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Original Article

Decoding PARP Inhibitor Resistance in Ovarian Cancer: Molecular Insights and Emerging Therapeutic Strategies

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Abstract

Ovarian cancer remains one of the most lethal gynecologic malignancies, primarily due to its late-stage diagnosis and frequent relapse. Poly (ADP-ribose) polymerase (PARP) inhibitors have emerged as promising agents in the management of ovarian neoplasms, particularly among patients with BRCA1/2 mutations or homologous recombination deficiency (HRD). Despite initial therapeutic successes, the development of drug resistance poses a significant challenge, limiting the long-term efficacy of these agents. This review analyzes the molecular mechanisms underlying PARP inhibitor resistance, including genetic reversion mutations in BRCA1/2, restoration of homologous recombination repair pathways, and alterations in drug efflux mechanisms. Furthermore, we explore strategies to overcome PARP inhibitor resistance, such as combination therapies with other targeted agents, using ATR inhibitors, and optimizing the timing of maintenance chemotherapy. Current advances in identifying predictive biomarkers for PARP inhibitor response are also discussed, offering potential pathways for personalized treatment approaches. Understanding the complex interplay of resistance mechanisms and the evolving therapeutic landscape is crucial to improving outcomes in patients with ovarian cancer. This review aims to summarize current knowledge on PARP inhibitor resistance and emerging strategies to enhance their therapeutic potential in ovarian neoplasms.

Keywords: ***ovarian neoplasms; Poly (ADP-ribose) polymerases; drug resistance, neoplasm; homologous recombination; BRCA1 protein; maintenance chemotherapy.***

Introduction

Ovarian cancer remains one of the most lethal gynecologic malignancies, typically diagnosed at an advanced stage and characterized by high recurrence and mortality rates [1-3]. While standard treatments, including cytoreductive surgery followed by platinum-based chemotherapy, have improved patient outcomes, the relapse of platinum-sensitive ovarian cancer is common, thereby underscoring the urgent need for novel therapeutic strategies [2-4].

The resistance to Poly (ADP-ribose) polymerase inhibitors (PARPi) in ovarian cancer remains a significant clinical challenge, limiting the long-term effectiveness of this class of drugs [3-5]. While PARPi therapies such as olaparib, niraparib, and rucaparib have transformed the treatment landscape for BRCA-mutated and homologous recombination repair (HRR)-deficient ovarian cancers, resistance inevitably emerges. Among the molecular resistance mechanisms, restoring HRR through reversion mutations in the BRCA1/2 genes is a primary contributor [6-8].

These mutations restore the function of BRCA1/2, effectively negating the synthetic lethality that PARPi exploits. However, our understanding of these reversion mutations' frequency and functional implications remains incomplete. Additionally, limited clinical tools are available to predict which patients will experience this resistance mechanism, creating an urgent need for biomarkers capable of identifying resistance early [9-11].

The introduction of poly (ADP-ribose) polymerase (PARP) inhibitors has significantly altered the treatment landscape of ovarian cancer, particularly for patients with BRCA1/2 mutations and homologous recombination deficiency (HRD) [12-14]. These agents, such as olaparib, niraparib, and rucaparib, have significantly improved progression-free survival (PFS). However, resistance to these agents poses a significant challenge to achieving durable responses and optimizing therapeutic outcomes [15-17].

The mechanism of action of PARP inhibitors is grounded in synthetic lethality. PARP enzymes play a critical role in the repair of single-strand DNA breaks via base excision repair. PARP inhibition prevents this repair process, accumulating DNA single-strand breaks that eventually convert into double-strand breaks (DSBs) during DNA replication [16-18]. In cells deficient in homologous recombination repair (HRR) such as those with BRCA mutations

these DSBs cannot be adequately repaired, leading to genomic instability and subsequent cell death. This has made PARP inhibitors highly effective in HR-deficient ovarian cancer [19-21].

Moreover, alternative DNA repair pathways, including non-homologous end joining (NHEJ) and microhomology-mediated end joining (MMEJ), have emerged as critical compensatory mechanisms in PARPi-resistant tumors [22]. While less accurate than HRR, these pathways enable tumor cells to bypass the defects in HR and maintain genomic stability, further complicating therapeutic strategies [23-25].

The exact contribution of these pathways across different ovarian cancer subtypes remains poorly characterized, and a deeper understanding of their role could inform the development of novel combination therapies [26].

