12-chromosome gene expression score in breast cancer patients treated with neoadjuvant chemotherapy

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BACKGROUND

Studies demonstrating the presence of immunologic gene activation1 and tumor-repressing lymphocytes in the breast tumor microenvironment suggest the importance of an effective anti-tumor immune response. Traditional clinical methods, which act as a screening tool for immune cells, influence the spatial organization of host immune response and the formation of organized extracellular fibroblast fibers, also known as epticoic lymph node-like structures2. In response to immune pressure, chronic inflammation, and solid tumors3. These structures likely attract T cells and activated B cells in response to tumor antigens. ELNs have been implicated in various clinical outcomes in patients with breast cancer, including breast cancer stage, and may represent a therapeutic target and/or a predictive biomarker for responses to immune checkpoint inhibitors. Pre-existing 3-7 chromosome gene signature was identified in colorectal cancer4 and in melanoma5. This gene signature has been associated with pathologic responses to durvalumab and overall survival in King and bladder cancer6. High chromosome score (CS) also predicts presence of tumor-localized ELNs in patients with invasive breast cancer7. Compared with low CS cases, patients with a high CS have high-risk clinical features, such as high grade, ER/PR-negative, and/or HER2-positive tumors, however, these clinical scores have also significantly better recurrence-free survival and overall survival7.

METHODS

Patients: Tumor specimens (FFPE) used in this retrospective analysis (n=92) were from breast cancer patients enrolled in either NLG (NCT01153487) or NBRM (NCT02473194) neoadjuvant registry trials from 2010-2016. Clinical data were collected with mailed consent. Neoadjuvant therapy was selected at the discretion of the physician. 91/92 patients received neoadjuvant chemotherapy; one patient received neoadjuvant endocrine therapy, and was excluded from pCR analysis. 28/53 HER2+ patients received neoadjuvant HER2-directed therapy; pCR was defined as absence of measurable cancer in the specimen.Residual Disease (RD) includes all other responses (partial, stable, progressive).

Genomic classification: MP, BP and full transcriptome data were generated by Agendia, Inc. MP patients were taken from Low Risk (LR), High Risk (HR), and Ultra High Risk (UHR) H and UHR similar to MP H1/MP2 and MP H2/MP2, respectively, reported in the I-SPY trial, which has demonstrated superior chemoresistance and pCR rates in tumors classified as UniRMP2. BP classified tumors as Luminal, Her2, or Basal type.

ELN assessment: Hematoxylin and eosin (H&E) stained tissue sections from core needle biopsies were evaluated for the presence of tumor-localized ELNs.

Chemokine score and statistical analysis: Same expression data were quantitatively normalized using R limma package. Principal component analysis (PCA) was performed on the normalized datasets using uniform p-value cutoff. The number of principal components (PCs) used to calculate the first principal component values were obtained from PCA. CS were compared with Western immunity index. High and low CS were defined as greater or less than the median CS in the group that achieved pCR. Rates of pCR and clinical factors were compared between groups using chi-square or Fisher’s Exact test.

RESULTS

Table 1. Clinical Characteristics

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Mean</th>
<th>Median</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>PM</td>
<td>56</td>
<td>56</td>
<td>54 (58)</td>
</tr>
<tr>
<td>NM</td>
<td>56</td>
<td>56</td>
<td>54 (58)</td>
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</tbody>
</table>

Table 2. Molecular and Pathology Characteristics

<table>
<thead>
<tr>
<th>First component value</th>
<th>0.006</th>
<th>0.027</th>
<th>0.024</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR</td>
<td>0.006</td>
<td>0.027</td>
<td>0.024</td>
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Figure 2: 2C in relation to MP risk group, BP subtypes, and pCR. CS was significantly higher in MP HR and UHR compared with MP LR, Basal BP, HR2, and Luminal B type tumors compared with Luminal A type tumors (B). CS was significantly higher in tumors with pCR compared with tumors with no pCR. CS demonstrated higher pCR rates in tumors with high pCR rate.

Figure 3: Table 3 and Figure 3: Rates of pCR in CS, MP, and BP groups. MP and BP were significantly associated with pCR.

CONCLUSIONS

• In support of previous studies, high CS was associated with improved clinical features, such as high histopathologic grade and lack of ER/PR expression.

• Tumor ELNs were only found in three specimens, likely due to the small tissue sample available from core needle biopsies; however, all of the tumor specimens with ELNs had high CS.

• The current study demonstrated a significantly higher CS in MP HR and UHR compared with MP LR index. 78% of high CS tumors were MP Ultra High Risk, suggesting a immunogenic phenotype within this group.

• Higher CS in BP Basal, HER2, and Luminal B tumors, suggests greater prevalence of ELNs, compared with Luminal A tumors. The CS may be particularly relevant in HER2 type tumors, which supports previous studies indicating a favorable outcome in patients with distant metastasis in HER2+ breast cancer.

• Higher mean CS was associated with pCR following neoadjuvant therapy, however, MP and BP were more predictive of pCR. These data suggest that prediction of pCR using CS may be improved by combining with MP and/or BP.

FUTURE DIRECTIONS

The current study was limited by the small sample size and limited available tissue for ELN assessment; future studies will evaluate CS in a larger dataset of neoadjuvant breast cancer patients.

Recent studies have demonstrated association of CS with response to durvalumab8, future studies may further explore the utility of this score in predicting responses to immunotherapies in breast cancer patients.

References