The Impact of Treatment Preferences in Second-Line Chemotherapy on the Prognosis of HER2-Negative Metastatic Breast Cancer

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Keywords

SELECT BC study · First-line chemotherapy · Second-line chemotherapy · Inverse probability weighting estimation

Abstract

Objective: We assessed the impact of treatment preferences in second-line chemotherapy on breast cancer prognosis using the SELECT BC study. **Methods:** The SELECT BC study was performed in patients with HER2-negative metastatic breast cancer treated with initial chemotherapy. From these patients, 618 were assigned to 2 groups (S-1 group, 309; taxane group, 309). The S-1 and taxane groups were each subdivided into 3 groups: crossover group, protocol-recommended group, and other group, and the analysis of overall survival (OS) was performed using Cox regression with inverse probability weighting, to adjust for postrandomization confounding. **Results:** In the taxane group, the OS of the crossover group (39.6 months) was better than that of the protocol-recommended group (35.7 months) and the other chemotherapy group (36.9 months) (vs. the protocol-recommended group, HR 0.72 [95% CI 0.52–0.98], $p = 0.037$; vs. the other chemotherapy group, HR 0.71 [95% CI 0.43–1.18], $p = 0.183$). In the S-1 group, there was no statistically

significant difference in OS between the 3 groups. **Conclusion:** The study of the combination of first-line chemotherapy and second-line chemotherapy showed that S-1 might be recommended as a second-line chemotherapy in patients in whom taxane was the primary chemotherapy.

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Introduction

Taxane is known as one of the standard first-line treatments for metastatic breast cancer; however, patients often suffer adverse events such as hair loss, peripheral nerve disorders, and/or edema; thus, such a reduction in quality of life (QOL) becomes a problem [1–3]. Moreover, all patients need to be treated in a healthcare facility because taxane is given as an injection. In contrast, S-1, which is an oral 5-FU agent, is frequently given to patients in Japan because of its ease of administration, and severe adverse effects are rarely observed [4].

Thus, SELECT BC, a phase III randomized controlled study of treatment with either S-1 or taxane-based chemotherapy drugs as the first-line chemotherapy against

HER2-negative metastatic breast cancer was performed [5].

The overall survival (OS) of the S-1 group was 35.0 months (95% CI 31.1–39.9) and that of the taxane group was 37.2 months (95% CI 33.0–40.1), implying that S-1 is not inferior to taxane drugs with respect to OS (hazard ratio [HR] 1.05, 95% CI 0.86–1.27, $p = 0.015$).

In addition, the S-1 group was significantly superior to the taxane group in terms of QOL, evaluated using the questionnaire of EORTC QOL-C30 in the secondary end-point (ex. global health status; mean difference 4.5 [95% CI 0.2–8.9], $p = 0.039$). As a result of this study, S-1 was added as a standard chemotherapy drug for the first-line chemotherapy in Japan [6].

Although the OS evaluated in the SELECT BC study was over 30 months, the time to treatment failure (TTF) of the S-1 group was 8.0 months and that of taxane was 8.9 months, indicating that duration of treatment after the second-line treatment was longer than TTF of the first-line chemotherapy. During the treatment period after the second-line treatment to death, TTF of the second-line chemotherapy accounted for a large percentage. We thus assessed whether the drug preferences of second-line chemotherapy influence OS using the SELECT BC study.

Because the primary endpoint was OS in the SELECT BC study, the second-line chemotherapy was chosen by the physician. We thus assessed the robustness of the current result showing that S-1 is not inferior to taxane drugs with respect to OS when used in various patterns of a second-line treatment.