The tumor microenvironment (TME) is another underexplored area in PARPi resistance. Hypoxia, a hallmark of solid tumors, promotes DNA damage and alters repair mechanisms, potentially facilitating resistance [27]. Additionally, the immunosuppressive nature of the TME, characterized by regulatory T cells, myeloid-derived suppressor cells, and tumor-associated macrophages, interacts with DNA damage response pathways, potentially influencing the efficacy of PARPi and immunotherapies. Strategies to modulate TME, including the use of immune checkpoint inhibitors, are still in their infancy in ovarian cancer but hold promise for overcoming resistance [28-30].

Ferroptosis, a newly recognized form of programmed cell death dependent on iron and lipid peroxidation, represents a potential novel target for overcoming resistance to PARPi [31]. While ferroptosis has been implicated in other cancers, its role in ovarian cancer remains to be fully elucidated. Initial studies suggest that inducing ferroptosis may sensitize cancer cells to PARPi, offering a potential strategy to circumvent resistance. However, much remains to be understood about how to integrate ferroptosis in therapeutic regimens for ovarian cancer effectively [32-34].

Given these emerging areas of interest, this review aims to critically evaluate the current understanding of PARPi resistance, focusing on the molecular mechanisms, alternative repair pathways, the role of the TME, and novel approaches such as ferroptosis. By addressing these gaps, we hope to outline future directions for research and clinical practice that could enhance the efficacy of PARPi in ovarian cancer treatment [35-37].

Nonetheless, resistance to these agents can emerge via various mechanisms, both intrinsic and acquired. One of the most prominent mechanisms of acquired resistance is the restoration of HRR, frequently mediated through secondary or "reversion" mutations in BRCA1/2 that restore protein function and enable DNA repair, thereby negating synthetic lethality [6,38-40].

Other genetic alterations, including those in RAD51C/D, PALB2, and FANCA, have been shown to restore HRR and confer resistance to PARP inhibitors similarly [41]. This highlights the critical need for comprehensive genomic profiling in patients treated with PARP inhibitors to anticipate and address potential resistance mechanisms [13,42].

Another key resistance mechanism is the stabilization of stalled replication forks. PARP inhibitors induce cytotoxicity by disrupting replication fork progression, leading to fork collapse and subsequent cell death [9,43].

However, cancer cells can adapt by upregulating fork protection proteins such as RAD51, BRCA1, and FANCD2 or downregulating nucleases like MRE11, which allows for fork stabilization and enables the survival of cancer cells despite PARP inhibition [17-19,44]. Additionally, PARP inhibitors interact with other DNA repair pathways, such as non-homologous end joining (NHEJ). Alterations in the balance between HRR and NHEJ, mainly through the 53BP1-RIF1 axis, can affect cellular responses to PARP inhibition and serve as potential therapeutic targets for overcoming resistance [16,20,45].

Epigenetic modifications also play a role in resistance to PARP inhibitors. Aberrant DNA methylation and histone acetylation patterns can alter the expression of DNA repair genes, influencing the cellular response to these agents. Furthermore, mutations in the ABCB1 gene, which encodes the P-glycoprotein efflux pump, can reduce intracellular concentrations of PARP inhibitors, thereby decreasing their effectiveness [17,21,46]. Therefore, the combination of PARP inhibitors with epigenetic modulators, such as histone deacetylase inhibitors, is being actively explored to overcome resistance [18,22,47].

The tumor microenvironment (TME) significantly influences the efficacy of PARP inhibitors. Hypoxia within the TME can induce HRR activity, enhancing DNA repair and contributing to PARP inhibitor resistance. Furthermore, immune cells within the TME, including tumor-associated macrophages, contribute to an immunosuppressive milieu that reduces the therapeutic response to PARP inhibitors [19,23,48]. Consequently, combining PARP inhibitors with immune checkpoint inhibitors such as PD-1/PD-L1 blockers represents an emerging strategy to stimulate an immunogenic response and potentially overcome resistance [49-51].

Combination therapies have emerged as a primary strategy to enhance the efficacy of PARP inhibitors and mitigate resistance. The combination of PARP inhibitors with agents targeting other DNA damage response (DDR) components such as ATR, CHK1/2, and WEE1 inhibitors has demonstrated promising results in preclinical models and early-phase clinical trials [52-54].

These combinations enhance replication stress and impair cell cycle checkpoints, ultimately inducing apoptosis in HR-deficient cells [21,25]. Anti-angiogenic agents like bevacizumab, which disrupt tumor vasculature and exacerbate hypoxia, have demonstrated synergistic effects when combined with PARP inhibitors [55-57].

