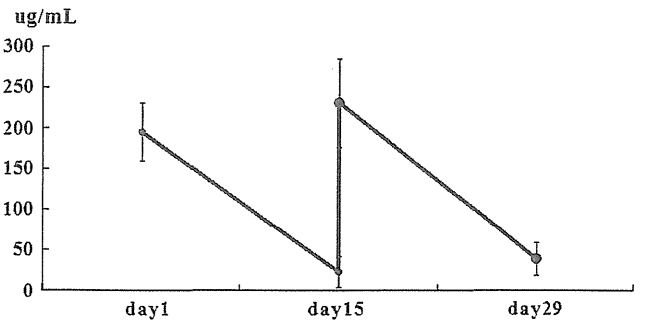

Fig. 3 Mean (±S.D.) peak and trough cetuximab serum concentrations day 1–day 29. The mean of Cmax was 195.20 ug/mL on day 1 and 230.80 ug/mL on day 15, and the mean of trough concentrations was 22.14 ug/mL on Day 15 and 38.34 ug/mL on day 29

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.

Funding None.

Conflict of interest statement None declared.

References

1. Jonker DJ, O'Callaghan CJ, Karapetis CS, Zalcberg JR, Tu D, Au HJ, Berry SR, Krahn M, Price T, Simes RJ, Tebbutt NC, van Hazel G, Wierzbicki R, Langer C, Moore MJ (2007) Cetuximab for the treatment of colorectal cancer. N Engl J Med 357:2040–2048
2. Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, Bets D, Mueser M, Harstrick A, Verslype C, Chau I, Van Cutsem E (2004) Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 351:337–345
3. Karapetis CS, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, Tebbutt NC, Simes RJ, Chalchal H, Shapiro JD, Robitaille S, Price TJ, Shepherd L, Au HJ, Langer C, Moore MJ, Zalcberg JR (2008) K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med 359:1757–1765
4. Di Fiore F, Blanchard F, Charbonnier F, Le Pessot F, Lamy A, Galais MP, Bastit L, Killian A, Sesboüé R, Tuech JJ, Queuniet AM, Paillot B, Sabourin JC, Michot F, Michel P, Frebourg T (2007) Clinical relevance of KRAS mutation detection in metastatic colorectal cancer treated by cetuximab plus chemotherapy. Br J Cancer 96:1166–1169
5. Lièvre A, Bachet JB, Boige V, Cayre A, Le Corre D, Buc E, Ychou M, Bouché O, Landi B, Louvet C, André T, Bibeau F, Diebold MD, Rougier P, Ducreux M, Tomasic G, Emile JF, Penault-Llorca F, Laurent-Puig P (2008) KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. J Clin Oncol 26:374–379
6. De Roock W, Piessevaux H, De Schutter J, Janssens M, De Hertogh G, Personeni N, Biesmans B, Van Laethem JL, Peeters M, Humblet Y, Van Cutsem E, Tejpar S (2008) KRAS wild-type state predicts survival and is associated to early radiological response in metastatic colorectal cancer treated with cetuximab. Ann Oncol 19:508–515
7. Benvenuti S, Sartore-Bianchi A, Di Nicolantonio F, Zanon C, Moroni M, Veronese S, Siena S, Bardelli A (2007) Oncogenic activation of the RAS/RAF signaling pathway impairs the response of metastatic colorectal cancers to anti-epidermal growth factor receptor antibody therapies. Cancer Res 67:2643–2648
8. NCCN Clinical Practice Guidelines in Oncology: Colon Cancer, version 2. 2010.
9. Shitara K, Yokota T, Takahari D, Shibata T, Ura T, Utsunomiya S, Inaba Y, Yamaura H, Sato Y, Najima M, Kawai H, Tajika M, Sawaki A, Yatabe Y, Muro K (2010) Phase II study of combination chemotherapy with irinotecan and cetuximab for pretreated metastatic colorectal cancer harboring wild-type KRAS. Invest New Drugs. 2010 Jan 14. [Epub ahead of print]
10. Tahara M, Shirao K, Boku N, Yamaguchi K, Komatsu Y, Inaba Y, Arai T, Mizunuma N, Satoh T, Takiuchi H, Nishina T, Sakata Y (2008) Multicenter Phase II study of cetuximab plus irinotecan in metastatic colorectal carcinoma refractory to irinotecan, oxaliplatin and fluoropyrimidines. Jpn J Clin Oncol 38:762–769
11. Tabernero J, Ciardiello F, Rivera F, Rodriguez-Braun E, Ramos FJ, Martinelli E, Vega-Villegas ME, Roselló S, Liebscher S, Kisker O, Macarulla T, Baselga J, Cervantes A (2010) Cetuximab administered once every second week to patients with metastatic colorectal cancer: a two-part pharmacokinetic/pharmacodynamic phase I dose-escalation study. Ann Oncol 21:1537–1545
12. Pfeiffer P, Nielsen D, Bjerregaard J, Qvortrup C, Yilmaz M, Jensen B (2008) Biweekly cetuximab and irinotecan as third-line therapy in patients with advanced colorectal cancer after failure to irinotecan, oxaliplatin and 5-fluorouracil. Ann Oncol 19:1141–1145
13. Martín-Martorell P, Roselló S, Rodríguez-Braun E, Chirivella I, Bosch A, Cervantes A (2008) Biweekly cetuximab and irinotecan in advanced colorectal cancer patients progressing after at least one previous line of chemotherapy: results of a phase II single institution trial. Br J Cancer 99:455–458
14. Yatabe Y, Hida T, Horio Y, Kosaka T, Takahashi T, Mitsudomi T (2006) A rapid, sensitive assay to detect EGFR mutation in small biopsy specimens from lung cancer. J Mol Diagn 8:335–341
15. Yokota T, Shibata N, Ura T, Takahari D, Shitara K, Muro K, Yatabe Y (2010) Cycleave polymerase chain reaction method is practically applicable for V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS)/V-raf murine sarcoma viral oncogene homolog B1 (BRAF) genotyping in colorectal cancer. Transl Res 156:98–105
16. Wilke H, Glynne-Jones R, Thaler J, Adenis A, Preusser P, Aguilar EA, Aapro MS, Esser R, Loos AH, Siena S (2008) Cetuximab plus irinotecan in heavily pretreated metastatic colorectal cancer progressing on irinotecan: MABEL Study. J Clin Oncol 26:5335–5343