Patients and Methods

Study Population

We analyzed data from the SELECT BC study. Patients with histologically confirmed HER2-negative and endocrine treatment-resistant breast cancer, aged 20–75 years, with metastatic disease at presentation or recurrence after surgery, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and no previous chemotherapy for their recurrent or metastatic disease were eligible. The degree of visceral organ involvement was not specified. Enrolled patients were randomly assigned in a 1:1 ratio to receive taxane (docetaxel 60–75 mg/m² at intervals of 3–4 weeks; paclitaxel 80–100 mg/m² weekly for 3 of 4 weeks; or paclitaxel 175 mg/m² at intervals of 3–4 weeks) or S-1 (40–60 mg twice daily for 28 consecutive days, followed by a 14-day break). Details of study design, eligibility and exclusion criteria, and study treatment have been published previously [5].

Second-Line Chemotherapy

Initiation of subsequent second-line chemotherapy was permitted after tumor progression or unacceptable toxicity. Second-

line chemotherapy was chosen by physicians. The study protocol recommended the following second-line chemotherapy regimens, which were regarded as standard when the study started: taxane, S-1, doxorubicin + cyclophosphamide (+ fluorouracil), epirubicin + cyclophosphamide (+ fluorouracil), capecitabine, vinorelbine, cyclophosphamide + methotrexate + fluorouracil, and irinotecan. Second-line chemotherapy was continued until physicians decided to stop it. In reality, endocrine therapy, radiotherapy, and other treatment were performed in some patients as second-line treatment in the SELECT BC study.

Statistical Analysis

We analyzed OS, which was defined as time from randomization to death, in the full analysis set of the study. We classified initiated second-line treatment into 3 categories: the crossover group (S-1 for patients in the taxane group, and taxane for patients in the S-1 group), the protocol-recommended group (who received the protocol-recommended chemotherapy), and the other group (including chemotherapy, endocrine therapy, radiotherapy, and other treatment).

We compared treatment strategies defined based on first- and second-line treatment using the novel statistical methods of inverse probability weighting (IPW) estimation for adaptive treatment strategies [7]. First, we compared first-line S-1 with taxane followed by various patterns of second-line treatment to assess the robustness of previously reported results of second-line treatment patterns. We determined the protocol-recommended treatment proportion as 0.3 and the fixed crossover proportion as 0.4 in accordance with the actual clinical conditions of the second-line treatment. Second, we classified initiated second-line chemotherapy into 3 categories: crossover group, protocol-recommended group and other chemotherapy group (chemotherapy alone in the other group). We compared combinations of first- and second-line chemotherapy, for example first-line S-1 and second-line taxane versus first-line S-1 and second-line protocol-recommended chemotherapy, to evaluate whether second-line chemotherapy affects OS.

We predicted the probabilities of each patient following each treatment strategy using multinomial logistic regression models, to adjust for potential measured baseline and time-varying confounders. Included baseline covariates were status of estrogen and progesterone receptors, liver metastasis, numbers of lymph node metastasis, time to recurrence from surgery, history of adjuvant taxane, oral fluorouracil, and endocrine therapy. Included time-varying covariates were time to second-line treatment initiation modeled by restricted cubic spline functions, ECOG performance status, progression status, and treatment withdrawal due to adverse events. We used multinomial logistic models in each group separately to account for group-by-covariate interaction. After calculating weights using the predicted probabilities above, we estimated survival curves of OS under each treatment strategy using the IPW Kaplan-Meier method and compared them by IPW Cox regression. Standard errors were estimated via the bootstrapping method when estimating hazard ratios for first- and second-line combinations; otherwise, the sandwich variance estimator was used to take IPW into account.

All the analyses were conducted using SAS version 9.4 (SAS institute, Cary, NC, USA). All the p values were two sided. $p < 0.05$ was considered nominally significant without multiplicity adjustment.

Fig. 1. A CONSORT diagram showing enrollment, randomization, and second-line treatment of the study patients.

Results

Patient Characteristics

Six hundred and eighteen patients were included in the SELECT BC study, with 309 patients assigned to each of 2 groups: the taxane group and the S-1 group. We excluded 10 patients that were ineligible and 16 patients that were not able to start assigned treatment, and then analyzed the remainder: a total of 286 patients in the taxane group and 306 patients in the S-1 group.

