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Original Article

Hormonal Therapy Resistant Estrogen-receptor Positive Metastatic Breast Cancer Cohort (HORSE-BC) Study: Current Status of Treatment Selection in Japan

Takayuki Iwamoto^{a*}, Naruto Taira^a, Tomomi Fujisawa^b, Kazuhiro Araki^c,
Kentaro Sakamaki^d, Takafumi Sangai^e, Yuichiro Kikawa^f, Tadahiko Shien^a,
Shintaro Takao^g, Masako Sato^h, Yoshinari Gotoⁱ, Takashi Yoshidaⁱ,
Masato Takahashi^h, Tomohiko Aihara^j, and Hirofumi Mukai^k

^aDepartment of Breast and Endocrine Surgery, Okayama University Hospital, Okayama 700-8558, Japan,

^bDepartment of Breast Oncology, Gunma Prefectural Cancer Center, Ota, Gunma 373-0828, Japan,

^cDepartment of Breast Medical Oncology, The Cancer Institute Hospital, Japanese Foundation for Cancer Research, Koto-ku, Tokyo 135-0063, Japan, ^dDepartment of Biostatistics and Bioinformatics, Graduate School of Medicine,

The University of Tokyo, Bunkyo-ku, Tokyo 133-8654, Japan, ^eDepartment of Breast and Thyroid Surgery, Chiba University Hospital, Chiba, 260-8677, Japan, ^fDepartment of Breast Surgery, Kobe City Medical Center General Hospital, Kobe 650-0047, Japan, ^gDepartment of Breast Surgery, Hyogo Cancer Center, Akashi, Hyogo 673-0021, Japan,

^hDepartment of Breast Surgery, National Hospital Organization Hokkaido Cancer Center, Sapporo 003-0804, Japan,

ⁱDepartment of Breast Surgery, Ota Memorial Hospital, Ota, Gunma 375-8585, Japan, ^jBreast Center, Aihara Hospital, Mino, Osaka 562-0004, Japan, ^kDivision of Breast and Medical Oncology, National Cancer Center Hospital East,

Kashiwa, Chiba 277-8577, Japan

The Hormonal therapy resistant estrogen-receptor positive metastatic breast cancer cohort (HORSE-BC) study is a multicenter observational study evaluating the efficacy and safety of secondary endocrine therapy (ET) for postmenopausal cases of metastatic breast cancer (MBC) with poor response to primary ET. In this initial report we analyze the HORSE-BC baseline data to clarify the current status of treatment selection for MBC in Japan. Baseline data for the 50 patients enrolled in HORSE-BC were analyzed, including patient characteristics, types of secondary ET, and reasons for selecting secondary ET. Postoperative recurrence was detected in 84% of patients (42/50) and *de novo* stage IV breast cancer in 16% (8/50). Forty-one patients (41/50; 82%) received fulvestrant, 5 patients (10%) received selective estrogen receptor modulators (SERMs), 3 patients (6%) received ET plus a mammalian target of rapamycin (mTOR) inhibitor, and 1 patient received an aromatase inhibitor (AI) as the secondary ET. Forty-five patients selected their secondary ET based on its therapeutic effect, while 14 patients selected it based on side effects. Most patients with progression after primary ET selected fulvestrant as the secondary ET based on its therapeutic and side effects. We await the final results from the HORSE-BC study.

Key words: breast cancer, secondary endocrine therapy, low sensitivity, primary endocrine therapy, fulvestrant

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*Corresponding author. Phone: +81-86-235-7265; Fax: +81-86-235-7269
E-mail: tiwamoto@cc.okayama-u.ac.jp (T. Iwamoto)