Characteristics and Outcomes of Patients With Advanced Gastric Cancer Who Declined to Participate in a Randomized Clinical Chemotherapy Trial

By Chiharu Tanai, MD, Takako Eguchi Nakajima, MD, PhD, Kengo Nagashima, Ken Kato, MD, PhD, Tetsuya Hamaguchi, MD, PhD, Yasuhide Yamada, MD, PhD, FACP, Kei Muro, MD, Kuniaki Shirao, MD, PhD, Hideo Kunitoh, MD, Yasuhiro Matsumura, MD, PhD, Seiichiro Yamamoto, PhD, and Yasuhiro Shimada, MD

Medical Oncology Division, National Cancer Center Hospital, Tokyo; Faculty of Pharmaceutical Science, Josai University, Saitama; Medical Oncology Division, Aichi Cancer Central, Aichi; Medical Oncology Division, Oita University, Oita; Investigative Treatment Division, Research Center for Innovative Oncology, National Cancer Center Hospital East, Chiba; Cancer Information Services and Surveillance Division, Center for Cancer Control and Information Services, National Cancer Center, Tokyo, Japan

Abstract

Purpose: There is insufficient data to verify whether participation in clinical trials in itself can lead to better clinical outcomes. We have analyzed the characteristics and outcomes of patients who declined to participate in a randomized trial in comparison with those who participated in the trial.

Patients and Methods: A randomized trial for naive advanced gastric cancer was offered to 286 patients. The trial investigated the superiority of irinotecan plus cisplatin and the noninferiority of S-1 compared with continuous fluorouracil infusion. We retrospectively reviewed the characteristics and outcomes for both participants and nonparticipants in this trial.

Results: Of the 286 patients, 98 (34%) declined to participate in the trial. The rate of declining was significantly higher among younger patients (P = .003), and it varied significantly between attending physicians (range, 23% to 58%; P = .004). There were no other significant correlations between rate of declining and patient characteristics. No significant differences were observed in the clinical outcomes between the participants and nonparticipants, for whom the median survival times were 367 versus 347 days, respectively. The hazard ratio for overall survival, adjusted for other confounding variables, was 1.21 (95% CI, 0.91 to 1.60). No interaction was observed between participation and the various regimens.

Conclusion: There was no difference in clinical outcomes between participants and nonparticipants. However, the patient's age and the doctor-patient relationship may have an effect on patient accrual to randomized trials.

Introduction

A randomized clinical trial (RCT) is the definitive method for comparing the efficacy of treatments, and an RCT is a crucial step in the development of any new cancer treatment. Nevertheless, there is a consistent problem in that low accrual rates limit the progress of RCTs.[1-3]

Several factors that act as barriers to participation in trials have been documented,[1-6] and some have been successfully targeted for improvement.[4-5] Major barriers include a lack of availability of appropriate trials, limitations of eligibility criteria, socioeconomic factors (including insufficient awareness of clinical trials, lack of medical insurance, and geographical limitations), physician triage, and patient decision making. Insufficient data are available on the actual outcomes for nonparticipants in RCTs in comparison with those for participants.[7-11]

We have previously analyzed the characteristics and outcomes of patients who had been referred and were eligible for, but declined to participate in, RCTs and compared them with those of participants, with the aim of developing an approach to improve patient accrual to RCTs.[12] We found no evidence to suggest any significant differences in the characteristics or clinical outcomes between participants and nonparticipants. We also reported that the trial design and the doctor-patient relationship might have an effect on patient accrual to RCTs.

In the present study, we reviewed the characteristics and clinical outcomes of patients who met the eligibility criteria of an RCT designed to compare three different types of therapy, including both injection and oral agents, the levels of toxicity of which were estimated to be quite different. Our analysis was designed to test our previous findings. We also analyzed whether participation in an RCT that compared several arms with different efficacies affected patient outcomes.

Patients and Methods

All the patients who were recruited into this study fulfilled the entry criteria for the Japan Clinical Oncology Group RCT on unresectable or recurrent gastric cancer (JCOG 9912). The patients were informed of all aspects of the trial and were invited to participate. Irrespective of their participation or nonparticipation in the RCT, all received first-line chemotherapy at the National Cancer Center Hospital, Tokyo, Japan, between November 2000 and January 2006. Signed informed consent was obtained from the patients to permit future statistical analysis of data from their clinical courses and outcomes, even if they were treated outside the clinical trials.

