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

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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

Characteristic	Participants		Non-participants		ROD (%)	Participants			Nonparticipants		
	No.	%	No.	%		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 ad-

justed 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 par-

ticipants.⁷⁻¹¹ Although several reports and a review⁷ 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.

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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 al⁴ 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.

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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.

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Author's Disclosures of Potential Conflicts of Interest

The author indicated no potential conflicts of interest.

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