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Metastatic breast cancer (MBC) typically requires life-long treatment, which aims to prolong survival and improve/protect quality of life. Thus, treatment for MBC is selected based on the cancer's clinical and pathological characteristics, especially regarding the statuses for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor type 2 (HER2), which predict clinical response and prognosis. An algorithm was proposed by Hortobagyi [1] to help guide this treatment selection process. Endocrine therapies (ETs) are the mainstay of treatment for hormone receptor-positive (HR+) cancers, and aromatase inhibitors (AI) have become the preferred first-line treatment among postmenopausal patients [2,3]. Unfortunately, some patients do not respond to first-line ET because of primary or acquired resistance [4]. Thus, after disease progression, the second-line treatment options include other steroid or nonsteroidal classes of AIs, fulvestrant (an ER antagonist), tamoxifen, and molecularly-targeted therapies (e.g., inhibitors of mammalian target of rapamycin [mTOR] and cyclin-dependent kinase [CDK4/6]) [5-8]. In cases that respond to primary ET, continued ET is needed because even secondary ET has an antitumor effect after the primary ET loses its efficacy. However, it remains challenging to treat cases with resistance to the primary ET, which indicates low sensitivity to ET.

Several models for classifying ET sensitivity and tolerance have been proposed based on the clinical course of the initial ET. For example, the second International Consensus Guidelines for Advanced Breast Cancer proposed classifying ET resistance for ER+ MBC based on the time from ET initiation to progression [9], with primary resistance defined as relapse during the first 2 years of adjuvant ET or disease progression during the first 6 months of first-line ET. Secondary (acquired) endocrine resistance was defined as relapse at >2 years during adjuvant ET, or relapse within 12 months of completing adjuvant ET, or for MBC, progression at ≥ 6 months after initiating ET while on ET. In addition, "very low" drug sensitivity has been proposed as a classification for cases with recurrence during the first 2 years after starting postoperative adjuvant ET or during the first 3 months after starting first-line ET, with "low" drug sensitivity defined as cases with recurrence at >2 years after starting postoperative adjuvant ET [4]. Thus, a clinically significant treatment effect may be obtained using secondary ET, even in cases with low sensitivity

to the primary ET. However, endocrine resistance is a significant problem in treating breast cancer, as approximately 30% of patients with MBC regress during initial ET and an additional 20% have prolonged stable disease [4, 10]. The durations of response to second and subsequent lines of therapy are substantially lower [11, 12]. Nevertheless, no clinical trials have evaluated the efficacy and safety of the numerous available secondary ETs for cases with poor responsiveness to the primary ET.

The Hormonal therapy resistant estrogen-receptor positive metastatic breast cancer cohort (HORSE-BC) study is a multicenter observational study that is currently underway to evaluate the efficacy and safety of secondary ETs among postmenopausal ER+ HER2-cases of MBC that did not respond favorably to primary ET, and to clarify the effect of any reactivity to the primary ET based on the tumor characteristics. This information will be useful to complement Hortobagyi's therapeutic algorithm. In this initial report, we analyze the baseline data from HORSE-BC to provide a description of the current status of treatment selection for MBC in Japan.

Patients and Methods

The multicenter observational HORSE-BC study is currently evaluating therapies that were selected based on physician and patient preferences in 50 cases that were registered between February 2016 and January 2017 [13]. This study's protocol was approved by our institutional review board (protocol number: K1606-001) and all patients provided written informed consent. The major inclusion criteria were 1) postmenopausal status; 2) stage IV breast cancer at the first visit or breast cancer with progression or recurrence after treatment; 3) planned ET for MBC; 4) previous ET using any endocrine drug as (a) continuous postoperative adjuvant therapy with recurrence within 5 years after starting ET or (b) initial treatment for MBC with disease progression within 9 months after starting ET; and 5) no previous chemotherapy for breast cancer or adjuvant chemotherapy during the last 6 months. Cases where $\geq 1\%$ of the tumor cells stained positive for ER and/or for PR were considered HR+, while HER2-cases were defined as having an immunohistochemistry score of 0/1+ or a HER2/CEP 17 ratio < 2.0 using fluorescence *in situ* hybridization.