The RCT was a three-arm, phase III trial conducted by JCOG to investigate the superiority of irinotecan (CPT-11) plus cisplatin (CDDP) combination chemotherapy and the

noninferiority of *S*-1 compared with continuous fluorouracil (FU) infusion.[13]

The criteria for inclusion of patients were as follows: histologically documented unresectable or recurrent gastric cancer; no prior systematic chemotherapy or radiation therapy except for adjuvant chemotherapy with one oral fluoropyrimidine agent other than *S*-1, completed 6 months earlier; age 20 to 75 years; Eastern Cooperative Oncology Group performance status (PS) of 0 to 2; no history of chemotherapy or radiation therapy for malignant disease other than gastric cancer; and adequate hematologic, hepatic, and renal functions. Those with severe peritoneal dissemination resulting in impaired bowel passage, ascites beyond the pelvic cavity, or wall deformity detected by barium enema were excluded. A measurable lesion was not mandatory. Each patient was required to submit written informed consent before taking part in the RCT.

The treatment schedule of each arm was as follows: (1) Continuous FU infusion: FU was infused continuously over 120 hours; this required hospitalization for 7 days. (2) CPT-11 plus CDDP combination chemotherapy: CPT-11 was infused on days 1 and 15, and CDDP was infused on day 1; this required hospitalization for 5 days. (3) *S*-1 monotherapy: *S*-1 was administered orally on days 1 through 28 and repeated every 6 weeks. Patients were required to undergo a medical examination every 2 weeks. Patients who declined to participate ultimately selected their treatment regimen after discussions with their families and physicians. We provided the selected therapies after confirming that patients fully understood that the standard therapy at that time was FU infusion and that the CPT-11 plus CDDP combination therapy and the *S*-1 monotherapy were still under evaluation.

In the RCT, CPT-11 plus CDDP therapy resulted in a longer survival rate, and *S*-1 showed significant noninferiority compared with FU.[13] The hazard ratio (HR) of CPT-11 plus CDDP versus FU was 0.82 (95% CI, 0.68 to 0.99; $P = .019$). The HR of *S*-1 versus FU was 0.83 (95% CI, 0.68 to 1.00, P for noninferiority $< .001$).

Six male physicians participated in the trial. At the start of the trial (November 2000), physicians A, B, C, D, E, and F had 8, 10, 11, 17, 19, and 19 years of experience, respectively, as gastrointestinal oncologists. One of these six attending staff physicians, together with one, two, or three residents or trainees, attended each consultation. They explained to the patients that this was a JCOG study, that standard therapy was continuous FU infusion, and that we could not tell which arm was superior, but the treatment schedule, toxicities, and required lengths of hospitalization were expected to be different among the various arms. If patients chose not to participate in the study, we recommended the standard therapy, but they could choose other, off-protocol regimens.

We reviewed all the medical records of patients who underwent chemotherapy for unresectable or recurrent gastric cancer between November 2000 and January 2006, and we selected 286 patients who were documented as having been offered the opportunity to participate in the RCT. During the study period, some other patients were judged to be ineligible for the study and were offered other treatments, as clinically indicated, but the number of such patients is not available. Paper and/or electronic medical records from the initial visit to our center to the end of follow-up were reviewed retrospectively. Demographic data (age and sex), medical information (tumor histology, clinical stage, PS, peritoneal dissemination, and therapy characteristics), and clinical outcomes (response rate [RR], follow-up time, overall survival [OS] time, and 1- and 2-year survival rates) were abstracted and analyzed. Response was evaluated by the attending physicians according to the Response Evaluation Criteria in Solid Tumors (RECIST).[14] It is our policy to assess clinical responses to RECIST, even in routine practice. The follow-up time at our institution was defined as the period from the first day of initial therapy to the last visit or the last day of hospitalization at our institution (including death during follow-up). Data on the survival of the patients who left our institution were collected through inquiries to the Japanese official agency for family registries.

The χ^2 test and logistic regression analysis were used to assess associations between patient characteristics and the rate of declining to participate. OS curves were prepared by using the Kaplan-Meier method and were compared with the results of the log-rank test. All participants (those who agreed to be enrolled onto the RCT), including two who were later found to be ineligible after random assignment, and all nonparticipants (those who declined to participate in the RCT), including one who was lost to follow-up, were included in the OS analysis. A Cox proportional hazards model was used to adjust for other potential confounding factors (ie, age, sex, histology, clinical stage, PS, nonsevere peritoneal dissemination, and treatment regimen) in comparing the OS of participants and nonparticipants. Interaction between participation and regimen was tested with an α level of 0.2; $P < .05$ was regarded as significant. Collected data were analyzed by using an SPSS II statistical package (SPSS, Chicago, IL). This study was approved by the institutional review board at the National Cancer Center and was conducted in accordance with the ethical principles stated in Japanese ethics guidelines for clinical and epidemiological studies. No patient explicitly refused to be analyzed for his or her outcome during this study period. The institutional review board approved the use of such clinical data for the study objective.

