Research Week 2020

Novel Poly(2-oxazoline) Micelle Formulation of PARP/PI3K Induces Immunogenic Cell Death, Enhancing Response to Triple Combination Therapy

Madeleine Landry, Allison N. DuRoss, Megan J. Neufeld, Lukas Hahn, Gaurav Sahay, Robert Luxenhofer, Conroy Sun

OHSU/OSU College of Pharmacy

Keywords

radiation, PARP/PI3K, polymeric nanoparticles

Abstract

Radiation therapy is commonly employed in cancer treatment regimens in concert with other treatments but is rarely effective as a monotherapy. Radiation can be enhanced by the application of small molecule checkpoint inhibitors. These drugs are hydrophobic, necessitating a drug delivery agent, such as a polymer. This approach has been applied to breast and ovarian cancer, but has not yet been explored in colorectal. The efficacy of chemo-radiation combination therapy has the potential to further be improved by the addition of immunotherapy. With the recent clinical approval of immunotherapy for metastatic colorectal cancer, triple combination therapy (i.e. radiation, chemo, immuno) is an area that warrants exploration.

PARP and PI3K inhibitors were screened in colon cancer CT26 cells to find an optimal combination, then loaded into a poly(2-oxazaline) micelle. A poly(2-oxazaline) polymer was chosen over traditional PEG and Pluronic as a delivery excipient for the high loading capacity, low toxicity, and enhanced uptake. The drug-loaded micelles were characterized and tested out in vitro with radiation for cell uptake, cell toxicity, double strand break induction, and ability to induce reproductive cell death and immunogenic cell death. The micelles were tested in vivo with radiation and anti-CTLA-4 antibodies for efficacy, tumor volume, safety, and immunogenic cell death.

The PARP/PI3K inhibitor combination was able to induce immunogenic cell death (ICD) both in vitro and in vivo when injected intratumorally. The triple combination therapy was able to increase the cure rate of mice implanted with CT26 tumors and had a slightly improved tumor volume curve relative to the radiation and anti-CTLA-4 only controls. The ability of the drug combination to induce ICD is important in the immune suppressive tumor environment and paired with CTLA-4 may lead to better outcomes. Increased tumor infiltrating lymphocytes were observed with intratumoral injection. However, the dosing and timing of therapy is critical. A mere 0.4% of the injected dose was able to reach the tumor, yet histological differences were still visible with only three injections of the

micelles. With increased and more frequent dosing of micelles, we would expect to see increased separation between the tumor volume curves.