The treatment choices were various medicines that are covered by the Japanese Medical Insurance as ET for postmenopausal breast cancer, excluding ET drugs that were used in the patient's previous treatment. Treatments were selected based on a discussion between the physician and patient, and their safety and efficacy were monitored for each of 3 patient groups: an SERM group (patients who received tamoxifen or toremifene, which are selective estrogen receptor modulators [SERMs]), an AI group (patients who received anastrozole, letrozole, or exemestane), a SERD group (patients who received fulvestrant, which is a selective estrogen receptor down-regulator [SERD]), and an mTORi group (patients who received any combination of ET and everolimus, which is an mTOR inhibitor).

In this initial report, we analyze the baseline data of the HORSE-BC, including the patient characteristics, types of adjuvant and first-line ET, types of secondary ET, and reasons for selecting the secondary ET, in order to provide a description of the current status of treatment selection for MBC in Japan.

Results

The characteristics of the 50 patients are summarized in Table 1. The median age was 66 years (range: 41-88 years), and the median body mass index (BMI) was 23.4 kg/m² (range: 16.4-31.9 kg/m²). All patients were ER+ and 80% (40/50) were PR+. Most patients (49/50) had a pre-treatment PS value of 0-1, with 90% (45/50) having invasive ductal carcinoma and 10% (5/50) having invasive lobular carcinoma. Postoperative recurrence was detected for 84% of the patients (42/50), and this recurrence group had a median duration of 30.5 months between surgery and recurrence (range: 5.3-58.9 months). *De novo* stage IV breast cancer was detected in 16% of the patients (8/50), and these patients had a median first-line ET duration of 5 months (range: 2.3-10.8 months). No adjuvant chemotherapy was provided to 42% of the patients (21/50), and 58% (29/50) received adjuvant chemotherapies including anthracycline- and/or taxane-containing regimens.

The adjuvant and first-line ETs are summarized in Table 2. Twenty patients with recurrence after surgery (20/42; 47.6%) received letrozole as the adjuvant ET, 17 patients (40.4%) received anastrozole, 2 patients received exemestane, and 3 patients received tamoxifen.

Table 1 Patient characteristics

Age (years)	66	(41-88)
BMI (kg/m ²)	23.4	(16.4-31.9)
ER		
0%	0	0%
1-9%	0	0%
≥ 10%	50	100%
PR		
0%	10	20%
1-9%	8	16%
≥ 10%	32	64%
PS		
0	42	84%
1	7	14%
2	1	2%
3	0	0%
4	0	0%
Histological type		
IDC	45	90%
ILC	5	10%
TNM staging at initial diagnosis		
I	2	4%
II	21	42%
III	18	36%
IV	8	16%
Unknown	1	2%

Data are reported as the median (range) or a number and percentage.

BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor; PS, performance status; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma.

Table 2 Adjuvant and first-line endocrine therapy

Adjuvant endocrine therapy	Patients	
Letrozole	20	47.6%
Anastrozole	17	40.5%
Exemestane	2	4.8%
Tamoxifen	3	7.1%
First-line endocrine therapy		
Letrozole	5	62.5%
Anastrozole	2	25.0%
Exemestane	0	0%
Tamoxifen	1	12.5%

Five cases of *de novo* stage IV cancer (5/8; 62.5%) were treated using letrozole, and the remaining cases were treated using anastrozole (2 cases) or tamoxifen (1 case).

The secondary ETs are summarized in Table 3. Forty-one patients (41/50; 82%) received fulvestrant, 5 patients (10%) received SERMs, 3 patients (6%) received

Table 3 Preference of secondary endocrine therapy in this cohort*

Agents	SERMs	AIs	SERD	mTORi
Number of cases	5	1	41	3
Reasons for choice				
Therapeutic effects	5	1	36	3
Side effects	1	0	13	0
Cost	0	0	2	0
Others	0	0	2	0

SERMs, selective estrogen receptor modulators; AIs, aromatase inhibitors; SERD, selective estrogen receptor down-regulator; mTORi, the combined use of an endocrine therapy and everolimus. Multiple answers were allowed.