Results

Table 1 shows the patient characteristics and the rates of declining. A total of 190 patients accepted, and 96 patients (34%) declined, entry into the RCT. There was no significant correlation between the declining rate and sex, clinical stage, PS, tumor histology, or peritoneal dissemination. Patients younger than 60 years declined to participate at a significantly higher frequency ($P = .003$). There were also significant differences in the declining rates between the various attending physicians who informed the patients about the trial and asked for their participation ($P = .004$). The patients were divided equally among the offering physicians by characteristic.

Table 1. Patient Characteristics and Rate of Declining to Participate in Randomized Clinical Trials

	Participants		Non-participants			Participants			Nonparticipants		
Characteristic	No.	%	No.	%	ROD (%)	OR	95% CI	*P*	OR	95% CI	*P*
No.	190		96		16						
Sex											
Male	146	77	64	67	30	1.66	0.97 to 2.85	.07	0.49	0.26 to 0.90	.02
Female	44	23	32	33	42						
Age, years											
< 60	48	25	41	43	46	0.45	0.27 to 0.76	.003	2.54	1.44 to 4.47	.01
≥ 60	142	75	55	57	28						
Clinical stage											
III	1	1	0	0	0						
IV	146	77	70	73	32	1.30	0.74 to 2.26	.36	0.55	0.29 to 1.04	.06
Recurrent	43	23	26	27	38						
PS											
0	104	55	51	53	30						
1	84	44	44	46	34	0.96	0.58 to 1.58	.87	0.85	0.49 to 1.47	.56
2	2	1	1	1	33	0.98	0.09 to 11.07	.99	0.51	0.03 to 7.04	.61
Histology											
Well differentiated	75	39	34	35	31	0.85	0.51 to 1.42	.55	1.05	0.59 to 1.89	.86
Poorly differentiated	115	61	61	64	35						
Undifferentiated	0	0	1	1	100						
Peritoneal dissemination											
Yes	85	45	51	53	38	0.71	0.44 to 1.17	.18	1.54	0.89 to 2.69	.13
No	105	55	45	47	30						
Physicians											
A	31	16	19	20	38			.04			< .01
B	27	14	10	10	27						
C	35	18	13	14	27						
D	25	13	27	28	52						
E	67	35	20	21	23						
F	5	3	7	7	58						

NOTE. Univariate analysis was performed with Pearson's χ^2 test; multivariate analysis was logistic regression analysis.
Abbreviations: ROD, rate of declining; OR, odds ratio; PS, performance status.

Table 2 shows the treatment options of patients who declined to participate in the RCT. Nearly 60% of all those who declined to participate selected *S*-1 monotherapy. Moreover, approximately 70% of nonparticipants who were under 60 years of age selected *S*-1 monotherapy. The proportion of those who selected CPT-11 plus CDDP, which was expected to be more beneficial but showed more severe toxicity and required hospitalization, was not necessarily higher among nonparticipants younger than 60 years than among older nonparticipants. No specific tendency was shown in selection of regimen in relation to the attending physician.

Post-therapy was analyzed in 188 of the participants. This group excluded all 96 nonparticipants, as well as two patients found to be ineligible after random assignment: one patient who developed gastrointestinal bleeding several hours after entry, and another who was later diagnosed with adenosquamous cell carcinoma. Survival was analyzed in the 190 participants and the 96 nonparticipants. There were no treatment-related deaths among either the participants or the nonparticipants. There was no difference in the number of cycles of first-line chemotherapy received by participants or nonparticipants: 53% of the participants and 58% of the nonparticipants received fewer than three cycles ($P = .406$). A total of 85% of the participants and 70% of the nonparticipants were given more than two chemotherapy regimens. Statistically, more participants than nonparticipants were given chemotherapy after the initial therapy ($P = .003$). A total of 14 (7%) of the participants and 6 (6%) of the nonparticipants in the RCT participated later in early-phase clinical trials of experimental therapies.

There were no major differences in clinical outcome between participants and nonparticipants (Figure 1). Clinical response to the initial therapy was analyzed in all 190 participants and 96 nonparticipants. The RR was 30.5% for the participants and 21.9% for the nonparticipants ($P = .121$). The median follow-up time at our hospital was not significantly different between the participants (317 days) and the nonparticipants (292 days). The median survival time (MST) was 367 days for the participants and

Table 2. Characteristics and First Treatment Regimen of Nonparticipants

Characteristic	FU		CPT-11 Plus CDDP		S-1		P*
	No.	%	No.	%	No.	%	
No.	31		8		57		
Sex							
Male	22	34	5	8	37	58	.819
Female	9	28	3	9	20	63	
Age, years							
< 60	10	24	3	7	28	68	.297
≥ 60	21	38	5	9	29	53	
Clinical stage							
IV	20	29	6	9	44	63	.438
Recurrent	11	42	2	8	13	50	
PS							
0	15	29	6	12	30	59	.641
1	16	36	2	5	26	59	
2	0	0	0	0	1	100	
Histology							
Well differentiated	10	29	4	12	20	59	.814
Poorly differentiated	21	34	4	7	36	59	
Undifferentiated	0	0	0	0	1	100	
Peritoneal dissemination							
Yes	16	31	1	2	34	67	.043
No	15	33	7	16	23	52	
Physicians							
A	5	26	1	5	13	68	.363
B	4	40	3	30	3	30	
C	4	31	0	0	9	69	
D	8	30	2	7	17	63	
E	8	40	2	10	10	50	
F	2	29	0	0	5	71	

Abbreviations: FU, fluorouracil; CPT-11, irinotecan; CDDP, cisplatin; PS, performance status.
* Pearson's χ^2 test.

