



Participants in a randomized controlled trial had longer overall survival than non-participants: a prospective cohort study

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Abstract

Purpose While some studies show improved outcomes in clinical trial participants as compared to non-participants, existence of such a trial effect has not been proved precisely.

Methods This was a prospective cohort study to compare the prognoses for participants in the randomized controlled trial (SELECT BC) and non-participants. SELECT BC compared S-1 and taxane as first-line treatment for metastatic breast cancer. Non-participants were all patients who met the eligibility criteria of SELECT BC and who had been requested to participate in that trial by attending doctors and declined. The study aimed to compare the prognoses between participants and non-participants. The primary endpoint was median overall survival.

Results The median OS in participants was significantly superior to that in non-participants with a statistically significant difference (36.8 months vs. 25.2 months. HR 1.48, $p=0.022$). A similar result was obtained when only patients who received the same chemotherapy (S-1 or taxane) used in SELECT BC after declining participation were assumed as non-participants (36.8 months vs. 22.0 months. HR 2.03, $p=0.006$).

Conclusions This study may suggest the existence of a trial effect, in which, for a given treatment, participation in a clinical trial is associated with a better outcome.

Keywords Overall survival · Prospective cohort study · Randomized control trial · SELECT BC · Trial effect

Introduction

The randomized controlled trial is a widely accepted procedure to establish a standard therapy. While some studies show improved outcomes in trial participants as compared to non-participants [1, 2], others report no trial effect [3, 4]. Peppercorn et al. reported that most studies comparing outcomes between trial and non-trial participants failed to control for potential confounding factors between the groups, and, therefore, available evidence does not support a trial effect on outcomes [5]. Most studies compared

characteristics and survival between clinical trial participants and a matched cohort of non-participants retrospectively.

It has not yet been concluded whether participation per se in a randomized controlled trial provides a better prognosis for patients.

This is an accompanying study to ‘selection of effective chemotherapy for breast cancer’ (SELECT BC) [6]. The SELECT-BC trial was one of the largest randomized controlled trials in Japan on metastatic or recurrent breast cancer patients. This prospective cohort study was designed so that study subjects were all patients who met the eligibility criteria of the SELECT-BC trial and who had been requested to participate by attending doctors. The study aimed to compare prognoses between participants and non-participants who declined to participate in SELECT BC. This study can minimize potential confounding factors in finding trial effect.

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Methods

Study design and patients

The study design, including eligibility criteria and exclusion criteria, has been described in detail elsewhere [7]. Briefly, this study was a prospective cohort study to compare the prognoses for participants in the randomized controlled trial (SELECT-BC trial) and non-participants (UMIN000021099). Non-participants were defined as ‘persons who met the eligibility criteria of the SELECT BC trial but declined to participate.’

The eligibility criteria of the SELECT-BC trial included women aged 20–75 years with histologically confirmed HER2-negative and endocrine treatment-resistant breast cancer, metastatic disease at presentation or recurrence after surgery, an Eastern Cooperative Oncology Group performance status of 0 or 1, no previous chemotherapy for their recurrent or metastatic disease (previous preoperative or postoperative adjuvant use of taxane or oral fluorouracil was allowed if at least 24 weeks had elapsed since the final day of treatment), at least one assessable lesion, a neutrophil count of at least 1500 cells per μL or a white blood cell count of at least 3.000 cells per μL , a platelet count of at least 100,000 cells per μL , aspartate aminotransferase and alanine aminotransferase concentrations of not more than 2.5 times the upper limit of normal at the laboratory where the test was done, and a serum creatinine concentration of not more than the upper limit of normal at the laboratory where the test was done. Patients were ineligible if they were pregnant, breastfeeding, or had HER2-positive tumors (by protein or gene analysis), a history of hypersensitivity to the protocol treatment drugs or their solvents, or a history of other cancers with a disease-free interval of 5 years or less. Patients were also ineligible if they had brain metastases requiring immediate treatment or life-threatening status, such as extensive liver metastases, lymphatic pulmonary metastases associated with subjective symptoms, or pleural effusion, ascites, or pericardial effusion requiring emergency treatment.

The SELECT-BC trial compared S-1 and taxane as first-line treatments for metastatic breast cancer and reported non-inferiority of S-1 with respect to overall survival. The primary endpoint of the SELECT-BC trial was overall survival.

From October 2006 to July 2010, 618 patients were enrolled in the SELECT-BC trial. From August 2009, when this study started, to July 2010, 228 patients were enrolled in SELECT BC and 65 non-participants were registered. The patient profiles of non-participants, including surgical procedure for primary breast cancer, hormone receptor status, and existence of liver metastasis, were reported at registration.

Details of treatments and survival if treatment was chemotherapy, 1st line, 2nd line, or 3rd line, were reported. The primary endpoint of this study was median overall survival.

Ethics

The study was done in accordance with the Ethical Guidelines for Clinical Research of the Japanese Ministry of Health, Labor and Welfare, and the Declaration of Helsinki. Each participant provided written informed consent. An independent ethics committee for each participating site approved the protocol.

