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Patient characteristics and treatment sequencing among HER2-low metastatic breast cancer patients with rapid vs delayed progression on first-line endocrine therapy

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Objective

- To describe the characteristics, treatment patterns, and clinical outcomes of patients with human epidermal growth factor receptor 2 (HER2)-low, hormone receptor–positive (HR+) metastatic breast cancer who have progressed on first-line treatment within 12 months of treatment initiation compared with those with disease progression after 12 months or those who did not develop disease progression by the end of the study period

Conclusions

- Many patients with rapid disease progression on first-line endocrine-based regimens continued to receive endocrine therapy in their next line of therapy and experienced poor clinical outcomes
- This preliminary chart review study highlights the unmet need for more effective treatments for those who rapidly develop disease progression while on endocrine therapy. Further research with a larger sample size and a longer follow up is warranted to confirm these findings

Plain language summary

Why did we perform this research?

Some patients with breast cancer have low but detectable levels of a protein called human epidermal growth factor receptor 2 (HER2)-low. These patients may receive initial treatment with a therapy that adds, blocks, or removes hormones (endocrine therapy) alone or in combination with other therapies when the cancer has spread from its original site. We performed this study to understand how these patients are treated and how well currently available treatments work in patients whose cancer rapidly grows, spreads, or gets worse (disease progression) after initial treatment.

How did we perform this research?

We collected information about the treatments and outcomes of patients with HER2-low metastatic breast cancer at three different cancer centers. We compared patients whose cancer grew, spread, or got worse within a year of starting treatment with those whose cancer did not.

What were the findings of this research?

Among patients who experienced rapid disease progression, 68% continued to receive endocrine therapy when their initial treatment failed or stopped working (second-line treatment). In this patient group, the timepoint at which half the patients experienced disease progression was 5.7 months after starting their second-line treatment.

What are the implications of this research?

There is potentially an unmet need for more effective treatments for patients who have rapid disease progression while receiving endocrine therapy as their first treatment for breast cancer that has spread from its original site.

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Introduction

- Evidence showing efficacy of antibody-drug conjugates in metastatic breast cancer with low but detectable levels of HER2 expression (immunohistochemistry [IHC] 1+ or IHC 2+ and in situ hybridization [ISH]–negative [ISH−]) has challenged the conventional dichotomous classification of HER2 expression to guide HER2-directed targeted therapy.[1] It is estimated that around 50% to 60% of patients with metastatic breast cancer present with HER2-low disease[2–4]
- Endocrine therapy is the mainstay treatment for patients with HR+/HER2-low disease, but it is not understood if patients who rapidly progress on first-line endocrine therapy would benefit from further lines of endocrine-based therapy
- In this subgroup analysis of US patients with HR+/HER2-low metastatic disease, we aimed to describe the characteristics, treatment patterns, and outcomes of patients with rapid vs delayed or no progression

Methods

- Study design: Retrospective cohort study via chart review
- Study sites: (1) Huntsman Cancer Institute, UT, US, (2) H. Lee Moffitt Cancer Center, FL, US, and (3) Winthrop P. Rockefeller Cancer Institute, AR, US
- Study population: Metastatic breast cancer patients with HER2-low (IHC 1+ or IHC 2+/ISH−), HR+ disease who were started on first-line endocrine therapy (see Table 1 for eligibility criteria)
- Study period: Between 2017 and 2021. Patients were followed up from diagnosis of advanced disease until death, last follow up at the study site, or December 31, 2021, whichever occurred earlier
- Patients were stratified by rapid vs delayed/no disease progression. Progression was identified based on documentation in clinical notes. Rapid disease progression was defined as progression within 12 months of first-line treatment initiation
- Outcomes of interest included (1) demographic and clinical characteristics at diagnosis of advanced disease, (2) first- and second-line treatment received, and (3) overall survival and progression-free survival
- Patient characteristics and treatment patterns were presented descriptively
- Overall survival was measured as the time between initiation of treatment and death, while progression-free survival was measured as the time between initiation of treatment and disease progression
- Survival outcomes were estimated using Kaplan-Meier analyses with censoring performed at date of last follow up or December 31, 2021, whichever occurred earlier

Table 1. Study eligibility criteria

Inclusion criteria
1. Diagnosis of metastatic breast cancer and initiation of first-line treatment
2. Aged 18 years and older at diagnosis of advanced breast cancer
3. Classified as HER2-low (IHC 1+ or IHC 2+/ISH−)
4. HR+ with endocrine therapy as part of first-line treatment
5. ≥2 encounters on separate dates for breast cancer within study period
Exclusion criteria
1. Diagnosis of primary cancers other than breast cancer

HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC−, immunohistochemistry–negative; ISH, in situ hybridization

Results and interpretation

- A total of 118 patients were included in the analysis with a median follow-up time of 27.5 months. All patients received first-line endocrine therapy, mostly in combination with a CDK4/6 inhibitor (n=87, 73.7%)
- Rapid progression was observed for 25 patients (21.2%), while delayed or no progression was noted for 93 patients (78.8%)
- Rapid progressors were more likely to be current smokers or have had liver metastasis at diagnosis of advanced disease but were less likely to have bone as the only site of metastasis (Table 2)
- A slightly lower proportion of rapid progressors (68.0%) were on CDK4/6 inhibitors in the first-line setting compared with delayed/non-progressors (75.3%). In the second-line setting, a substantial proportion of rapid progressors continued to receive endocrine-based regimens (70.8%), including some who received endocrine monotherapy (25.0%) (Table 3 and Figure 1)
- Among patients who continued to a second-line treatment, median overall survival and progression-free survival from second-line treatment initiation was 14.1 months (95% confidence interval [CI] 6.8, 24.2) and 5.7 months (95% CI 3.2, 10.6) for rapid progressors (Figure 2), compared with 29.2 months (95% CI 14.4, upper bound not reached) and 9.2 months (95% CI 3.1, 13.7) among delayed/non-progressors

