Association of DNA damage response and repair gene (DDR) mutations and microsatellite instability (MSI), PD-L1 expression, tumor mutational burden (TMB) in gastroesophageal cancers

Michael Cerniglia BS1, Joanne Xiu PhD1, Axel Grotthuy MD2, Michael Pitsch CONF MD PhD1, Jimmy Hwang MD1, John Marshall MD1, Ari M. VanderWalde MPH1, Anthony F. Shields MD PhD1, Heinz-Joseph Lenz MD2, W. Michael Korn MD1, Mohamed Salem MD4, Philip A. Proph MD PhD1, Richard M. Goldberg MD8, Sunnie S. Kim MD1

1 Comprehensive Lengtntial Compensations Cancer Center, Washington, DC. 2 Gail Life Sciences, Framingham, MA. 3 West Cancer Center, Germantown, TN. 4 Killearn Cancer Institute, Wayne State University, Detroit, MI. 5 University of Southern California, Los Angeles, CA. 6 Karmanos Cancer Institute, Wayne State University, Detroit, MI. 7 Division of Medical Oncology, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA. 8 West Virginia University Cancer Institute, Morgantown, WV.

BACKGROUND

• DNA damage response and repair genes (DDR) encode proteins that serve in homologous recombination repair. These proteins interact with other DNA repair proteins and form a system for DNA damage repair.
• The prevalence of genetic deficiencies in the mechanism of homologous recombination across all tumor types has been well characterized. Certain genetic cancers have been shown to harbor deficiencies in the homologous recombination pathways.
• Studies also show DDR mutations upregulate PD-L1, increase tumor mutational burden, and are associated with higher tumor infiltrating lymphocytes.
• Therefore deficient homologous recombination and biomarkers for immune checkpoint inhibition are a possible opportunity for immunotherapy in upper GI cancers.
• We investigated the association of DDR mutations in gastric (GC), esophageal (EC), and gastroesophageal junction (GEJ) cancers with known predictors for immune checkpoint inhibition.

OBJECTIVES

To compare the association of known predictive biomarkers (MSI, PD-L1, TMB) to checkpoint inhibitors in DDR-mutated upper GI malignancies vs. non-DDR.

METHODS

To correlate specific DDR alterations (e.g. MSI was assessed by NGS or fragment analysis, PD-L1 by IHC (22c3 for CPS or SP142), and TMB by NGS (TMB-high ≥10 mutations/megabase [mt/MB]).

RESULTS

Gastroesophageal DDR mutation rates

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Total Gastroesophageal</th>
<th>GC</th>
<th>EC</th>
<th>GEJ</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSI-H (MSI-H)</td>
<td>18%</td>
<td>40%</td>
<td>60%</td>
<td>20%</td>
</tr>
<tr>
<td>MSI-L (MSI-L)</td>
<td>11.50%</td>
<td>17.40%</td>
<td>10.0%</td>
<td>25.0%</td>
</tr>
</tbody>
</table>

PD-L1 (22c3 or SP142) and TMB by NGS (TMB-high ≥10)

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>TMB Low</th>
<th>TMB High</th>
<th>TMB-M</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC</td>
<td>6</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>EC</td>
<td>9</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>GEJ</td>
<td>12</td>
<td>14</td>
<td>15</td>
</tr>
</tbody>
</table>

Table 1: DDR Mutation Rates

MSI-H has significantly more common in the DDR-mutated cohort (DDR-M) compared to non-mutated cancers (15% vs. 1% p < 0.0001). Table 1 shows the highest TMB compared to DDR-M EC and GEJ (mean: 13.8 vs. 7.7 vs. 7.6 mt/MB).

Figure 6: DDR-M correlated with MSI

MSI-H (MSI-H) was significantly more common in the DDR-mutated cohort (DDR-M) compared to non-mutated cancers (15% vs. 1% p < 0.0001). Table 1 shows the highest TMB compared to DDR-M EC and GEJ (mean: 13.8 vs. 7.7 vs. 7.6 mt/MB).

DDR-mutated cohort vs. non-DDR-mutated cohort

MSI-H (MSI-H) was significantly more common in the DDR-mutated cohort (DDR-M) compared to non-mutated cancers (15% vs. 1% p < 0.0001). Table 1 shows the highest TMB compared to DDR-M EC and GEJ (mean: 13.8 vs. 7.7 vs. 7.6 mt/MB) (Figure 1). DDR mutations were more frequent in the PD-L1 positive group (CPS ≥50) compared to CPS < 50 (4.3% vs. 1.2% p = 0.0001) (Figure 2).

Table 2: TMB mean DDR-M

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Mass DDR-M</th>
<th>Mass DDR-associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC</td>
<td>13.9 mt/MB</td>
<td>7.7 mt/MB</td>
</tr>
<tr>
<td>EC</td>
<td>9.4 mt/MB</td>
<td>6.3 mt/MB</td>
</tr>
<tr>
<td>GEJ</td>
<td>10 mt/MB</td>
<td>7.6 mt/MB</td>
</tr>
</tbody>
</table>

Figure 7: DDR-M correlated with PD-L1 (CPS > 10)

Figure 8: DDR-M correlated with MSI

Conclusions

• Based on the molecular profiles examined in this study, DDR mutations are prevalent across all gastroesophageal cancers. In out of esophageal, gastric, and gastroesophageal junction cancers, DDR-mutations are most prevalent in gastric cancers.
• Biomarker expression of MSI-H, TMB-high, and high PD-L1 are significantly more prevalent in the DDR-mutated cohort compared to the non-DDR-mutated cohort.
• Out of the 20 DDR mutations examined, alterations in ARID1A, ATRX, BRCA2, and PTEN are correlated with MSI-H and TMB-high. In contrast ARID1A, BRCA2, ATRX, and PTEN are correlated with increased PD-L1 expression. These highly prevalent DDR mutations should be investigated as possible biomarkers for treatment.
• These findings may help identify patients for targeted immunotherapy approaches in future clinical trials. By further characterizing associations of DDR alterations and immune-mondo predictive biomarkers, rational drug combinations may be implemented in the treatment of upper gastroesophageal cancers.

REFERENCES