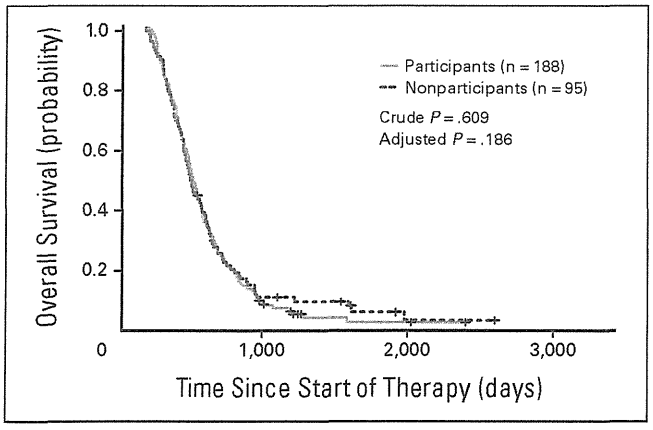

Figure 1. Overall survival of nonparticipants in randomized trials compared with that of participants. No significant difference were observed.

347 days for the nonparticipants. There were no significant difference in OS between the participants and the nonparticipants (Figure 1), and the HR was 1.07 (participants *v* nonparticipants; 95% CI, 0.83 to 1.38). With the Cox proportional hazards model adjusted for sex, age, tumor histology, clinical stage, PS, peritoneal dissemination, and treatment regimen, the HR of participants versus nonparticipants was 1.21 (95% CI, 0.91 to 1.60; $P = .19$). Furthermore, the RR and OS were not significantly different between the participants and the nonparticipants for each regimen. The RR in participants versus nonparticipants was 9.5% versus 6.5% for FU ($P = .646$), 54.0% versus 62.5% for CPT-11 plus CDDP ($P = .648$), and 28.1% versus 24.6% for *S*-1 ($P = .657$). MST in participants versus nonparticipants was 358 days versus 335 days for FU, 435 days versus 458 days for CPT-11 plus CDDP, and 338 days versus 345 days for *S*-1. The HR values for OS were 0.91 (95% CI, 0.57 to 1.44; $P = .679$) for FU, 0.99 (95% CI, 0.38 to 2.56; $P = .981$) for CPT-11 plus CDDP, and 1.22 (95% CI, 0.81 to 1.83; $P = .333$) for *S*-1 (Appendix Figures A1-A3, online only).

We analyzed the interaction between participation and regimen. The *P* value for the interaction term was greater than the α level of 0.2; it was 0.75 for participants and CPT-11 plus CDDP, and 0.28 for participants and *S*-1 (Appendix Table A1, online only).

Discussion

We previously analyzed the characteristics and outcomes of patients who had been referred and were eligible for, but declined to participate in, two RCTs for naive, advanced, non–small-cell lung cancer and compared them with those of participants.[12] Trial 1 was a comparison of four similar combinations of injection therapies (cisplatin-irinotecan, carboplatin-paclitaxel, cisplatin-gemcitabine and cisplatin-vinorelbine), and Trial 2 compared two sequences of injection and oral therapies (four courses of carboplatin-paclitaxel followed by gefitinib or gefitinib until disease progression, followed by carboplatin-paclitaxel). We found that the rate of declining to participate in a trial in which similar injection therapies were compared was lower than that in a trial in which injection and oral therapies were compared (16% *v* 37%). We also reported that there was no evidence to suggest any difference, except for that of the attending physician, in the characteristics and clinical outcomes between participants and nonparticipants.

In the present study, we compared three different regimens, two of which were given by injection and the other as an oral agent. The rate of declining in the present study was 34%, which was as high as that of Trial 2 in our previous study. It is easy to understand that more difficulty is experienced in accepting the randomization of different types of therapy.[8,15] The therapy arms of the present study used different methods of administration; moreover, the estimated toxicities and the need for hospitalization were quite different among the various arms. We thus confirmed our previous finding that trial design influences trial accrual.

Nearly 60% of those who declined entry into the trial selected *S*-1 monotherapy, which may reflect the patients' desire for convenience and a higher quality of life. Younger patients, in particular, preferred this oral agent. We speculate that they may attach greater importance to avoiding hospitalization than to uncertain efficacy. This difference between age groups was a new finding of the present study.

As noted in our previous report, the rate of declining also appeared to be greatly affected by the attending physician. No record was available of which person actually took the initiative and offered the trial at each consultation; however, even when a resident or trainee offered the trial, the attending physician would have taken the responsibility for the consultation. No relationship was found between the length of experience of the physician as a gastrointestinal oncologist and the rate of declining. Each attending physician attempted to present the three regimens equally without showing favor toward any particular regimen; this suggests that individual consultations were not the source of bias. Physicians' clinical communications have been noted as affecting patients' decision making regarding participation in clinical trials.[16] Improved communications and more frequent interventions by clinical research coordinators and other medical staff members for all eligible patients might improve the accrual rate.[17-19] This study did not clarify whether differences in communication skills between physicians led to differences in rates of declining; further investigations of this effect are warranted.