Statistical analysis

Baseline characteristics were compared between participants and non-participants. OS was defined as the timespan from the start of this study until death. For the primary analysis, the Kaplan–Meier method was used to estimate survival curves for participants and non-participants, and an unadjusted log-rank test was used to compare the two groups. Also, an additional Cox regression analysis adjusting for baseline covariates was performed to assess the robustness of the unadjusted OS results. Similar analyses were done for participants and non-participants whose first treatment was S-1 or taxane.

All statistical tests were two-sided, and no adjustment for multiplicity was done.

Results

In our study, 65 patients were enrolled from 41 institutions from August 2009 to July 2010 (non-participants). During the same period, 228 patients were enrolled in SELECT BC (participants). Table 1 shows patients’ baseline characteristics. The median age was 58 years; approximately 70% of patients expressed hormone receptor positive; patients with liver metastasis accounted for over 30%. Although de novo stage IV breast cancer was more observed in the participants, there was no background difference between participants and non-participants.

Table 2 shows the first treatment non-participants received. A total of 52 patients received chemotherapy, and 36 patients received either S-1 or taxane. A total of 11 patients received endocrine therapy, and two patients received no treatment.

Table 3 shows the second treatment subsequently administered in each participant and non-participant after their enrollment. A total of 42 non-participants received chemotherapy; among them, 16 patients received either S-1 or taxane. Nine patients received endocrine therapy, and twelve patients received no systematic treatment. Regarding

Table 1 Baseline characteristics

Characteristics	Participants (n = 228)	Non-participants (n = 65)	p*
Age, years			
Median (range)	58 (29–75)	58 (29–74)	0.57
Hormone receptor status, no. (%)			
ER (+) and/or PgR (+)	165 (72)	46 (71)	0.92
ER (–) and PgR (–)	63 (28)	17 (26)	
Unknown	0	2 (3)	
Liver metastasis, no. (%)			
Yes	84 (37)	21 (32)	0.61
No	144 (63)	42 (65)	
Disease-free interval, no. (%)			
< 2 years	40 (18)	13 (20)	0.26
2–5 years	77 (33)	26 (40)	
> 5 years	71 (31)	19 (29)	
Stage IV breast cancer	40 (18)	5 (8)	
Unknown	0	2 (3)	

*Fisher's exact test was used for categorical variables and the Wilcoxon two-sided test for continuous variables

Table 2 Treatment of non-participants

Treatment	No. of patients (%)
Chemotherapy	52 (80)
Protocol treatment	
Docetaxel	6 (9)
Paclitaxel	13 (20)
S-1	17 (26)
Non-protocol treatment	
Capecitabine	8 (12)
Vinorelbine	3 (5)
EC (CEF)	1 (2)
Other	4 (6)
Endocrine therapy	11 (17)
No systemic treatment	2 (3)

chemotherapy, the patients who received taxane were more likely in participants; however, there was no major difference between two groups.

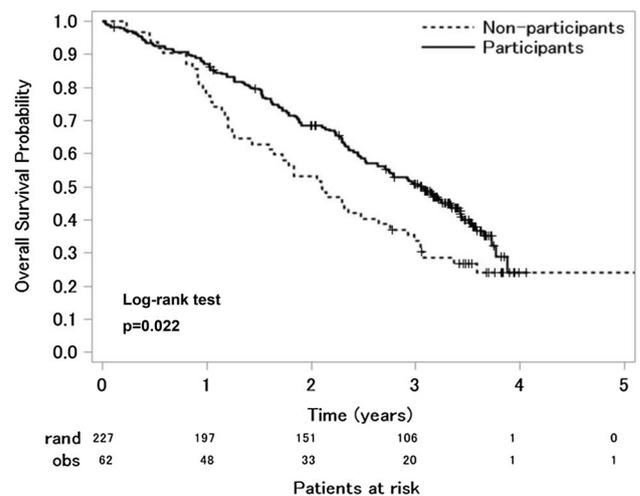
Figure 1 shows the OS of both participants and non-participants. The median OS in participants was significantly superior to that in non-participants with a statistically significant difference (36.8 months vs. 25.2 months. HR 1.48, $p = 0.022$, adjusted HR 1.54, $p = 0.013$).

Figure 2 shows the OS of patients who received either S-1 or taxane among non-participants and participants. The median OS in participants was significantly superior to that in non-participants with a statistically significant difference (36.8 months vs. 22.0 months. HR 2.03, $p = 0.006$).

Table 3 Second treatment of participants and non-participants

Treatment	No. of patients (%)	
	Participants	Non-participants
Chemotherapy	144 (63)	42 (65)
Protocol treatment		
Docetaxel	14 (6)	3 (5)
Paclitaxel	29 (13)	4 (6)
S-1	36 (16)	9 (14)
Non-protocol treatment		
Capecitabine	16 (7)	5 (8)
Vinorelbine	6 (3)	5 (8)
AC (CAF)	5 (2)	1 (2)
EC (CEF)	10 (4)	5 (8)
Nab-paclitaxel ^a	4 (2)	1 (2)
Irinotecan	0 (0)	1 (2)
Gemcitabine	11 (5)	2 (3)
Other	13 (4)	6 (9)
Endocrine therapy	35 (15)	9 (14)
Immunotherapy	1 (0.4)	0 (0)
No systemic treatment	38 (17)	12 (18)
Unknown	10 (4)	2 (3)

^aNanoparticle albumin-bound paclitaxel

**Fig. 1** Kaplan–Meier survival curves for participants and non-participants

The SELECT-BC study was conducted on 618 patients enrolled from October 2006 to July 2010. Appendix Fig. 1 shows a comparison of the OS of these 618 cases as participants with 65 non-participants. In addition, Appendix Fig. 2 shows a comparison of OS between non-participants who received chemotherapy and participants (almost all participants received chemotherapy).

