Prevalence and prognosis of ER-loss in advanced invasive lobular carcinoma

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Background
• Estrogen receptor (ER) loss occurs in about 20% of recurrent breast cancers (BC) and is associated with unresponsiveness to endocrine therapy (ET) and poor prognosis.
• ILC is the second most common histologic type, accounting for 10-15% of breast cancers and is typically ER-positive.
• ILC differs from invasive ductal carcinoma (IDC) in terms of clinicopathologic characteristics, molecular alterations and response to treatment, with studies showing less response to chemotherapy.
• Prior studies evaluating ER-loss included predominately patients with IDC, and therefore the impact of ER-loss in ILC is unclear.

In this retrospective analysis, using real-world data, we aimed to determine the prevalence and clinical significance of ER-loss in ILC.

Methods
• Advanced breast cancers were molecularly profiled at Caris Life Sciences (Phoenix, AZ) with NextSeq Sequencing of DNA (52 gene panel) or whole-exome sequencing), RNA (whole transcriptome sequencing, WTS) and immunohistochemistry (IHC) of select markers.
• A large real-world evidence (RWE) database combining Caris’ molecular data with clinical information obtained from insurance claims data (CODIA), was interrogated and overall survival (OS) was calculated from time of tissue collection to last patient contact. We assumed that any patient without a claim for more than 100 days had died, which holds true for more than 95% of patients with a recorded death in the NDI.
• Definition of ER-loss: A tumor was considered to have ER-loss if therapies approved only for ER-positive breast cancer (ET, COX-2, mTOR inhibitors) were prescribed prior to obtaining a negative ER IHC result (IHC 0).
• Median overall survival (time from tissue collection to last day of contact) was used to determine “responders” vs. “non-responders”.
• OS was compared using Kaplan-Meier estimates for defined patient cohorts with significance defined as p-value <0.05. For molecular analyses, Fisher’s exact or Chi-Square tests were used to determine p-values. Correlation for multiple comparisons was performed using Benjamin-Hochberg to calculate q-values.

Results

Patient Characteristics
• RWE database included 14,824 patients with advanced BC, with the majority classified as breast carcinoma NOS.
• The final analytical cohort included 1,338 patients who had previously been treated with therapies approved only for ER-positive BC, were classified as ductal or lobular histology and had data available for ER IHC.
• ER-loss was identified in 11.4% of ILC (N=192/1683) compared to 19.6% of IDC (N=2120/10757) (p=0.017).

Data with clinical information obtained from insurance claims data (CODEai).

Overall Survival for ILC with or without ER-loss

All patients with ER-loss* regardless of histology
• In the breast cancer cohorts evaluated, median OS (collection time to last day of contact) was 360 days.
• “Non-responders” defined by OS less than 360 days (N=914)
• Wilcoxon’s test shows differentially expressed genes between “responders” vs. “non-responders”
• Most genes were enriched in responders (899 genes significantly differentially expressed).

“Responders” defined by prior therapies as described in methods.

Conclusions
• In this large real-word dataset, ER-loss likely occurred in 11.4% of ILC and was associated with worse OS compared to IDC with ER-loss and ILC without ER-loss.
• Genomic analysis identified significant differences between treatment “responders” and “non-responders” in patients with ER-loss.
• Our analysis had several limitations: Definition of ER-loss was based on prior treatment, could not distinguish between de novo and recurrent metastatic disease and time of tissue collection was not standardised.
• This study does suggest that ER-loss occurs in a subset of patients with ILC and has poor prognostic implications.

Future work is needed to confirm these findings and to identify new therapeutic targets for patients ILC and ER-loss.

References


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