On the other hand, inadequate data are available on the actual outcomes for RCT nonparticipants compared with those of participants.[7-11] Although several reports and a review[7] have suggested the existence of a "trial effect" in which participants enjoy more favorable outcomes, other studies, especially those that attempted to exclude confounding factors, have refuted this finding.[8-11] Our study revealed that the outcomes for participants were no better than those of nonparticipants. Furthermore, our results showing that interactions between participants or nonparticipants and the treatment regimen were not significant (Table 3) may suggest that the conclusion of this RCT could be generalized. The HR for OS between participants and nonparticipants was very close to 1 (0.91; 95% CI, 0.57 to 1.44) in the FU arm, which was the control arm in the trial, and numerically favorable for nonparticipants in the CPT-11 plus CDDP arm and the *S*-1 arm (CPT-11/CDDP: 0.99; 95% CI, 0.38 to 2.56; *S*-1: 1.22; 95% CI, 0.81 to 1.83), which were the testing arms in the trial. This suggests the possibility of a self-selection bias.

Our study has several limitations. First, we selected the participants and nonparticipants retrospectively among those who underwent chemotherapy for advanced gastric cancer during the period in which we conducted the RCT. The fact that all the patients accepted treatment of some sort is, in itself, a selection process, and information on patients who declined all active treatments at our institution remains elusive. There may have been some patients who did not want to continue active treatment and who instead opted for supportive care only, or other patients who declined to participate in the RCT and went to other hospitals. We did not review this population, and if there were any such patients, this may have affected the survival analysis.

Second, the present study was conducted at a single academic institution, and there was an insufficient number of patients. As a result, the numbers of patients in the various subsets were quite small, and it is difficult to rule out significant differences in some of these because of a lack of statistical power. Our investigation should therefore be interpreted as exploratory and hypothesis generating. Our results require further validation at other institutions, preferably on a multi-institutional basis, because the situation may well be different at other institutions.

Third, no data were available regarding the reasons for participation or nonparticipation. Such information would be useful for analyzing factors that affect consent or refusal to participate and would help in improving the accrual rate. However, so that patients are not coerced into participating in the study, reasons for their participation or refusal need to be collected by independent investigators.

In conclusion, we confirmed that the rate of declining to participate in RCTs was influenced by the design of the trial and by the referring physician. The age of the patients also had an effect on the rate of declining, suggesting that some patients may attach a greater importance to not having their normal schedule disrupted than to expectations of efficacy. There was no evidence of any difference in the RRs and survival times between participants and nonparticipants, and the interaction between participants or nonparticipants and the treatment regimen was not significant.

Accepted for publication on September 28, 2010.

Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** None **Stock Ownership:** None **Honoraria:** Hideo Kunitoh, Taiho Pharmaceutical, Yakult **Research Funding:** None **Expert Testimony:** None **Other Remuneration:** None

Author Contributions

Conception and design: Chiharu Tanai, Takako Eguchi Nakajima, Ken Kato, Tetsuya Hamaguchi, Yasuhide Yamada, Kei Muro, Kuniaki Shirao, Hideo Kunitoh, Seiichiro Yamamoto, Yasuhiro Shimada

Administrative support: Takako Eguchi Nakajima

Collection and assembly of data: Chiharu Tanai

Data analysis and interpretation: Chiharu Tanai, Takako Eguchi Nakajima, Kengo Nagashima, Hideo Kunitoh, Seiichiro Yamamoto

Manuscript writing: Chiharu Tanai

Final approval of manuscript: Chiharu Tanai, Takako Eguchi Nakajima, Kengo Nagashima, Ken Kato, Tetsuya Hamaguchi, Yasuhide Yamada, Kei Muro, Kuniaki Shirao, Hideo Kunitoh, Yasuhiro Matsumura, Seiichiro Yamamoto, Yasuhiro Shimada

Corresponding author: Takako Eguchi Nakajima, MD, PhD, Gastrointestinal Oncology Division, National Cancer Center Hospital, Tokyo, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan; e-mail: tnakajima@marianna-u.ac.jp.

DOI: 10.1200/JOP.2010.000106

References

1. Lara PN Jr, Higdon R, Lim N, et al: Prospective evaluation of cancer clinical trial accrual patterns: Identifying potential barriers to enrolment. J Clin Oncol 19:1728-1733, 2001

2. Corrie P, Shaw J, Harris R: Rate limiting factors in recruitment of patients to clinical trials in cancer research: Descriptive study. BMJ 327:320-321, 2003

3. Go RS, Frisby KA, Lee JA, et al: Clinical trial accrual among new cancer patients at a community-based cancer center. Cancer 106:426-433, 2006

4. Nott L, Yeend S, Pirc L, et al: Successfully improving access and accrual to oncology clinical trials. Cancer 109:1451-1453, 2007

5. Umutyan A, Chiechi C, Beckett LA, et al: Overcoming barriers to cancer clinical trial accrual. Cancer 112:212-219, 2008

6. Giuliano AR, Mokuau N, Hughes C, et al: Participation of minorities in cancer research: The influence of structural, cultural and linguistic factors. Ann Epidemiol 10:S22-S34, 2000

7. Braunholtz DA, Edwards SJ, Lilford RJ, et al: Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect." J Clin Epidemiol 54:217-224, 2001

8. Schmoor C, Olschewski M, Schumacher M, et al: Randomized and non-randomized patients in clinical trials: Experience with comprehensive cohort studies. Stat Med 15:263-271, 1996

