

Treatment Sequencing Is Not Predictive of PARP Inhibitor Outcomes in Metastatic Castration-Resistant Prostate Cancer

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Background

PARP inhibitors are approved for patients with metastatic castration-resistant prostate cancer (mCRPC) harboring homologous recombination repair (HRR) deficiencies. However, treatment outcomes vary, and there is no consensus on therapeutic sequencing. This stresses the need for real-world data to refine patient selection.

Methods

We performed a multi-center retrospective study of patients with mCRPC treated with PARPi between 1/1/2013 and 12/31/2024. Clinical and genomic data were obtained from electronic medical records. Multivariable analyses were performed to evaluate baseline characteristics and clinical outcomes.

Results

We identified 129 patients who met the eligibility criteria. The median age at treatment initiation was 70 years. The most prevalent HRR alterations were *BRCA2* (45.7%), *ATM* (20.9%), *CHEK2* (17.1%), and *CDK12* (15.5%). The most common PARPi was olaparib (87.6%), followed by talazoparib (7.0%) and rucaparib (5.4%). PARPi was administered as first-line therapy in 12.4% of patients, second-line in 17.1%, and third-line or later in 70.5%. Most patients (55.0%) were treated with chemotherapy, while 11.6% had prior 177Lu-PSMA-617. The median time to treatment failure (TTF) on PARPi was 26.6 weeks (95% CI 19.0–32.1), compared with 17.7 weeks (95% CI 15.0–24.3) for the immediately preceding line of therapy ($p = 0.148$). A PSA50 response was observed in 32.6% of all patients, including 50.7% of those with *BRCA* alterations and 13.1% of those with non-*BRCA* mutations. In multivariable analysis, *BRCA* mutation status (HR = 0.49, 95% CI 0.30–0.79, $p = 0.003$) and having a PSA50 response (HR = 0.20, 95% CI 0.11–0.39, $p < 0.001$) were independently associated with longer TTF. Only PSA50 was independently associated with both TTF and overall survival. Prior exposure to chemotherapy or 177Lu-PSMA-617 was not associated with clinical outcomes with PARPi.

Conclusion

In this cohort of heavily pre-treated patients, PARPi demonstrated clinical efficacy similar to previous reports. *BRCA* alterations were linked to improved clinical outcomes, suggesting that PARPi should be prioritized in this population. Our findings support the use of broad genomic profiling in to guide individualized treatment strategies.

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Conflicts of interest

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