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Cancer Science & Pediatrics 2019: Overexpression of PARP is an independent prognostic marker for poor survival in Middle Eastern breast cancer and its inhibition can be enhanced with embelin co-treatment - Khawla Al-Kuraya - King Faisal Specialist Hospital and Research, Saudi Arabia

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Patients with aggressive breast cancer (BC) subtypes usually do not have favorable prognosis despite the improvement in treatment modalities. These cancers remain a major cause of morbidity and mortality in females. This has fostered a major effort to discover actionable molecular targets to treat these patients. Poly ADP ribose polymerase (PARP) is one of these molecular targets that are under comprehensive investigation for treatment of such tumors. However, its role in the pathogenesis of BC from Middle Eastern ethnicity has not yet explored. Therefore, the authors examined the expression of PARP protein in a large cohort of over 1000 Middle Eastern BC cases using immunohistochemistry. Correlation with clinico-pathological parameters was performed.

Nuclear PARP overexpression was observed in 44.7% of all BC cases and was significantly associated with aggressive clinico-pathological markers. Interestingly nuclear PARP overexpression was an independent predictor of poor prognosis. PARP overexpression was also directly associated with XIAP overexpression, with PARP and XIAP co-expression in 15.8% (159/1008) of our cases. It was observed that the combined inhibition of PARP by olaparib and XIAP by embelin significantly and synergistically inhibited cell growth and induced apoptosis in BC cell lines.

Finally, co-treatment of olaparib and embelin regressed BC xenograft tumor growth in nude mice. The results revealed the role of PARP in Middle Eastern BC pathogenesis and prognosis. Furthermore, the study data support the potential clinical development of combined inhibition of PARP and XIAP, which eventually could extend the utility of olaparib beyond BRCA deficient cancer. Breast cancer is a leading cause of morbidity and mortality in women worldwide. In Saudi Arabia, BC is the most common cancer among females, accounting for 28.7% of newly diagnosed female cancers and the incidence continues to increase every year. BC is a heterogeneous disease containing several subgroups with molecular signature.

Triple negative breast cancer (TNBC) is the most aggressive histological subtype of BC representing 15–20% of all BCs with a high potential for metastasis and resistance to standard therapies. Therefore, identifying molecular therapeutic target for aggressive and metastatic BC is warranted. Poly (ADP-ribose) polymerases (PARPs) are a family of enzymes that share a catalytic PARP homology domain and the ability to poly (ADP-ribosyl) ate protein substrate. PARP proteins involved in several cellular processes including transcriptional regulation, DNA repair, cell survival, cell division, apoptosis, maintenance of genomic stability and telomere integrity. PARP-1 is the most abundant member as well as best-characterized DNA repair enzyme of PARP super family and is responsible for the majority of PARP activity in the cell. PARP-1 protein overexpression has been reported in various human malignancies, including BC. PARP inhibitors target DNA repair defects in hereditary BC.

PARP inhibitors as monotherapy or in combination therapy have yielded promising results against different cancers in recent clinical trials. Olaparib is an orally active PARP inhibitor that selectively kills cancer cells with deficient BRCA1 and BRCA 2, which encode proteins known to function in DNA repair through homologous recombination (HR). However, BRCA – mutant tumors represent only a small fraction (2–3%) of all BCs and only 12.5% of TNBCs, which might limit the therapeutic use of PARP inhibitor monotherapies.

In this study, we first investigated the expression of PARP protein in more than 1000 Middle Eastern BC cases and their clinico-pathological correlations including patient survival. Then, we were able to demonstrate the superiority and synergism of inhibition of PARP (using olaparib) and XIAP (using embelin) together overusing single inhibitor alone. This synergistic effect on cell proliferation, apoptosis and tumor growth is demonstrated both in vitro and in vivo. These data clearly demonstrate that PARP plays a significant role in the Middle Eastern BC pathogenesis and its combined inhibition with XIAP may expand the role of PARP inhibition therapy beyond BRCA-deficient BCs.

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