The patients who started second-line treatment comprised 241 patients in the taxane group and 266 patients in the S-1 group. The crossover group in the taxane group comprised 110 patients (45.6%), the protocol-recommended group comprised 76 (31.5%), and the other group comprised 55 patients (22.8%). The crossover group in the S-1 group included 114 patients (42.9%), the protocol-recommended group included 68 (25.6%), and the other group 84 patients (31.6%) (Fig. 1). The back-

ground of patients in the taxane group and in the S-1 group in the second-line treatment was very similar (Table 1).

Comparison under Various Patterns of Second-Line Treatment Proportion

As the actual ratio of the crossover group, protocol-recommended group, and other group was 0.4:0.3:0.3 in the SELECT BC study, we calculated the HR of the S-1 group in comparison with the taxane group in 2 ways: one by changing the ratio of the crossover group and the other group while keeping the ratio of the protocol-recommended group fixed at 0.3, and the other by changing the ratio of the protocol-recommended group and the other group while keeping the ratio of the crossover group fixed at 0.4 (Table 2). Fitted multinomial regression models are presented in online supplementary material (see www.karger.com/doi/10.1159/000479033 for all online suppl. material).

Table 1. Baseline characteristics of each second-line treatment

Characteristics	Taxane		S-1			<i>p</i> value
	crossover (<i>n</i> = 110)	protocol- recommended (<i>n</i> = 76)	other (<i>n</i> = 55)	protocol- recommended (<i>n</i> = 68)	other (<i>n</i> = 84)	
Median age, years	57.0 (50.0–62.0)	58.0 (50.5–65.5)	58.0 (50.0–65.0)	58.5 (52.5–65.5)	59.0 (52.5–65.5)	0.950
Hormonal receptor status						
ER positive and/or PgR positive	80 (72.7)	59 (77.6)	47 (85.5)	48 (70.6)	68 (81.0)	0.440
ER negative and PgR negative	28 (25.5)	16 (21.1)	8 (14.5)	17 (25.0)	15 (17.9)	
Unknown	2 (1.8)	1 (1.3)	0 (0.0)	3 (4.4)	1 (1.2)	
Liver metastasis						
Yes	43 (39.1)	23 (30.3)	17 (30.9)	20 (29.4)	23 (27.4)	0.200
No	67 (60.9)	53 (69.7)	38 (69.1)	48 (70.6)	61 (72.6)	
HER2						
Negative	99 (90.0)	70 (92.1)	53 (96.4)	62 (91.2)	77 (91.7)	0.757
Unknown	11 (10.0)	6 (7.9)	2 (3.6)	6 (8.8)	7 (8.3)	
Disease-free interval						
≤2 years	28 (25.5)	12 (15.8)	10 (18.2)	17 (25.0)	11 (13.1)	0.128
2–5 years	33 (30.0)	31 (40.8)	21 (38.2)	22 (32.4)	36 (42.9)	
≥5 years	32 (29.1)	21 (27.6)	19 (34.9)	16 (23.5)	30 (35.7)	
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	1 (1.2)	
Without surgery	17 (15.5)	12 (15.8)	5 (9.1)	12 (17.6)	6 (7.1)	
Components of (neo)adjuvant treatment						
Taxane	33 (30.0)	21 (27.6)	18 (32.7)	22 (32.4)	26 (31.0)	0.078
Oral fluoropyrimidine	14 (12.7)	10 (13.2)	10 (18.2)	7 (10.3)	9 (10.7)	0.801
Endocrine therapy	62 (56.4)	49 (64.5)	39 (70.9)	60 (52.6)	58 (69.0)	0.044

Data are *n* (%) or *n* (IQR). There were no significant differences between the groups in any of the characteristics listed in this table. ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor. Taxane was docetaxel or paclitaxel.

