High Prevalence of HER2-Low Among ILC with Residual Disease Following Neoadjuvant Therapy Provides Therapeutic Opportunities with HER2-Antibody-Drug Conjugates

Guadalupe Garcia[1] , Paula Gonzalez-Ericsson[1], Leonel Maldonado[1-2], Laura Kennedy[1-3], Melinda E. Sanders[1-2].

Vanderbilt-Ingram Cancer Center[1], Departments of Medicine, Pathology, Microbiology and Immunology[2] and Medical Oncology Division[3], Vanderbilt University Medical Center, Nashville, TN, USA

Lay Abstract

The goal of this study is to investigate the prevalence of HER2-low expression in patients with invasive lobular carcinoma (ILC) treated at our institution, including patients with ILC treated with presurgical (neoadjuvant) therapies. Patients with invasive lobular carcinoma who are selected for neoadjuvant chemo- or endocrine therapy have primary tumor characteristics associated with more aggressive disease. HER2-low breast cancer (BC) is a newly defined subset of HER2-negative BC with a HER2 immunohistochemical score of 1+ or 2+ and lacking HER2 gene amplification. Recent clinical trials have demonstrated significant clinical benefit from novel HER2 antibody-drug conjugates to treat HER2-Low BC. We found 52% of patients with ILC at our institution are categorized as HER2-Low and 55% of patients with large volume of residual tumor after neoadjuvant treatment were HER2-Low. High prevalence of HER2-low among ILC, especially in patients with residual disease following NET, provides therapeutic opportunities with HER2-antibody-drug conjugates.

Abstract

Background: Invasive lobular carcinoma (ILC) accounts for 5-15% of breast cancer (BC). Most ILCs are strongly hormone receptor positive. Adjuvant endocrine therapy (ET) is the usual treatment. The use of chemotherapy alone or in combination with ET is controversial and does not improve survival outcomes for most patients with ILC compared to ET alone. However, neo-adjuvant ET (NET) may be warranted to downstage some ILC permitting breast conservation. HER2-Low BC spectrum demonstrates variable HER2 expression and HR status. HER2-Low BC are defined by an immunohistochemical score of 1+ or 2+ with negative FISH. The prevalence and implications of HER2-Low in ILC are poorly characterized. This study investigates rates of HER2-Low among patients with ILC treated with neoadjuvant therapy (NAT) and correlates HER2-Low with clinicopathologic features predictive of outcome.

Methods: Patients with ILC treated from 2018 to 2022 at our institution were identified from a breast cancer database. HER2-Low status was correlated with tumor characteristics and treatment data.

Results: Between 2018 and 2022, 196 women with ILC were treated at our institution. Median age at diagnosis was 63 years (25–90). The majority of ILC were HR+/HER2- (93%), intermediate to low grade (81%), and HER2-Low (52%). Among the HR+/HER2- patients, 11 received neoadjuvant chemotherapy and 27 received NET. Patients receiving NAT presented with pT2/pT3 (82%), multifocal tumors (69%) and positive nodes (67%). Twenty-one (54%) were HER2-Low. No difference in clinicopathologic features was observed between HER2-0 and HER2-Low. Among HR+/HER2- patients receiving NAT, none achieved pCR and 89% were RCB II/III. Among NAT patients with RCB II/III, 55% were HER2-Low and among NET patients with RCB II/III, 68% were HER2-Low.

Conclusion: HER2-low status is common in this ILC cohort, including patients who received NAT. High prevalence of HER2-low among ILC with residual disease following NAT provides therapeutic opportunities with HER2-antibody-drug conjugates.

Background

Invasive lobular carcinoma (ILC) accounts for 5-15% of breast cancer (BC). Most ILCs are strongly hormone receptor positive. Adjuvant endocrine therapy (ET) is the usual treatment. The use of chemotherapy alone or in combination with ET is controversial and does not improve survival outcomes for most patients with ILC compared to ET alone. However, neo-adjuvant ET (NET) may be warranted to downstage some ILC permitting breast conservation. HER2-Low BC spectrum demonstrates variable HER2 expression and HR status. HER2-Low BC are defined by an immunohistochemical score of 1+ or 2+ with negative FISH. The prevalence and implications of HER2-Low in ILC are poorly characterized. This study investigates rates of HER2-Low among patients with ILC treated with neoadjuvant therapy (NAT) and correlates HER2-Low with clinicopathologic features predictive of outcome.

