P4-13-09 Sequential 2nd Line Endocrine Therapies Is Still Effective Strategy for Endocrine Less Sensitive Postmenopausal ER+ and HER2- Advanced Breast Cancer Patients

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BACKGROUND

- ✓ Several classification models for sensitivity and resistance to endocrine therapies have been proposed for the clinical course associated with initial endocrine therapy.
- ✓ Although endocrine therapy remains a foundation of treatment for hormone receptor-positive advanced breast cancer in the era of current molecular targeted drug, it has been unclear how to choose sequential strategy during the clinical course in terms of endocrine responsiveness.

OBJECTIVES

- ◆ **Endpoint:** To evaluate the efficacy and safety of secondary endocrine therapy among estrogen receptor (ER)-positive, and human epidermal growth receptor (HER) 2-negative postmenopausal metastatic breast cancer patients who had (very) low sensitivity to initial endocrine therapy.

METHODS

Study Design and Patients

◆ A multicenter observational cohort study (**H**orm**O**nal therapy **R**esi**S**tant **E**strogen receptor-positive **B**reast cancer **C**ohort: HORSE-BC) was performed for 2nd-line treatment of physician and patient preference.

Major Inclusion Criteria

1. ER-positive breast cancer.
2. Postmenopausal status.
3. Stage IV or progression /recurrence advanced breast cancer.
4. Planned endocrine therapy for advanced breast cancer.
5. ECOG performance status of 0 or 1.
6. Previous endocrine therapy with any endocrine drugs.
7. Definition of Endocrine Sensitivity
   a. “Low-sensitivity” : recurrence within 5-year during adjuvant ET, or progression within 9-month of initial ET for ABC.
   b. “Very low-sensitivity” : recurrence within 2-year during adjuvant ET, or progression within 3-month of initial ET for ABC.
8. No previous chemotherapy for advanced breast cancer.
9. Chemotherapy given as peri-operative adjuvant therapy completed at 6 months before this study.

Major Exclusion Criteria

1. HER2-positive breast cancer.
2. Endocrine therapy must be inappropriate.
3. Any patients that a physician determines to be unsuitable for participation in this study.

4. Statistical Hypothesis

5. To achieve the primary objective, clinical benefit rates (CBR: defined as patients (pts) who achieved CR or PR or SD for 24 weeks) were expected 50%, the null hypothesis that a CBR is 30 % was tested at one-sided alpha of 5%.
6. 90% confidence intervals (CIs) were calculated in relation with hypothesis tests.

Efficacy and Safety Measures

1. Tumors were assessed by computed tomography or any imaging methods according to RECIST version 1.1 at baseline, 3 and 6 months after initiation of secondary endocrine therapy.
2. Adverse events were graded for severity according to the National Cancer Institute Common Terminology Criteria version 4.0.
3. Medical treatment and examination of subjects in this study is conducted within the normal range of regular clinical practice. Therefore, the risk of adverse events in subjects who participate in this study is similar to that in regular clinical practice. For this reason, information about adverse events of Grade 2 or milder is not collected in this study.

RESULTS

Table 1. Characteristics of the Patients

Characteristic		Number	(%)
February 2016 to January 2017	Registered patients	56	100
	Eligible patients	49	87.5
	Ineligible patients	7	12.5
		Mean (SD)	Median (range)
	Age (years)	65.8 (8.9)	66 (41-88)
Body Mass Index (kg/sqm)		23.9 (3.7)	23.4 (16.4-31.9)
Hormone-receptor status		Number	(%)
ER-positive	≧10%	49	100
PgR-positive	0%	10	20.4
	1-9%	8	16.3
	≧10%	31	63.3
PS	0	41	83.7
	1	7	14.3
	2	1	2.0
TNM staging	Ⅰ	2	4.1
	ⅡA	9	18.4
	ⅡB	11	22.5
	ⅢA	7	14.3
	ⅢB	4	8.2
	ⅢC	7	14.3
	Ⅳ	8	16.3
	Unknown	1	2.0
Histological type	IDC	44	89.8
	ILC	5	10.2
Metastatic site	Visceral	24	49.0
	Non-visceral	25	51.0
Liver	No	34	69.4
	Yes	15	30.6
Lung	No	37	75.5
	Yes	12	24.5
Local	No	42	85.7
	Yes	7	14.3
Bone	No	25	51.0
	Yes	24	49.0
Lymph node	No	31	63.3
	Yes	18	36.7

Table 2. Adjuvant and First-Line Endocrine Therapy

Characteristic		Mean (SD)	Median (range)
Duration of recurrence after operation (months)		32.2 (16.2)	31.7 (3.5-64.9)
Duration of recurrence after adjuvant chemotherapy (months)		30.3 (14.4)	29.6 (5.3-58.9)
		N	(%)
Adjuvant endocrine therapy	Anastrozole	17	34.7
	Exemestane	2	4.1
	Letrozole	20	40.8
	Tamoxifen	3	6.1
		Mean (SD)	Median (range)
Duration of 1st line endocrine Tx (months)		5.7 (2.8)	5 (2.3-10.8)
		N	(%)
1st line endocrine therapy	Anastrozole	2	4.1
	Letrozole	6	12.2
	Tamoxifen	1	2.0

