Correlation of Clinical Outcomes and Poly ADP Ribose Polymerase Activity in High Grade Serous Ovarian Cancer

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Topic: Ovarian

Objectives

PARP proteins are regulators of DNA damage repair in the cell. PARP inhibitors (PARPi) are a class of drugs used to treat ovarian cancer especially in patients with BRCA 1/2 gene mutations and homologous recombination deficiencies. These have previously been used as biomarkers to predict response to PARPi. Preclinical studies suggest that the levels of PARP-1, DDX21, and poly ADP ribosylation (PAR) are indicators of PARP activity. ADP ribosylation (PAR/ MAR) have been suggested as biomarkers to predict PARPi sensitivity. We sought to evaluate the correlation between PARP-1, DDX21, and mono-ADP ribosylation (MAR) expression with response to treatment with PARPi and survival outcomes.

Methods

Tissue samples were collected from primary or metastatic sites of 49 patients with high grade serous ovarian cancer who had been prescribed a PARPi. A tumor microarray was made and immunohistochemistry (IHC) for MAR, PARP-1, and DDX21 was performed. IHC staining was graded on a 3-point scale. Clinical data collected included demographics, stage, presence of BRCA mutation, cytoreductive status, time on PARPi, other adjuvant and salvage treatments, and survival outcomes. Kaplan-Meier analysis and Cox regression analysis were used to determine the effect of the biomarkers on survival outcomes and time on PARPi.

Results

We found longer treatment with PARPi was associated with improved overall survival ($p< 0.01$). PARP-1 expression directly correlated with DDX21 expression but it did not reach statistical significance ($p= 0.062$). On Cox regression analysis cytoplasmic MAR approached significance ($p=0.055$) in predicting progression free survival (PFS) after frontline treatment.

Conclusions

In our patient cohort, we saw a direct correlation between PARP-1 and DDX21 and an inverse correlation between MAR and PARP-1. Mono ADP ribosylation may predict PFS after frontline treatment. Pre-treatment biopsies and poly ADP ribosylation should be studied to further explore these biomarkers in predicting PARPi response.