9. Burgers JA, Arance A, Ashcroft L, et al: Identical chemotherapy schedules given on and off trial protocol in small cell lung cancer response and survival results. Br J Cancer 87:562-566, 2002

10. Peppercorn JM, Weeks JC, Cook EF, et al: Comparison of outcomes in cancer patients treated within and outside clinical trials: Conceptual framework and structured review. Lancet 363:263-270, 2004

11. West J, Wright J, Tuffnell D, et al: Do clinical trials improve quality of care? A comparison of clinical processes and outcomes in patients in a clinical trial and similar patients outside a trial where both groups are managed according to a strict protocol. Qual Saf Health Care 14:175-178, 2005

12. Tanai C, Nokihara H, Yamamoto S, et al: Characteristics and outcomes of patients with advanced non-small cell lung cancer who declined to participate in randomized clinical chemotherapy trials. Br J Cancer 100:1037-1042, 2009

13. Boku N, Yamamoto S, Fukuda H, et al: Randomized phase III study of 5-fluorouracil (5-FU) alone versus combination of irinotecan and cisplatin (CP) versus S-1 alone in advanced gastric cancer (JCOG 9912). Lancet Oncol 10: 1063-1069, 2009

14. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92:205-216, 2000

15. Jenkins V, Fallowfield L: Reasons for accepting or declining to participate in randomized clinical trials for cancer therapy. Br J Cancer 82:1783-1788, 2000

16. Albrecht TL, Eggly SS, Gleason MEJ, et al: Influence of clinical communication on patients' decision making on participation in clinical trials. J Clin Oncol 26:2666-2673, 2008

17. Wright JR, Whelan TJ, Schiff S, et al: Why cancer patients enter randomized clinical trials: Exploring the factors that influence their decision. J Clin Oncol 22:4312-4318, 2004

18. Stryker JE, Wray RJ, Emmons KM, et al: Understanding the decisions of cancer clinical trial participants to enter research studies: Factors associated with informed consent, patient satisfaction, and decisional regret. Patient Educ Couns 63:104-109, 2006

19. Fallowfield LJ, Jenkins V, Brennan C, et al: Attitudes of patients to randomised clinical trials of cancer therapy. Eur J Cancer 34:1554-1559, 1998 41q; 445q;

Commentary: Clinical Trials Represent the Best Cancer Care. Or Do They?

By Charles D. Blanke

The Mayo clinic Web site states "it's not uncommon for your cancer doctor....to discuss the option of a clinical trial as the *best treatment* [emphasis mine]...for your cancer.[1] In fact, it has long been argued that trial participants have better outcomes than those not enrolled onto such studies.[2] Many possible explanations for such a phenomenon exist: patients treated on study are likely to be closely monitored (allowing for early dose adjustments, including escalations, as well as prompt treatment of toxic events); study patients may be more health conscious in general than those not electing to participate; perhaps newer treatments do tend to be better than older standards; and, although it would certainly be hard to definitively prove, it has even been argued clinicians who recruit to trials are in general superior physicians. Of course, reports that attempt to compare trial participants with those treated off-study often attempt to match up different populations with various underlying

imbalances, automatically leading to biases that can skew long-term results.[3]

In this issue of *Journal of Oncology Practice*, Tanai et al[4] describe characteristics and outcomes of patients with gastric cancer who declined to participate in a chemotherapy randomized clinical trial (RCT). In brief, The Japan Clinical Oncology Group recently conducted a three-arm, phase III trial testing irinotecan plus cisplatin versus *S*-1 versus continuous fluorouracil infusion in patients with incurable gastric cancer. Tanai et al actually reviewed medical records of all patients undergoing chemotherapy for advanced stomach cancer between November 2000 and January 2006, and selected 286 patients who were eligible for and had been offered participation in that trial. A variety of information was retrospectively gathered (demographics, performance status, clinical stage, etc), and response and survival outcomes were abstracted. Standard statistical analyses were used in comparing patient characteristics in the groups who participated in the RCT and those who declined, as well as in matching up clinical outcomes. The authors sought to determine whether trial participation itself affected patient outcome, and to confirm whether participants and nonparticipants shared the same characteristics.

Approximately one-third (34%) of patients declined to participate in the RCT. Although FU was recommended to this group, they were allowed to select their own chemotherapy regimen, and approximately 60% elected to take single-agent *S*-1. The RCT itself reported that combination chemotherapy effected longer survival and that *S*-1 was noninferior compared with FU. No significant correlations between rate of declining and sex, stage, or performance status were found; younger patients (< 60 years) refused to participate at a much higher frequency. Rates among each of the six physicians offering the trial also differed significantly. There were no major differences in outcome between participants and nonparticipants. Response rate was 9% lower ($P = .121$) and median survival approximately 5% worse for nonparticipants. Interestingly but probably not surprisingly, given the limited treatment options, similar percentages of participants and nonparticipants went on to participate in early-phase experimental trials. The authors concluded patients may have had difficulty in accepting random allocation to study arms expected to have markedly different toxicity (and perhaps efficacy) rates, not to mention different routes of administration for the included drugs. They also suggested the rate was affected by who was offering the trial, though this did not correlate with the physicians' years of experience as a GI oncologist. Finally, they concluded outcomes for participants in the RCT were no better.