Table 2. Comparison of the first-line chemotherapy with S-1 and taxane under various proportions of second-line treatment

Proportion			Hazard ratio (95% CI)
crossover	protocol- recommended	other	
A <i>Under fixed protocol-guided treatment proportion at second-line treatment</i>			
0.0	0.3	0.7	0.91 (0.67–1.24)
0.1	0.3	0.6	0.94 (0.71–1.23)
0.2	0.3	0.5	0.96 (0.75–1.23)
0.3	0.3	0.4	0.98 (0.78–1.23)
0.4	0.3	0.3	1.00 (0.81–1.24)
0.5	0.3	0.2	1.03 (0.83–1.26)
0.6	0.3	0.1	1.05 (0.85–1.30)
0.7	0.3	0.0	1.07 (0.85–1.35)
B <i>Under fixed crossover proportion at second-line treatment</i>			
0.4	0.0	0.6	1.04 (0.79–1.38)
0.4	0.1	0.5	1.03 (0.80–1.32)
0.4	0.2	0.4	1.01 (0.81–1.27)
0.4	0.3	0.3	1.00 (0.81–1.24)
0.4	0.4	0.2	0.99 (0.80–1.22)
0.4	0.5	0.1	0.98 (0.79–1.22)
0.4	0.6	0.0	0.97 (0.76–1.24)

The minimal value of HR was 0.91 (95% CI 0.67–1.24) when the ratio of the protocol-recommended group was fixed at 0.3 when the ratio of the crossover group was 0 and that of the other group was 0.7; the maximal value was 1.07 (95% CI 0.85–1.35) when the ratio of the crossover group was 0.7 and that of the other group was 0.

Also, as the ratio of the crossover group was fixed at 0.4, the minimal value of HR was 0.97 (95% CI 0.76–1.25) when the ratio of the protocol-recommended group was 0.6 and that of the other group was 0; the maximal value was 1.04 (95% CI 0.79–1.38) when the ratio of the protocol-recommended group was 0 and that of the other group was 0.6.

Comparison of All Chemotherapies

We calculated OS for each combination of the first-line chemotherapies and the second-line chemotherapies (Table 3). When the first-line chemotherapy was taxane and the second-line chemotherapy was either crossover, protocol-recommended, or other chemotherapies, the OS of the crossover group was 39.6 months, that of the protocol-recommended group was 35.7 months, and that of the other chemotherapy group (chemotherapy alone in the other treatments) was 36.9 months. The OS of the

crossover group was better than the other 2 groups (vs. protocol-recommended group, HR 0.72 [95% CI 0.52–0.98], $p = 0.037$; vs. other chemotherapy group, HR 0.71 [95% CI 0.43–1.18], $p = 0.183$) (Fig. 2a).

When the first-line chemotherapy was S-1, the OS of the crossover group was 34.0 months, that of the protocol-recommended group was 38.9 months, and that of the other chemotherapy group was 42.0 months. Despite the differences in median OS, survival curves were close to each other except around 3 years (Fig. 2b), indicating that there was no significant difference between them (Table 3).

Discussion

In the current study, we found that the hazard ratio of the S-1 arm to the taxane arm for OS was almost unchanged under various patterns of second-line treatment proportion. According to these data, our results of the SELECT BC study demonstrated the robustness of the current result, showing that the effect of S-1 as the first-line chemotherapy is not inferior to taxane drugs independent of the choice of the second-line chemotherapy.

The increase in the number of drugs for treatment of metastatic breast cancer has resulted in improved breast cancer prognosis [8, 9]. Therefore, it is crucial not only to choose the first-line chemotherapy but also to establish drug preferences after the first-line chemotherapy [10].

Regarding the current use of anthracycline and taxane to treat HER2-negative metastatic breast cancer, it has been reported that there was no difference in OS for patients treated with these 2 drugs, regardless of the order [11]. In addition, some controlled trials of the second-line chemotherapies in patients who have become anthracycline-resistant showed the superiority of taxane [12, 13].

