Frequency of homologous recombination deficiency in a large community-based cohort of epithelial ovarian cancer cases

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Background

- Approximately 41-50% of ovarian carcinomas are estimated to exhibit homologous recombination deficiency (HRD)
- Germline and somatic tumor tissue testing (TTT) for mutations in BRCA1/2 and assessment of HRD informs prognosis and treatment decisions
- NCCN guidelines (V1.2022) recommend germline and somatic TTT and assessment of HRD for all women with invasive EOC
- Data on the frequency of HRD is based primarily on analysis of EOC patients treated at academic medical centers and/or enrolled in clinical trials and may not be representative of a larger population of women in a community setting
Homologous Recombination Repair (HRR) is a pathway for repair of double strand breaks in DNA.
In Homologous Recombination Deficiency (HRD), DNA repair is inhibited which results in genomic instability.
HRD is a useful predictor of treatment response to PARP inhibitor in patients with mBRCA1/mBRCA2
How do you test for HRD?

Germline mutation screening of genes related to HRR

- Germline mutational testing (GMT)

Somatic mutation screening of genes related to HRR

-Somatic Tumor Tissue Testing (TTT)

Evaluation of genomic instability secondary to HRD via a genomic instability score (GI) or loss of heterozygosity (LOH)
GI score results from combined analysis of three different biomarkers

**Loss of heterozygosity (LOH)**
Presence of a single allele

**Telomeric allelic imbalance (TAI)**
A discrepancy in the 1:1 allele ratio at the end of the chromosome (telomere)

**Large-scale state transitions (LST)**
Transition points between regions of abnormal and normal DNA or between two different regions of abnormality
Objective

To identify the frequency of HRD based on mutations in homologous recombination repair (HRR) genes, genomic instability (GI), and loss of heterozygosity (LOH) scores in a large community-based cohort of EOC patients (study population as described previously)

- Additional data collected
  - HRR genes separate from BRCA1/2 include: ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R1A, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L
  - GI as measured by Myriad myChoice test, LOH as measured primarily by Caris and Foundation tests

- Data analysis
  - Descriptive statistics were tabulated
  - Chi-squared analysis was performed to compare frequencies
Rates of HRD in Patients who had Genomic Testing

<table>
<thead>
<tr>
<th></th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>LOH/GI</th>
<th>Other HRR Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Pts Tested</td>
<td>10%</td>
<td>6%</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>I</td>
<td>7%</td>
<td>3%</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>II</td>
<td>6%</td>
<td>3%</td>
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<td>9%</td>
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<tr>
<td>III</td>
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<td>6%</td>
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<td>3%</td>
</tr>
<tr>
<td>IV</td>
<td>12%</td>
<td>7%</td>
<td>3%</td>
<td>3%</td>
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<td>6%</td>
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<td>3%</td>
</tr>
<tr>
<td>Test Type</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Germline</td>
<td>8%</td>
<td>5%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Somatic TTT</td>
<td>9%</td>
<td>5%</td>
<td>8%</td>
<td>3%</td>
</tr>
</tbody>
</table>
Rates of LOH and GI

- LOH: Positive, 34 (29%)
- LOH: Negative, 66 (57%)
- LOH: Indeterminate, 16 (14%)

- GI: Positive, 9 (23%)
- GI: Negative, 28 (70%)
- GI: Indeterminate, 3 (7%)

n = 156

GI testing Rate: 1%
LOH Testing Rate: 4%
Rates of PARPi treatment

- HRD: $X^2=10.4$, $p=.0013$
- WT: $X^2=40.5$, $p<.0001$
- HRD No testing: $X^2=12.4$, $p=.0004$
Conclusions

- Somatic TTT identified evidence of HRD in 130 of 507 (26%) patients tested

- Pathogenic somatic TTT mutations in HRR genes were identified in 87 (17%) patients including BRCA1 (n=47), BRCA2 (n=23), ATM (n=8), CHEK2 (n=4), PALB2 (n=2), RAD51b (n=1), CDK12 (n=1) and BRIP1 (n=1)

- Molecular alterations were identified in tumors of all stages, suggesting that broad based somatic TTT may be of value

- A large fraction of patients with HRD may not be receiving indicated PARPi therapy