Study limitations

- Overall, the sample size of US patients was relatively small, and this was compounded by many patients not progressing within the study follow-up period

Table 2. Demographic and clinical characteristics of patients

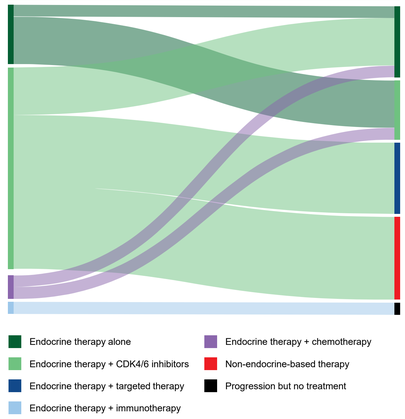
Variable	Delayed/no progression (n=93)	Rapid progression (n=25)	P-value
Age at diagnosis, median (IQR)	57.8 (47.7, 69.0)	55.3 (49.9, 61.8)	0.41
Ethnicity, n (%)			0.59
White/Caucasian	79 (84.9)	20 (80.0)	
Black/African American	3 (3.2)	1 (4.0)	
Hispanic/Latino	7 (7.5)	2 (8.0)	
Native American/AAPI/Others	3 (3.3)	2 (8.0)	
Unknown	1 (1.1)	0 (0)	
Insurance plan, n (%)			0.36
Commercial	51 (54.8)	12 (48.0)	
Medicare/Medicaid	32 (34.5)	10 (40.0)	
Uninsured/Self-pay/Others	10 (10.8)	2 (8.0)	
Unknown	0 (0)	1 (4.0)	
Smoking status, n (%)			**0.015**
Current	7 (7.5)	6 (24.0)	
Former	19 (20.4)	8 (32.0)	
Never	67 (72.0)	11 (44.0)	
Menopausal status, n (%)			0.76
Premenopausal	25 (26.9)	7 (28.0)	
Postmenopausal	66 (71.0)	18 (72.0)	
Male – not applicable	2 (2.2)	0 (0)	
Histology type, n (%)			0.80
Lobular	13 (14.0)	5 (20.0)	
Ductal	68 (73.1)	18 (72.0)	
Other	8 (8.6)	1 (4.0)	
Unknown	4 (4.3)	1 (4.0)	
Histology grade, n (%)			0.29
Grade 1	7 (7.5)	1 (4.0)	
Grade 2	55 (59.1)	11 (44.0)	
Grade 3	23 (24.7)	11 (44.0)	
Unknown	8 (8.6)	2 (8.0)	
Metastasis site(s), n (%)			
Brain	2 (2.2)	0 (0)	0.46
Lung	17 (18.3)	5 (20.0)	0.84
Liver	17 (18.3)	11 (44.0)	**0.007**
Bone	75 (80.6)	21 (84.0)	0.70
Bone only with no other site(s)	46 (49.5)	6 (24.0)	**0.023**
ECOG status, n (%)			0.20
Grade 0 or 1	70 (75.3)	16 (64.0)	
Grade 2 or 3	5 (5.3)	4 (16.0)	
Unknown	18 (19.4)	5 (20.0)	

AAPI, Asian American Pacific Islander; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range

Table 3. Treatment regimens received by patients in first- and second-line settings

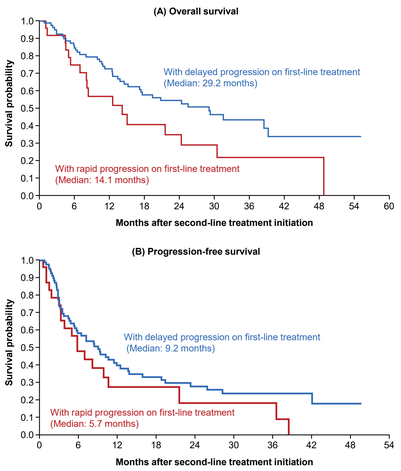
Treatment regimen	Delayed/no progression (n=93)	Rapid progression (n=25)
First-line setting, n (%)		
Endocrine therapy alone	15 (16.1)	5 (20.0)
Endocrine therapy + CDK4/6 inhibitors	69 (74.2)	17 (68.0)
Endocrine therapy + chemotherapy	8 (8.6)	2 (8.0)
Endocrine therapy + chemotherapy + CDK4/6 inhibitors	1 (1.1)	0 (0)
Endocrine therapy + immunotherapy	0 (0)	1 (4.0)
Second-line setting, n (%)		
Received second-line treatment	**n=39**	**n=24**
Endocrine therapy alone	10 (25.6)	6 (25.0)
Endocrine therapy + CDK4/6 inhibitors	9 (23.1)	5 (20.8)
Endocrine therapy + targeted therapy	7 (17.9)	6 (25.0)
CDK4/6 inhibitors alone	2 (5.1)	0 (0)
Chemotherapy alone	7 (17.9)	5 (20.8)
Chemotherapy + targeted therapy	0 (0)	2 (8.3)
Immunotherapy + targeted therapy	2 (5.1)	0 (0)
Clinical trials	2 (5.1)	0 (0)
No second-line treatment	**n=54**	**n=1**
No progression	53 (98.1)	0 (0)
Progression but no treatment	1 (1.9)	1 (100)

Figure 1. Treatment patterns of rapid progressors



First-line treatment is represented by the left bar, and second-line treatment is represented by the right bar. Widths of flows indicate the number of patients who received the treatment regimen

Figure 2. Survival outcomes in second-line setting



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