PARP Inhibitors for Ovarian Cancer Treatment

Paige Baldwin1,2, Shifalika Tanguturi1,3, Srinivas Sridhar2,3

1. Department of Bioengineering, Northeastern University, 2. Nanomedicine Science and Technology Center, Northeastern University, 3. Radiation Oncology, Dana Farber Cancer Institute

Abstract

Poly(ADP-ribose) polymerase (PARP) is a protein which plays a role in a number of DNA repair pathways. PARP inhibitors, such as Olaparib and BMN-673, act by inhibiting DNA damage repair and thus accumulating deleterious mutations leading to genetic instability. Olaparib has been recently approved for advanced ovarian cancer patients who exhibit defective BRCA1/2 genes, which are associated with DNA repair processes. Current PARP inhibitors are only available in an oral formulation, which must undergo first pass metabolism, resulting in low accumulation in tumors, poor efficacy, and systemic toxicity. A nanoformulation offers 100% bioavailability in the vasculature, greater tumor accumulation, and reduced systemic toxicity, suggesting greater drug efficacy with less side effects. PARP inhibitors nanoformulations were characterized to be tested in vitro. Dose response curves of Olaparib and BMN-673 along with the respective nanoformulations were generated for a number of ovarian cancer cell lines with varying genetic profiles. The IC-50’s of the drugs can then be correlated to the genetic profiles of the cell lines to gain a greater understanding of which patients, if any, would most benefit from this treatment beyond those with BRCA mutations. The IC-50 values have indicated that all cell lines with BRCA mutations display sensitivity to PARP inhibition, while some cell lines without BRCA mutations display high sensitivity. This corresponds to the broadening reach of PARP inhibitors beyond the currently approved BRCA1/2 mutations. A greater understanding of response profiles will allow for treatment to be tailored to the patient and thus more personalized medicine.

Background

- PARP-1 is a DNA repair protein which plays a role in a number of DNA repair pathways (HR, BER, NHEJ)
- PARP inhibitors prevent cells with DNA damage from repairing themselves
  - Applicable for tumors with prior defects in DNA repair pathways

Ovarian Cancer Cell Line Genomic Profiles

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Homozygous Deletion</th>
<th>Amplification</th>
</tr>
</thead>
<tbody>
<tr>
<td>KURAMOCHI</td>
<td>TP53</td>
<td>BRCA1, BRCA2, PTEN, KRAS</td>
</tr>
<tr>
<td>OVSANO</td>
<td>PALB2</td>
<td></td>
</tr>
<tr>
<td>PAI1</td>
<td>HBO2</td>
<td></td>
</tr>
<tr>
<td>COV318</td>
<td>SKOV3</td>
<td></td>
</tr>
<tr>
<td>403</td>
<td>404</td>
<td></td>
</tr>
<tr>
<td>4306</td>
<td>4412</td>
<td></td>
</tr>
</tbody>
</table>

Results

Figure 1. TEM micrograph of NanoOlaparib (A) and corresponding characteristics of the nanoformulation (B). NanoOlaparib releases preferentially at tumor pH (C).

Figure 2. IC-50’s of ovarian cancer cell lines treated with Olaparib (A) and NanoOlaparib (B). Graph comparing IC-50 values with Olaparib and NanoOlaparib (C).

Figure 3. IC-50’s of ovarian cancer cell lines treated with BMN-673 (A) and NanoBMN-673 (B). Graph comparing IC-50 values with BMN-673 and NanoBMN-673 (C).

Conclusion

Both nanoformulations show similar if not better efficacy than the free drugs 404, 4412, and 403 and show the greatest sensitivity to both drugs and all have PTEN deletions—PARP inhibitors are applicable to cancers with PTEN mutations. Some cell lines with BRCA1/2 mutations are not as sensitive to PARP inhibition as those without BRCA1/2 mutations. Genomic profiles alone do not confer sensitivity—cell lines with the same mutations and deletions do not always display the same drug sensitivities. Clinical tests for stratifying patients who will benefit from PARP inhibitor therapy should include more than BRCA1/2 mutations.

Acknowledgements

Supported by IGERT grant NSF-DGE- 0965843 and Army W81XWH-14-1-0092

References