Since we suspected that adherence to a drug administration schedule might not be good in non-participants, the

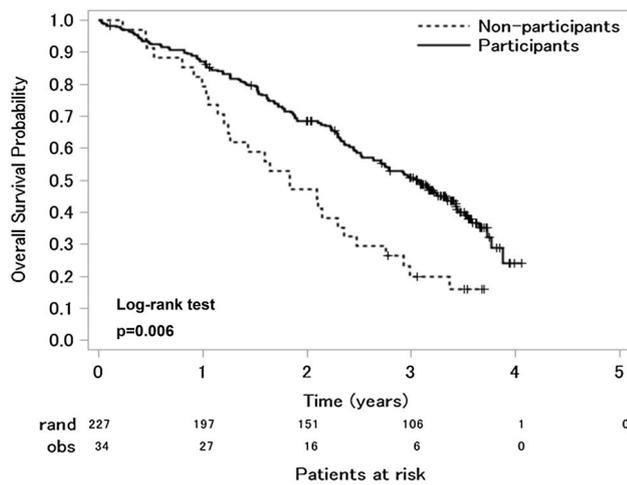


Fig. 2 Kaplan–Meier survival curves for participants and non-participants. (1st treatment regime: TS-1 or taxane)

OS of participants and non-participants who received S-1 were compared; however, there was no significant difference between them (Appendix Fig. 3A). In contrast, a comparison of OS of patients who received taxane showed that the OS of participants was superior to that of non-participants with a statistically significant difference (Appendix Fig. 3B).

Discussion

Comparing the OS of patients who accepted or declined participation in a clinical trial during the same time period, the OS of trial participants was superior to the OS of those who declined, with a statistically significant difference. A similar result was obtained in the case where all patients enrolled in the SELECT-BC study were assumed as participants or only patients who received chemotherapy after declining participation were assumed as non-participants.

There are four possible reasons for trial participants to have improved outcomes when compared with non-trial controls [5]. First, there might be an experimental treatment effect, in which the experimental treatment offered in the trial was better than standard therapy. Second, there might be a participation effect, in which aspects of trial participation other than exposure to investigational therapy might cause the improvement. Third, the improved outcome might result from confounding, or from differences in baseline characteristics that are associated with both enrolment and outcome, rather than from trial participation itself. Fourth, the improvement in outcomes might be due to bias resulting from how the data were gathered.

First, since drugs approved in Japan, such as taxane and S-1, were used in the SELECT-BC study, and there was

no significant difference in the OS between both groups, it could not be an experimental treatment effect. Regarding that this study was a prospective study, the physician in charge judged that participants and non-participants were suitable subjects for the SELECT-BC study. The two groups were formed according to the intentions of the patients, so there seems to be few possibilities to encounter confounding factors. Considering the baseline characteristics, there was no great difference between the groups (Table 1), except that de novo stage IV breast cancer tended to occur more often in participants.

Since the primary endpoint of the SELECT-BC study was the OS, it is unlikely that imaging and follow-up procedures could cause a bias.

Although it is necessary to evaluate carefully whether the results of our study might suggest the presence of trial effects, it would be possible to interpret the obedient patients who tended to participate in the trial had a better prognosis. Although one of the eligibility criteria in the SELECT-BC study was “Endocrine therapy-resistant patients judged by physicians,” 11 patients among non-participants received endocrine therapy. We speculate that in these cases patients’ preference played a major role.

The limitations of our study were as follows: the dose intensity was not evaluated in non-participants; the number of enrolled patients in non-participants was small; the ratio of participants to non-participants could be different in each hospital.

In conclusion, a comparative study of the OS between patients who accepted or declined the proposal of participating in a clinical trial by physicians during the same time period showed that the OS of participants was superior to that of non-participants with a statistically significant difference.

This study may suggest the existence of a trial effect, in which, for a given treatment, participation in a clinical trial is associated with a better outcome.

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Compliance with ethical standards

Conflict of interest SO has received remuneration from Chugai, Eisai Pfizer, AstraZeneca, Kyowa Hakko Kirin, and Taiho; funding from Taiho, Eisai, Chugai, and Daiichi Sankyo. HM has received remuneration from Astra Zeneca, Pfizer, Daiichi Sankyo, Taiho, and Novartis; funding from Japanese government, Eisai, Daiichi Sankyo, and Nip-

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Ethical approval All procedures performed in study involving participants were in accordance with the ethical standards of the institutional or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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