In the current study, we assessed the impact of the combination of the first-line chemotherapy and the second-line chemotherapy on metastatic breast cancer. Our study shows that OS was improved by S-1 treatment as the second-line chemotherapy following the first-line chemotherapy with taxane. Of interest, P-glycoprotein, which is overexpressed on the cell membrane of cancer cells, is known to contribute to taxane resistance. In fact, HCT-15 cells derived from human colorectal cancer cells which express high levels of P-glycoprotein showed resistance to taxane [14, 15]. On the other hand, it was reported that HCT-15 cells are sensitive to S-1 treatment [16], suggesting that S-1 is effective on cancer cells which are resistant to taxane. Some other preclinical data were also

Fig. 2. Kaplan-Meier estimates of overall survival. **a** Taxane as the first-line chemotherapy. **b** S-1 as the first-line chemotherapy.

Table 3. Comparison of different chemotherapies

Second-line treatment	Median overall survival, months	Hazard ratio (95% CI) <i>p</i> value for superiority	
		vs. A3	vs. A2
A Taxane as first-line chemotherapy			
A1: Crossover	39.6	0.71 (0.43–1.18) <i>p</i> = 0.183	0.72 (0.52–0.98) <i>p</i> = 0.037
A2: Protocol-recommended	35.7	0.99 (0.61–1.62) <i>p</i> = 0.971	–
A3: Other chemotherapy	36.9	–	–
Second-line treatment	Median overall survival, months	Hazard ratio (95% CI) <i>p</i> value for superiority	
		vs. B3	vs. B2
B S-1 as first-line chemotherapy			
B1: Crossover	34.3	1.06 (0.74–1.53) <i>p</i> = 0.739	1.16 (0.85–1.60) <i>p</i> = 0.350
B2: Protocol-recommended	38.9	0.91 (0.62–1.34) <i>p</i> = 0.644	–
B3: Other chemotherapy	42.0	–	–
C Either taxane or S-1 as first-line chemotherapy			
C1: Crossover	36.5	0.89 (0.66–1.19) <i>p</i> = 0.423	0.92 (0.74–1.15) <i>p</i> = 0.461
C2: Protocol-recommended	37.8	0.96 (0.72–1.29) <i>p</i> = 0.810	–
C3: Other chemotherapy	38.6	–	–

reported [17, 18]. Our study showed that the use of S-1 as the second-line chemotherapy is more beneficial for patients when taxane is used as the first-line chemotherapy.

The strength of this analysis is that the population was well defined and well followed for survival outcomes. Another strength is that several dosing regimens were permitted in the taxane arm. The regimens reflect standard of care, thus making this trial more of a “real-world comparison.”

There are a few limitations which are inherent to the parent study. The mixed subtypes of HER2-negative patients make it difficult to parse out whether triple-negative patients have the same magnitude of benefit as the ER-positive patients. Because second-line chemotherapy was chosen by physicians, postrandomization confounding would be introduced for second-line chemotherapy [19]. This confounding can be adjusted by the IPW estimation technique if sufficient confounders were measured. In the current study, the expected prognosis factor was adjusted by IPW, but we still cannot exclude the possibility that unknown confounding factors may be present.

In this study, our data from the SELECT BC study showed the robustness of the current result demonstrating that the effect of S-1 as the primary chemotherapy is not inferior to taxane drugs independent of the choice of

the second-line chemotherapy. Moreover, our study of various combinations of the first-line chemotherapy and second-line chemotherapy indicated that S-1 could be recommended for second-line chemotherapy in patients in whom taxane was used as the primary chemotherapy.

Statement of Ethics

All procedures performed in this study were in accordance with the ethical standards of the institutional or Japanese ethical guidelines for epidemiological research and with the 1964 Helsinki Declaration and its later amendments.

Disclosure Statement

H.M. received research grants from Novartis, Taiho, and Pfizer. The other authors declare no competing interests.

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