Methods

Patients with ILC treated from 2018 to 2022 at our institution were identified from a breast cancer database. HER2-Low status was correlated with tumor characteristics and treatment data.

Results

	# of patients	%
Cohort Patients	196	
Female	196	100%
Mean Age	63	
Low	37	19%
Intermediate	144	73%
High	15	8%
HR status		
HR positive	192	98%
HR Negative	4	2%
HER2 status		
HER2 negative	185	**94**%
HER2-Low	97	52%
HER2 zero	88	48%
HER2 positive	11	**6**%
NAT regimen	44	22%
Chemotherapy	17	38%
Endocrine therapy (NET)	27	62%

Table 1: Clinical and pathological characteristics of 196 patients with ILC diagnosed between 2018-2022. The majority of ILC were HR+/HER2- (93%), intermediate to low grade (81%), and HER2-Low (52%).

Results

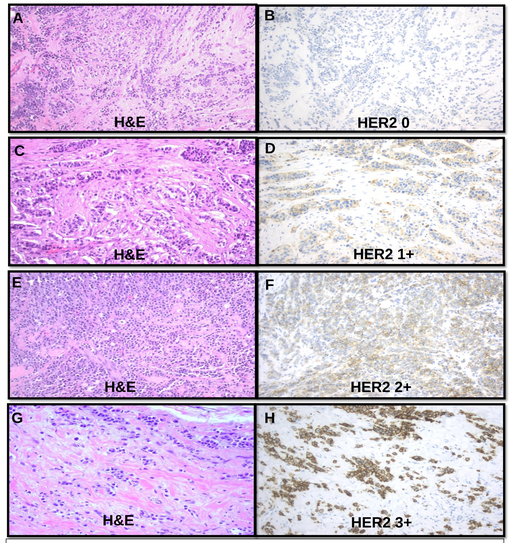

Figure 1: Immunohistochemical staining for HER2.

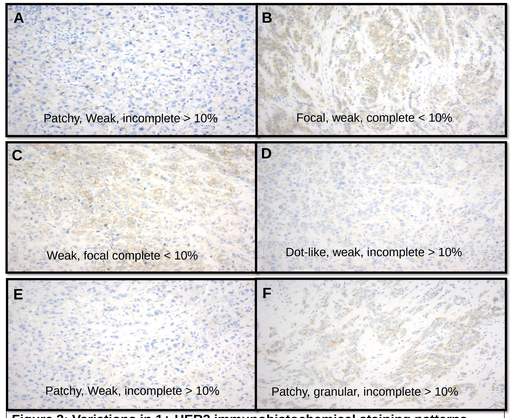

Figure 2: Variations in 1+ HER2 immunohistochemical staining patterns

Results

	HER2 zero	%	HER2 low	%
Total	18	46%	21	54%
Tumor size				
pT1	2	11%	2	10%
pT2/pT3	15	83%	17	81%
Lymph nodes				
pN0	4	22%	7	33%
pN1 or more	14	78%	12	57%
Grade				
G1	5	28%	5	24%
G2/G3	12	67%	16	76%
Multifocal tumor	12	67%	15	71%
Tumor response				
RCB I	2	11%	2	10%
RCB II/III	15	83%	19	90%

Table 2: Among the HR+/HER2- patients, 12 received neoadjuvant chemotherapy and 27 received NET. Patients receiving NAT presented with pT2/pT3 (82%), multifocal tumors (69%) and positive nodes (67%). Twenty-one (54%) were HER2-Low. No difference in clinicopathologic features was observed between HER2-0 and HER2-Low.

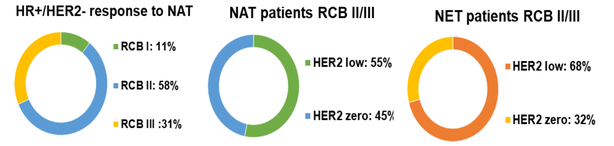

Figure 3: Among HR+/HER2- patients receiving NAT, none achieved pCR and 89% were RCB II/III. Among NAT patients with RCB II/III, 55% were HER2-Low and among NET patients with RCB II/III, 68% were HER2-Low.

Conclusion

HER2-low status is common in this ILC cohort, including patients who received NAT. High prevalence of HER2-low among ILC with residual disease following NAT provides therapeutic opportunities with HER2-antibody-drug conjugates.