This article has several limitations, many acknowledged by the authors themselves. All patients accepted treatment of some kind, and the authors had no information on the characteristics of patients who elected best supportive care alone. That group very well might differ from those who accepted active chemotherapy, whether given as part of an RCT or not. Patients included in this article still signed informed consent allowing statistical analysis of their clinical course and outcome; those willing to do so might also differ from patients who refused to participate in a trial of any kind. Numbers were very small, so the numerically different outcomes might have become significant with a larger patient pool, particularly calling into question whether those treated off trial truly do as well as those participating in a study. No data were available regarding the reasons underlying refusal to participate; that information could possibly have been useful in overcoming patient resistance and increasing accrual to future studies. Information garnered might not be generalizable because of the nondiverse patient population, with the situation worsened by the fact the study was limited to a single academic institution.

The authors state their data are exploratory, and they do not make any highly controversial conclusions. However, the interesting questions of whether those participating in a trial are different than the overall nonparticipants with the same disease and whether care on a trial is the best care remain unanswered.

Accepted for publication on February 18, 2011.

Author's Disclosures of Potential Conflicts of Interest
The author indicated no potential conflicts of interest.

Charles D. Blanke is with the University of British Columbia and British Columbia Cancer Agency, Division of Medical Oncology.

DOI: 10.1200/JOP.2011.000253

References

1. Ness SM: Living with cancer blog: Cancer clinical trials a choice for cancer treatment. http://www.mayoclinic.com/health/cancer-clinical-trials/MY01391

2. Braunholtz DA, Edwards SJ, Lilford RJ: Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect." J Clin Epidem 54:217-224, 2001

3. Tanai C, Nokihara H, Yamamoto S, et al: Characteristics and outcome of patients with advanced non-small-cell lung cancer who declined to participate in randomised clinical chemotherapy trials. Br J Cancer 100:1037-1042, 2009

4. Tanai C, Nakajima TE, Nagashima K, et al: Characteristics and outcomes of patients with advanced gastric cancer who declined to participate in a randomized clinical chemotherapy trial. J Oncol Pract 7:148-153, 2011

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2012;42(2)134–138
doi:10.1093/jjco/hyr180
Advance Access Publication 12 December 2011

FOLFIRI Plus Bevacizumab 5 mg/kg Versus 10 mg/kg as Second-line Therapy in Patients with Metastatic Colorectal Cancer Who Have Failed First-line Bevacizumab Plus Oxaliplatin-based Therapy: A Randomized Phase III Study (EAGLE Study)

Hideyuki Mishima[1,*], Koji Oba[2], Junichi Sakamoto[3], Kei Muro[4], Takayuki Yoshino[5], Ichinosuke Hyodo[6] and Yoshihiko Maehara[7]

[1]Department of Surgery, National Hospital Organization, Osaka National Hospital, Osaka, [2]Translational Research and Clinical Trial Center, Hokkaido University Hospital, Hokkaido, [3]Social Life Science Specified Non-profit Corporation Epidemiological Clinical Trial Research Support Organization, Nagoya University Graduate School of Medicine, Aichi, [4]Department of Clinical Oncology, Aichi Cancer Center Hospital, Aichi, [5]Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Chiba, [6]Department of Gastroenterology, Institute of Clinical Medicine, University of Tsukuba Graduate School of Comprehensive Human Sciences, Ibaraki and [7]Department of Surgery and Science, Graduate School of Medical Science, Kyushu University, Fukuoka, Japan

*For reprints and all correspondence: Hideyuki Mishima, Department of Surgery, National Hospital Organization, Osaka National Hospital, 2-1-14, Hoenzaka, Chuo-ku, Osaka-shi, Osaka 540-0006, Japan. E-mail: hmishima@onh.go.jp

Received June 1, 2011; accepted November 15, 2011

We planned a multicenter randomized phase III study to evaluate the efficacy of appropriate dose of bevacizumab (5 or 10 mg/kg) with FOLFIRI in patients with advanced/metastatic colorectal cancer who have failed prior bevacizumab plus oxaliplatin-based therapy. The primary endpoint is progression-free survival. The secondary endpoints are the toxicity, response rate, time to treatment failure, overall survival, overall survival from the start of the first-line treatment and second progression-free survival (time duration from the initiation of the first-line treatment until progression after the protocol treatment). A total of 370 patients were considered to be appropriate for this trial.

Key words: bevacizumab – FOLIRI – irinotecan – beyond progression – advanced/metastatic colorectal cancer

INTRODUCTION

Age-adjusted prevalence of colorectal cancer (CRC) is the second largest percentage after that of gastric cancer in males and breast cancer in females in Japan (1). According to the CONCORD study, it is reported that Japanese men attain the first place and Japanese women attain sixth for a 5-year survival rate with CRC in the world (2). Japanese patient's clinical registered data from 1991 to 1994 by the Japanese Society for Cancer of the Colon and Rectum is superior to the same period's data from Survival Epidemiology and End Results and National Cancer Data Base for each of Stage I, II, III CRC, at most 20%.

It is estimated that the number of CRC patients will be 480 396 in 2015 and 512 225 in 2020 (1). It is also expected that the incidence of CRC will overtake that of breast cancer after 2010. Although CRC screening rates were improved, considerably large number of patients had a locally advanced or metastatic disease at the time of diagnosis. For patients with metastatic CRC, recommended first-line regimens by guidelines are FOLFOX or FOLFIRI (3,4) plus biological agents.