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Role of PARP Inhibitors in Ovarian Cancer

James P. Patel*

Senior Researcher, Institute for Precision Cancer Research, Chicago, IL

Abstract

Ovarian cancer, a leading cause of gynecologic cancer mortality, is characterized by DNA repair deficiencies in up to 50% of cases, particularly in BRCA-mutated and homologous recombination-deficient (HRD) tumors. Poly (ADP-ribose) polymerase (PARP) inhibitors, such as olaparib, niraparib, and rucaparib, exploit these vulnerabilities, offering significant therapeutic advances. This article reviews the mechanisms, clinical trial outcomes, and challenges of PARP inhibitors in ovarian cancer treatment. Results demonstrate prolonged progression-free survival (PFS) in maintenance and recurrent settings, though resistance remains a hurdle. Future directions include combination therapies and biomarker development to optimize patient selection.

Keywords: Ovarian cancer; PARP inhibitors; BRCA mutation; Homologous recombination deficiency; Maintenance therapy; Clinical trials; Progression-free survival; Resistance; Precision medicine; Gynecologic oncology

Introduction

Ovarian cancer accounts for 4% of cancers in women but has a disproportionate mortality rate, with over 200,000 deaths annually worldwide [1]. Most patients are diagnosed at advanced stages, where five-year survival is below 30% [2]. Genomic instability, particularly in BRCA1/2-mutated or HRD tumors, is a hallmark of high-grade serous ovarian cancer, making these cancers susceptible to PARP inhibitors [3]. These agents induce synthetic lethality by blocking DNA single-strand break repair, leading to double-strand breaks that HRD tumors cannot repair [4]. This article synthesizes evidence from pivotal trials, discusses resistance mechanisms, and explores the evolving role of PARP inhibitors in ovarian cancer management.

Discussion

PARP inhibitors have transformed ovarian cancer treatment, particularly for BRCA-mutated and HRD tumors. The SOLO-1 trial demonstrated that olaparib maintenance therapy in newly diagnosed BRCA-mutated advanced ovarian cancer extended median PFS to 56 months compared to 13.8 months with placebo [5]. Similarly, the PRIMA trial showed niraparib's benefit in HRD tumors, with a median PFS of 21.9 months versus 10.4 months [6]. Rucaparib, evaluated in the ARIEL3 trial, improved PFS in both BRCA-mutated and HRD populations, with response rates of 18–26% in recurrent disease [7]. Despite these advances, resistance to PARP inhibitors, driven by mechanisms like BRCA reversion mutations or HR restoration, limits durability [8]. Up to 50% of patients develop resistance within 12–18 months [9]. Combination strategies, such as PARP inhibitors with anti-angiogenic agents (e.g., bevacizumab in the PAOLA-1 trial), have shown synergistic effects, with a median PFS of 22.1 months in HRD patients. Immune checkpoint inhibitors are also being explored, though early trials show modest activity. Biomarker development is critical to identify patients likely to benefit. While BRCA and HRD status are primary predictors, emerging markers like RAD51 foci formation may refine selection. Challenges include managing toxicities (e.g., anemia, fatigue) and addressing cost-effectiveness, as PARP inhibitors are expensive.

Results

Clinical trials consistently show significant PFS benefits with PARP inhibitors. In SOLO-1, olaparib achieved a 70% reduction in disease progression risk in BRCA-mutated patients (HR 0.30) [9]. PRIMA reported a 57% risk reduction in HRD tumors with niraparib (HR 0.43). ARIEL3 demonstrated rucaparib's efficacy, with a median PFS of 16.6 months in BRCA-mutated patients versus 5.4 months with placebo. Combination therapy in PAOLA-1 extended PFS to 22.1 months in HRD patients. Resistance occurs in 40–50% of patients within 18 months, with BRCA reversion mutations detected in 20% of resistant cases [10]. Toxicities, including grade 3 anemia (20%) and fatigue (15%), are common but manageable with dose adjustments.

Conclusion

PARP inhibitors have revolutionized ovarian cancer treatment, offering substantial PFS benefits in BRCA-mutated and HRD tumors. However, resistance and toxicities pose ongoing challenges. Combination therapies and improved biomarkers hold promise for enhancing efficacy and personalizing treatment. Continued research into resistance mechanisms and cost-effective strategies will be essential to maximize the impact of PARP inhibitors in gynecologic oncology.

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***Corresponding author:** James P. Patel, Senior Researcher, Institute for Precision Cancer Research, Chicago, IL, E-mail: jppatel@ipcr.edu

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