PARP Inhibitor Nanotherapy for Cancer Treatment

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Abstract
Poly(ADP-ribose) Polymerase (PARP) plays an important role in a number of DNA repair pathways. PARP inhibitors, such as Olaparib exploit the concept of synthetic lethality by selectively targeting cancer cells with defective DNA repair pathways, while leaving healthy cells with multiple repair pathways unharmed. These drugs are currently only available in oral form which results in limited bioavailability, poor tumor accumulation, and systemic toxicity. Nanoparticle formulations of Olaparib were developed to allow intravenous (IV) or intraperitoneal (IP) delivery, providing greater bioavailability and tumor accumulation, while limiting systemic toxicities. NanoOlaparib was synthesized and characterized before further testing in vitro and in vivo. In vitro it has been tested in a panel of ovarian cancer cell lines to elucidate sensitivity profiles. NanoOlaparib was also tested in an ovarian cancer IP spread model. Animals were treated IP with NanoOlaparib alone, and in combination with cisplatin. Bioluminescence imaging illustrated that NanoOlaparib administered IP daily resulted in a greater inhibition of tumor growth than those treated with oral Olaparib daily. Radiosensitization with NanoOlaparib was tested in a radiation resistant prostate cancer cell line, FK01 and a xenograft model with the same cells to mimic castration resistant prostate cancer. The FK01 xenografts are highly radiosensitive with little difference between untreated and radiation only animals. NanoOlaparib delays tumor growth, while the combination of radiation and NanoOlaparib shrinks tumors. These results show that NanoOlaparib amplifies the therapeutic efficacy of PARP inhibition and imply a promising role for the nanof ormulation in a variety of cancers.

Objective
Develop and characterize nanoparticle formulations (NanoOlaparib) of the PARP inhibitor Olaparib to enhance delivery to the tumor site. The nanof ormulation allows for intravenous delivery and 100% availability in the vasculature or intraperitoneal delivery for cancers such as ovarian cancer in which the tumor is disseminated throughout the IP cavity.

Background

PARP Inhibition

• PARP-1 is a DNA repair protein which plays a role in:
  • Base Excision Repair
  • Homologous Recombination
  • Non-Homologous End Joining
  • Transcriptional Regulation

Ovarian Cancer

Figure 1. NanoOlaparib characterization via (a) transmission electron micrograph, (b) nanoparticle tracking laser scattering size distribution, and (c) release profile. Average diameter is 71.7 nm and formulation can be loaded up to 11.52 mM.

Figure 2. Dose response curves for (a) Olaparib and (b) NanoOlaparib and (c) comparison of IC50 values. Chart (d) displays genomic profiles of tested cell lines.

Figure 3. IP spread model using 404 cells derived from BRCA2, TP53, PTEN/GEMMs. Animals were treated with (a) empty nanoparticles, (b) 50 mg/kg NanoOlaparib IP or (c) 50 mg/kg oral Olaparib daily. Average fold change in bioluminescence during treatment (d) and Kaplan meier survival curve (e).

Prostate Cancer

Figure 4. Subcutaneous engraftment of FK01 cells, derived from Pten1/1;Trp531/1 mice. Animals were treated intravenously with 40 mg/kg NanoOlaparib twice weekly. Animals received a single dose of 10 Gy radiation on day 10. Fold change in tumor volume (a) and a Kaplan meier survival curve depicting the lifespan of each group (b).

Conclusions
• PAI is most sensitive to NanoOlaparib which may be attributed to genetic instability at 11/13 polymorphic loci, each containing (CA)n microsatellites possibly causing mutations in critical genes with coding repeat sequences.
• The high sensitivity of 4412 and 4306 cell lines suggests that PTEN deletion confers similar sensitivity to PARP inhibitors as BRCA2 deletion. The results indicate that BRCA mutations and deletions are just as susceptible as PTEN deletions while high genetic instability showing the greatest sensitivity.
• NanoOlaparib is highly potent, when delivered IP effectively treats the tumor, leading to 50% reduction in tumor volume.
• Toxicity can be attributed to 100% of the dose being delivered directly to the peritoneal cavity with a sustained release, therefore, overdosing the mice with the daily administration, leading to toxicity (death).
• Dosing needs to be tailored to the pharmacokinetics of the nanof ormulation rather than the oral formulation, to determine the optimal dose regime.
• The FK01 xenografts are highly radiosensitive with little difference between untreated and radiation only animals.
• NanoOlaparib as a monotherapy delays tumor growth but does not shrink tumors.
• The combination of Radiation and NanoOlaparib clearly shrinks tumor growth. Some animals show very small tumors, while tumors seem to regrow in others.

Future Directions
• Determination of the optimal dosing regime for the nanof ormulations.
• Characterization of a nanof ormulation for a more potent PARP inhibitor, Talazoparib.
• Development of a combination nanof ormulation for delivery of a PARP inhibitor and a DNA damaging agent such as cisplatin.

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References