

Discovery of Ruthenium (II) Metallocompounds and Olaparib Synergy: From a Single Agent to a Promising Cancer Combination Therapy

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Abstract

Combination therapy has also proven to be a highly successful cancer strategy whereby synergistic drug combinations offer improved cancer specificity, and reduced side effects compared to single-agent treatment and can also combat the challenge of drug resistance. As such, the isolation of new combination therapy strategies that include a DNA damage response inhibitor alongside another therapeutic represent a leading approach to combat aggressive cancers. Poly(ADP-ribose) polymerase (PARP) inhibitors have been successfully developed as single-agent therapy for breast cancer patients. However, acquired drug-resistance and the fact that BRCA-deficient breast cancers account for a relatively small subset of patients (<20% of TNBC patients) are substantial limitations in the use of PARPi in treating TNBC. Synergistic combination therapy using PARPi, for example, olaparib alongside a chemical sensitizer has emerged as a new concept in oncology to address these challenges. To identify new synergistic combinations for PARPi, we screened a “micro-library” comprising a mix of commercially available drugs and DNA-binding ruthenium(II) polypyridyl complexes (RPCs) for Olaparib synergy in BRCA proficient TNBC. This identified three hits: the natural product Curcumin and two ruthenium(II)-rhenium(I) polypyridyl metallomacrocycles. All combinations identified were effective in BRCA-proficient breast cancer cells, including an Olaparib-resistant cell line, and spheroid models. Mechanistic studies indicated that synergy was achieved via DNA damage enhancement and resultant apoptosis. Overall, this work supports the concept that the PARP inhibitor combination therapy represents a promising approach for cancer treatment, including toward aggressive strains such as TNBC.

Keywords: *Combination therapy, Ruthenium Polypyridyl Complex, PARP inhibitor, Cancer, Synergism*