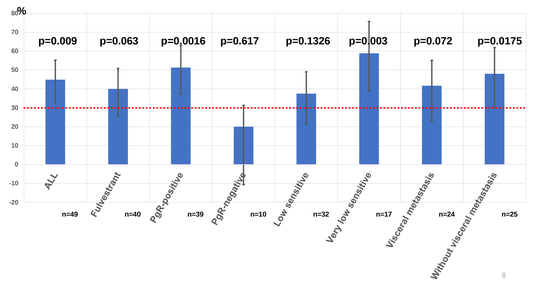
Table 3. Choice of 2nd Line Endocrine Treatment after registration

Preference of 2nd line endocrine therapy		Number	(%)
Total number of patients		49	100
	Letrozole	1	2.0
	Tamoxifen	3	6.1
	Toremifene	2	4.1
	Fulvestrant	40	81.6
	Exemestane + Everolimus	3	6.1
Additional use of bone-modifying agents			
Bisphosphonate	No	40	81.6
	Yes	9	18.4
Denosumab	No	34	69.4
	Yes	15	30.6

Table 4. Reasons for Preference of Secondary Endocrine Therapy

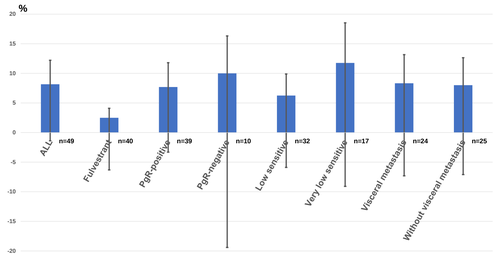
Reasons for choice	All		Fulvestrant		EVE + EXE		Tamoxifen		Toremifene		Letrozole	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Therapeutic effects	45	90	36	87.8	3	100	3	100	2	100	1	100
Side effects	14	28	13	31.7	_	_	1	33.3	_	_	_	_
Costs	2	4	2	4.9	_	_	_	_	_	_	_	_
Others	2	4	2	4.9	_	_	_	_	_	_	_	_

Figure 1. Prespecified Subgroup Analysis of Clinical Benefit Rates



- ✓ The null hypothesis that a clinical benefit rate (CBR) of at least 30% can be expected (Red dots line).
- ✓ The overall CBR was 47.9% (90% CI: 34.6-57.6, p=0.009), and CBR was similar across following subgroups (PgR+: n=39, 51.3%, 90% CI: 39.6-65.2, p=0.0016; very low sensitive group: n=17, 58.8%, 90% CI: 42.0-78.8, p=0.003; non-visceral metastases: n=25, 40%, 90% CI; 34.1-65.9, p=0.0175). However, there were not statistically significant CBR in PgR- (n=10, 20.0%, 90% CI; 8.73-50.7, p=0.617), fulvestrant subgroup (n=40, 40.0 %, 90% CI; 29.2-54.2, p=0.063), low sensitive group (n=32, 37.5%, 90% CI; 26.0-53.6, p=0.1326), and visceral metastases (n=24, 48%, 90%CI; 28.2-60.3 p=0.072).
- ✓ Bar graph indicates point estimation, solid line indicates 90% confidence interval. Abbreviation: CI, confidence interval; PgR, progesterone receptor; +, positive; -, negative; n, number of patients; %, percentage.

Figure 2. Prespecified Subgroup Analysis of Clinical Response Rates



Clinical response rate (CRR) were evaluated as a secondary endpoints.
The overall CRR was 8.16%, n=49, 90% CI: 4.11-17.7, fulvestrant subgroup: n=40, 8.2 %, 90% CI; 4.1-17.7; PgR+: n=39, 7.69%, 90% CI: 3.58-18.7; PgR-:n=10, 10%, 90% CI; 3.7-39.4; low sensitive group: n=32, 6.25%, 90% CI; 2.6-18.4; very low sensitivity group: n=17, 11.8%, 90% CI: 5.0-32.6; visceral metastases: n=24, 8.3%, 90%CI; 3.4-23.1; non-visceral metastases: n=25, 8%, 90% CI; 3.4-23.1.
Bar graph indicates point estimation, solid line indicates 90% confidence interval. Abbreviation: CI, confidence interval; PgR, progesterone receptor; +, positive; -, negative; n, number of patients; %, percentage.

Table 5. Treatment-Emergent Adverse Events (≧Grade 3)

Fulvestrant (n=3)	Grade 3	Grade 3	Grade 3	Grade 3
	Increased AST	Increased total bilirubin	Fatigue	Increased γ-glutamyl transpeptidase
	Case 1		Case 4	Case 6

Letrozole (n=1)	Grade 3	Grade 4	Grade 3
	Depression	Depression	Insomnia
	Case 20		

Everolimus + Exemestane (n=2)	Grade 3	Grade 3	Grade 3	Grade 3	Grade 3
	Interstitial pneumonia	Appetite loss	Fatigue	Fatigue	Oral mucositis
	Case 46			Case 47	

DISCUSSION and CONCLUSIONS

- ✓ Since CBR was better than we expected, in the era of shared decision making, second line endocrine therapy that was chose based on patients preference could be an optimal strategy.
- ✓ Our subgroup analysis indicated that PgR-positive, very low sensitivity, and non-visceral metastasis might have a clinical benefit from 2nd line endocrine therapy.
- ✓ Although both PgR-positive and non-visceral metastasis could be a possible explanation factors, it was still unknow that “very low sensitive group” has better CBR than that of “low sensitive group”. Since small sample size and/or multiple comparisons problem might effect our results, further larger study or real world cohort big data should be expected to explore the predictive marker of second line endocrine therapy.

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REFERENCES

- Iwamoto T., et al. Acta Med. Okayama, 2018, 72, 369
- Taira et al., J Clin Trials 2016, 6:2