Exploring homologous recombination deficiency thresholds for predicting response to platinum-based treatment in triple negative breast cancer

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BACKGROUND

- Homologous recombination deficiency (HRD) status can be used to identify patients who are eligible for treatment with DNA damaging agents.
- Studies have previously examined the association between HRD status and outcomes in patients with triple negative breast cancer (TNBC) using a 3-biomarker Genomic Instability Score (GIS).
- These studies have used a threshold of ≥42, set as the 1st percentile for BRCA deficient tumors. Evidence suggests that a GIS threshold of ≥33, set as the 1st percentile for BRCA deficient tumors, may be more appropriate.

METHODS

- Patients across 5 cohorts (TBCRC030, TBCRC008, NCT01372579, PR0CG0105, combined cisplatin cohort) were included in this analysis if they had a primary TNBC diagnosis, received neoadjuvant platinum-based treatment, and had a valid GIS, and had known pathologic complete response (pCR) status.
- GIS was determined by a combination of loss of heterozygosity, telomeric-allelic imbalance, and large-scale state transitions.4,5
- BRCA mutation status was defined by loss of function resulting from a pathogenic variant in BRCA1 or BRCA2.
- Logistic regression models were fit with binary threshold status predicting pCR status.
- Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated by comparing binary threshold status and binary pCR status.
- A total of 211 tumors (171 BRCAwt, 35 BRCAm; 5 unknown) were included (Figure 1).
  - pCR to platinum-based treatment occurred in 55 cases (26%; 39 BRCAwt, 15 BRCAm; 1 unknown).
  - The pre-specified threshold of GIS ≥33 is a significant predictor of pCR status in the full cohort and in BRCAwt samples only (Table 1).
  - A threshold at GIS ≥33 results in a higher odds ratio than a threshold GIS ≥42 (Table 1, Figure 2).
  - Sensitivity, specificity, PPV, and NPV were comparable between the GIS and ≥42 GIS thresholds, with the ≥33 threshold producing higher sensitivity values, but lower specificity (Figure 3).

RESULTS

- We conducted an exploratory analysis if they had a primary TNBC diagnosis, combined cisplatin cohort
- Logistic regression models were fit with binary GIS ≥33 status and binary GIS ≥42 status predicting pCR
- Odds Ratios

Table 1. Results of logistic regression models fit with binary threshold status, predicting pCR status

<table>
<thead>
<tr>
<th>GIS Threshold</th>
<th>All Samples (N=211)</th>
<th>BRCAwt (N=171)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIS ≥33</td>
<td>(11.1, 3.9, 47.1)</td>
<td>(3.6, 0.6, 21.0)</td>
</tr>
<tr>
<td>GIS ≥42</td>
<td>(8.2, 3.5, 22.3)</td>
<td>(3.6, 1.1, 15.8)</td>
</tr>
<tr>
<td>BRCAwt</td>
<td>(9.4, 3.2, 40.4)</td>
<td>(3.6, 0.8, 21.3)</td>
</tr>
<tr>
<td>BRCAm</td>
<td>(2.9, 19.6)</td>
<td>(3.0, 0.9, 13.7)</td>
</tr>
</tbody>
</table>

*Binary models fit with binary GIS ≥33 status and binary GIS ≥42 status predicting pCR

CONCLUSIONS

- To increase detection of patients likely to benefit from treatment while maintaining good PPV, a GIS of ≥33 (1st percentile of BRCA deficient tumors) may be the most appropriate threshold to predict response to platinum-based treatment in patients with TNBC; however, a prospective trial will be needed to confirm this finding.
- Additional studies will be important to determine whether this threshold may be appropriate to determine eligibility for other DNA-damaging agents such as PARP inhibitors.

REFERENCES:
1) Ann Oncol. 2020
2) J Nucl Med. 2015
3) Breast Cancer Res Treat. 2015
4) Clin Cancer Res. 2016
5) Breast Cancer Res Treat. 2014

All Samples (N=211)
BRCAwt (N=171)

Figure 1. Distribution of GIS by pCR status in (A) the full cohort, and (B) BRCAwt samples only

Figure 2. Odds ratios from models with threshold status predicting pCR in both the full and BRCAwt cohorts

Figure 3. Sensitivity, specificity, and predictive values for pCR to platinum-based treatment by threshold GIS

Dashed vertical lines denote the pre-defined thresholds at GIS=33 and GIS=42