Immune checkpoint expression, microsatellite instability, and mutational burden: Identifying immune biomarker phenotypes in uterine cancer

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Background

Endometrioid endometrial cancer (EEC) is categorized on a histologic continuum from Grade 1 to 3 (G1 or low grade (LG), G2, G3 or high grade (HGI)). Increasing grade is associated with aggressive behavior and poor prognosis. Treatment options for advanced/recurrent disease are limited. Emerging data has shown promise of immune checkpoint therapy (IT) in gynecologic malignancies 1. MSI-H status, tumor mutation burden, and high PD-L1 expression have been associated with higher response rates 2. Herein we identify distinct immune "biomarker phenotypes" to identify patients who may benefit from immune therapy (IT).

Methods

- 621 endometrioid endometrial tumors were retrospectively analyzed for immune biomarker phenotype by multiparameter profiling: 156 grade 1, 172 grade 2, 113 grade 1, 180 unknown.
- NextGen sequencing (NGS) was performed on 592 genes (Illumina NextSeq platform).
- Mutational burden was calculated based on somatic nonsynonymous missense mutations; TMB-high was defined as >21 mutations/megabase.
- Microsatellite Instability (MSI) was determined by examining altered microsatellite loci using NGS (124 loci).
- Antibody used for PD-L1 was SP142 and positivity was defined as ≥2+ (>5% staining on tumor cells).
- Data were compared using chi-square tests.

Results

Figure 1. Overview of Immune Biomarker Phenotypes in EECs.

<table>
<thead>
<tr>
<th>MSI</th>
<th>TMB</th>
<th>PD-L1</th>
</tr>
</thead>
<tbody>
<tr>
<td>N %</td>
<td>N %</td>
<td>N %</td>
</tr>
<tr>
<td>Grade 1/well diff</td>
<td>35 153</td>
<td>25 112</td>
</tr>
<tr>
<td>Grade 1/moderately diff</td>
<td>55 172</td>
<td>32 149</td>
</tr>
<tr>
<td>Grade 1/poorly diff</td>
<td>58 156</td>
<td>37 138</td>
</tr>
</tbody>
</table>

Figure 2. MSI in EEC. A. MSI high (MSI-H), equivocal and stable in histologic grades 1, 2, and 3 EECs. B. Overall, MSI-H was found in 33% (203/621) of EECs: 22% in G1/well-differentiated tumors, 32% in G2/moderately differentiated tumors, and 37% in G3/poorly-differentiated tumors (p<0.007).

Figure 3. Tumor Mutational Burden (TMB) in EECs. A. High TMB (TMB-H) levels in histologic grades 1, 2, and 3 EECs. B. Overall, TMB-H was identified in 25% (152/619) of EECs: 13% in G1/well-differentiated tumors, 23% in G2/moderately differentiated tumors, and 14% in G3/poorly-differentiated tumors (p=0.006).

Figure 4. PD-L1 Expression via IHC in EECs. A. PD-L1 expression in histologic grades 1, 2, and 3 EECs. B. Overall, PD-L1 expression was found in 5.5% (33/603) of EECs: 1% in G1/well-differentiated tumors, 3% in G2/moderately differentiated tumors, and 12% in G3/poorly-differentiated tumors (p=0.0001).

Figure 5. Evaluation of 3 markers in EECs. A. Combined markers in histologic grades 1, 2, and 3 EECs. B. Triple negative phenotype was identified in 60% of all EECs: 72% in G1, 60% in G2, 52% in G3. Double positive markers were present in 9% of G1, 19% of G2, and 30% of G3.

Conclusions

- We evaluated TMB, MSI and PD-L1 expression in over 600 EECs.
- MSI and TMB are highly correlated in low grade, intermediate and high grade tumors while the correlation of PD-L1 expression with MSI or TMB is not seen.
- High grade tumors appear to be more immunogenic than low grade tumors, and may preferentially benefit from IT providing a potentially powerful treatment option. Conversely, LG tumors are less likely to benefit from IT.

References

2. Goodman 2017 Mol Cancer Ther 16(11):2598-2608