Selinexor, a Selective Inhibitor of Nuclear Export (SINE) Compound, Shows Enhanced Anti-Tumor Activity in Combination with the PARP Inhibitor, Olaparib, in Models of Triple Negative Breast Cancer (TNBC)

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ABSTRACT

Background: Selinexor is a SINE (Selective Inhibitor of Nuclear Export) compound currently in Phase I and II clinical trials for the treatment of hematological and solid malignancies. Selinexor induces cell death by blocking the key nuclear export protein XPO1 and forcing nuclear retention of tumor suppressor proteins (TPPs), including p53, BRCA1/2, and FOXO3A. Recent work from our lab suggests that selinexor inhibits DNA damage repair by inhibiting Ch11 and Rad11 expression. Olaparib is a FDA approved therapy for BRCA1/2 mutated ovarian cancer, which inhibits Poly-ADP-Ribose Polymerase (PARP) and prevents DNA damage repair. Furthermore, Olaparib is being evaluated for the treatment of Triple Negative Breast Cancer (TNBC). We hypothesized that combination of selinexor and olaparib would enhance cancer cell death by accumulation of DNA damage that cannot be resolved in TNBC. We aim to test the combination of selinexor and olaparib in TNBC harboring wild or mutated BRCA1 genes.

Methods: The effects of selinexor alone or in combination with olaparib were tested on a panel of 7 TNBC cell lines using soft agar colony formation assay in parallel with FACS analysis. Combination index (CI) values were determined using the CompuSyn software and treatment was considered synergistic when CI < 1. Comparative in vivo efficacy of single-agent or combination therapy was evaluated in MDA-MB-468 (BRCA1 WT), MDA-MB-468 (Brca1/2 mutant) and MDA-MB-468 xenograft tumor models.

Results: The median IC50 values for selinexor and olaparib were 1.88 µM (range: 0.37 µM to 7.5 µM) and 10.2 µM (range: 2.5 µM to >100 µM), respectively. Combination treatment led to synergistic inhibition of proliferation in the 7 TNBC cell lines evaluated. The median CI tested on the panel of cell lines was 0.98 (range: 0.4 to 0.98). FACS analysis revealed an additive effect of combination therapy on DNA replication and G2 phase progression and G2 arrest in both BRCA1 mutant and BRCA1 wild type cell lines. Furthermore, Annexin V/FITC staining showed dose-dependent effect on cell death. Combination therapy was tested on the MDA-MB-468 xenograft model. 98% tumor growth inhibition was observed in the combination group compared to 77% and 81% TGI in single-agent selinexor and olaparib, respectively. This effect is additive by E-Biomas modeling. In contrast, the MDA-MB-436 model of TNBC (BRCA1 mutant)attested the effect of the combination was synergistic, with 86% TGI in combination vs. 40% in selinexor and 16% in olaparib.

Conclusions: Selinexor and olaparib act additively or synergistically to induce apoptosis in TNBC cells and robustly enhance anti-tumor effects in BRCA1-derived xenograft models. These data provide a rational basis to support the study of selinexor-olaparib combination in clinical trials.

INTRODUCTION

Olaparib is a PARP1 and PARP2 inhibitor approved for the treatment of BRCA1/2-mutated ovarian cancer. The BRCA1/2-mutant tumors are more sensitive to PARP inhibition due to synthetic lethality. Loss of BRCA1/2 in combination with availability of RAD51 in TNBC results in an accumulation of DNA damage that cannot be repaired leading to cell death. Considering BRCA1/2 are cargo proteins of XPO1 and selinexor has shown to act in part through inhibition of DNA damage repair, we hypothesized that combination of selinexor and PARP would be synergistic in models of TNBC. The objectives of the study are to determine whether selinexor would increase sensitivity of TNBC cells (BRCA1/2 WT) to olaparib and to compare the effect of combining selinexor and olaparib in-vivo in models of BRCA1-mutated breast cancer (MDA-MB-231 and MDA-MB-157) and BRCA1-wt tumors (HCC-1937).

RESULTS

Selinexor Sensitizes BRCA-WT and BRCA-Mutant TNBC Cells to Olaparib

Additive Effect of Selinexor-Olaparib Combination on Tumor Growth of MDA-MB-468 Xenografts

Selinexor and Olaparib Has Additive Effects on TNBC Cell Apoptosis in Both WT and Mutant BRCA1

Synergistic Effect of Selinexor–Olaparib Combination on Tumor Growth of MDA-MB-436-derived Xenografts (BRCA1 Mutated)

CONCLUSIONS

• Combination of selinexor and olaparib induces robust anti-tumor activity in vitro and in vivo.
• Selinexor–olaparib combination has led to an additive effect on tumor growth inhibition in MDA-MB-468 xenografts (BRCA1 wt and Brca1/2 mutant). The combination showed robust synergistic effect in xenograft model of MDA-MB-436 (BRCA1 mutant cells). Mechanisms leading to the different effects of the combination in the two models are yet to be explored.

Figure from: Polyak K, Nature Med 2011

Tumor cell line MDA-MB-436 and MDA-MB-468 were treated with either vehicle, selinexor (1 µM), olaparib (250 µM), or Olaparib + Selinexor for 24 h. Cell lysates were blotted with antibodies to detect changes in DNA damage response.

MDA-MB-436 showed inhibition of DNA and Rad11 expression in cells treated with selinexor-olaparib, suggesting induction of the DNA damage response.

DNA damage response proteins were not altered in vehicle, selinexor-olaparib combination treatment group in MDA-MB-468. However, an increase in p53 expression, suggests an overall increase in DNA damage.

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