ET plus an mTOR inhibitor, and only 1 patient received an AI. In collaboration with their physicians, 45 patients selected their secondary ET based on its expected therapeutic effect, 14 patients selected it based on side effects, and 2 patients selected it based on cost (multiple answers were allowed) (Table 3).

Discussion

The present study revealed that most patients with progression after primary ET had low sensitivity and selected fulvestrant as a secondary ET. In this context, fulvestrant suppresses estrogen signaling by binding to ER and inducing a conformational change [14,15], which subsequently blocks dimerization and triggers accelerated degradation and down-regulation of ER [14]. Fulvestrant may exhibit a lack of cross-reactivity with tamoxifen, and cancers that progress during fulvestrant treatment may remain sensitive to further ET [16]. Ellis *et al.* have reported that fulvestrant treatment (500 mg) improved overall survival, compared to anastrozole, in the first-line setting for ER+ advanced breast cancer [17]. First-line fulvestrant therapy (500 mg) is also supported by the results of the phase III double-blind FALCON trial [18], which evaluated patients with locally advanced or metastatic breast cancer using a strict definition for ET-naïve disease [18]. In addition, the comparison of 500 mg versus 250 mg of fulvestrant in the CONFIRM trial revealed that the higher dose provided an overall survival advantage in the second-line setting [19]. Moreover, treatment was associated with only mild or moderately severe adverse events (e.g., arthralgia), which did not require treatment

interruption or lead to mortality [18,19]. However, during the enrolment period for the present study, fulvestrant was not approved as a first-line ET for advanced or stage IV breast cancers in Japan, although it has subsequently been approved for HR+ advanced or stage IV breast cancers, which will significantly change the selection of first-line ET in Japan.

Interestingly, only 3 patients selected mTOR inhibitor treatment. The combination of an mTOR inhibitor plus a steroidal AI is a valid option for some postmenopausal patients who experience progression after non-steroidal AI treatment, as it significantly prolongs progression-free survival (PFS), although it does not improve overall survival [20]. Nevertheless, a higher proportion of patients discontinue mTOR inhibitor treatment because of adverse events (29%) [20], which is consistent with earlier reports [7,21]. Thus, combination treatments should be considered on a case-by-case basis, especially in the context of related toxicities [22]. The present study revealed that side effects were the second most important factor influencing treatment selection. In this context, the combination of ET and CDK4/6 inhibitors is the most important advance for managing HR+ cases, and first-line AI plus CDK4/6 inhibitor therapy for postmenopausal patients provides a significant improvement in PFS, with an acceptable toxicity profile, although the overall survival benefit remains unclear [22].

Cost was the third most important factor influencing treatment selection in the present study. In this context, drugs receiving accelerated approval enter the market as Food and Drug Administration-approved products, despite unclear evidence regarding their clinical benefit, and insurers must decide whether and how to pay for them. Those decisions are becoming increasingly complex in light of the rising prices for drugs [23]. Thus, it is important to identify patients with the greatest anticipated benefit, although there are no biomarkers (aside from HR status) for predicting the benefit from drugs. It is possible that *ESR1* mutation will be a biomarker for HR+ advanced breast cancers after prolonged AI treatment, as the SoFEA study revealed improved PFS in patients with this mutation who received fulvestrant (vs. exemestane), whereas no significant difference was observed among patients with the wildtype *ESR1* [24]. Moreover, the PALOMA3 study revealed *ESR1* mutations in plasma samples from 25.3% of patients with other mutations that were associ-

ated with acquired resistance to prior AI.

The main strength of the present study was that the patients and physicians were able to select any endocrine agent without a defined treatment algorithm. This information is important, as better data are needed to clarify the efficacy and safety of secondary ETs for breast cancer with low sensitivity to the primary ET, and to facilitate evidence-based selection of an appropriate secondary ET. In conclusion, the baseline data of the HORSE-BC study revealed that most patients with progression after primary ET selected fulvestrant as the secondary ET based on its therapeutic and side effects. We await the final results from this study.

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