Identifying and validating predictive biomarkers for response and resistance to PARP inhibitors is critical for optimizing therapeutic outcomes. While BRCA mutation status remains a crucial predictor of sensitivity, additional biomarkers such as HRD status, loss of heterozygosity (LOH), and tumor mutational burden (TMB) are under investigation for their predictive value [22,58].

Other potential biomarkers, including immune signatures within the TME and liquid biopsy approaches such as circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs) are being explored for real-time monitoring of resistance development and treatment response [14,27,59].

The timing, sequencing, and duration of PARP inhibitor therapy are critical considerations in clinical practice. Debate continues regarding their optimal use, including whether they should be administered as maintenance therapy following first-line chemotherapy, in the setting of recurrent disease, or combination with other agents from the outset [3,24,60]. The development of cross-resistance between PARP inhibitors and platinum-based chemotherapy raises additional challenges in treatment sequencing and impacts long-term outcomes for patients [25,28,61].

Efforts to improve the therapeutic potential of PARP inhibitors have included developing next-generation agents with improved potency and tolerability profiles. Talazoparib, for example, is characterized by a superior PARP-trapping ability compared to earlier agents and has shown clinical promise in trials [26,62-64]. Moreover, optimizing dosing regimens, such as individualized starting doses based on body weight and platelet

count, is being explored to maximize efficacy while minimizing toxicity, as demonstrated in studies like the PRIMA trial [9,27,65].

The broader implications of PARP inhibitor resistance are not limited to ovarian cancer, as these agents are being explored across a range of malignancies, including breast, pancreatic, and prostate cancers, particularly in patients with BRCA or HRD mutations [28-30,66]. Insights gained from these diverse clinical contexts may offer translational opportunities to enhance the efficacy of PARP inhibitors across multiple tumor types. Preclinical research is uncovering novel mechanisms of resistance, such as ferroptosis a form of iron-dependent programmed cell death which may present new avenues for therapeutic intervention (**Figure 1; Figure 2**) [29,67-69].

This review aims to comprehensively analyze the molecular mechanisms underlying PARP inhibitor resistance in ovarian cancer, current and emerging strategies to overcome this resistance, and the evolving clinical landscape of PARP inhibitor use. By addressing critical knowledge gaps and highlighting future research directions, this review seeks to contribute to the ongoing effort to optimize PARP inhibitor therapy and improve outcomes for patients with ovarian cancer.

Methods

This comprehensive review was conducted to explore the role of Poly (ADP-ribose) polymerase (PARP) inhibitors in the treatment of ovarian neoplasms and to investigate the mechanisms underlying resistance to these agents. A systematic search was performed across multiple databases, including PubMed, Scopus, Embase, Web of Science, SciELO, and Google Scholar, to identify relevant literature from inception to the present. The search strategy utilized specific keywords related to the topic: "ovarian neoplasms," "Poly (ADP-ribose) polymerases," "drug resistance, neoplasm," "homologous recombination," "BRCA1 protein," and "maintenance chemotherapy." Boolean operators (AND, OR) were applied to refine and optimize the search results to capture a broad spectrum of studies focusing on therapeutic mechanisms, clinical efficacy, and resistance to PARP inhibitors. The review included a range of study designs, such as randomized controlled trials, cohort studies, case-control studies, cross-sectional analyses, case series, systematic reviews, meta-analyses, and preclinical studies that evaluated the application of PARP inhibitors in ovarian cancer treatment, including their mechanisms of action, clinical outcomes, and interactions with other therapeutic modalities. Studies were selected based on their relevance to the review's objectives, focusing on resistance mechanisms, clinical efficacy, and combination strategies with other treatments. Two independent reviewers screened titles and abstracts to identify eligible studies, ensuring the selection process was unbiased and comprehensive. Any conflicts or disagreements between reviewers were resolved through discussion or consultation with a third reviewer, maintaining a consistent approach. Reviewers were blinded to study details during selection to minimize potential biases. Data extraction was conducted using a standardized form, capturing essential study characteristics such as authorship, publication year, study design, population characteristics, interventions, and outcomes related to PARP inhibitor use and resistance in ovarian cancer. The review used a thematic analysis to synthesize the findings, grouping results into critical themes, including resistance mechanisms to PARP inhibitors, the role of homologous recombination, the impact of BRCA mutations, and strategies for maintenance chemotherapy. The synthesis aimed to provide an integrated understanding of the current knowledge, challenges, and future directions in the field, focusing on the clinical application and potential for overcoming drug resistance in ovarian cancer. The conclusions drawn reflect a critical evaluation of the available evidence, aiming to provide a comprehensive perspective on the role of PARP inhibitors in managing ovarian neoplasms.

Results and Discussion

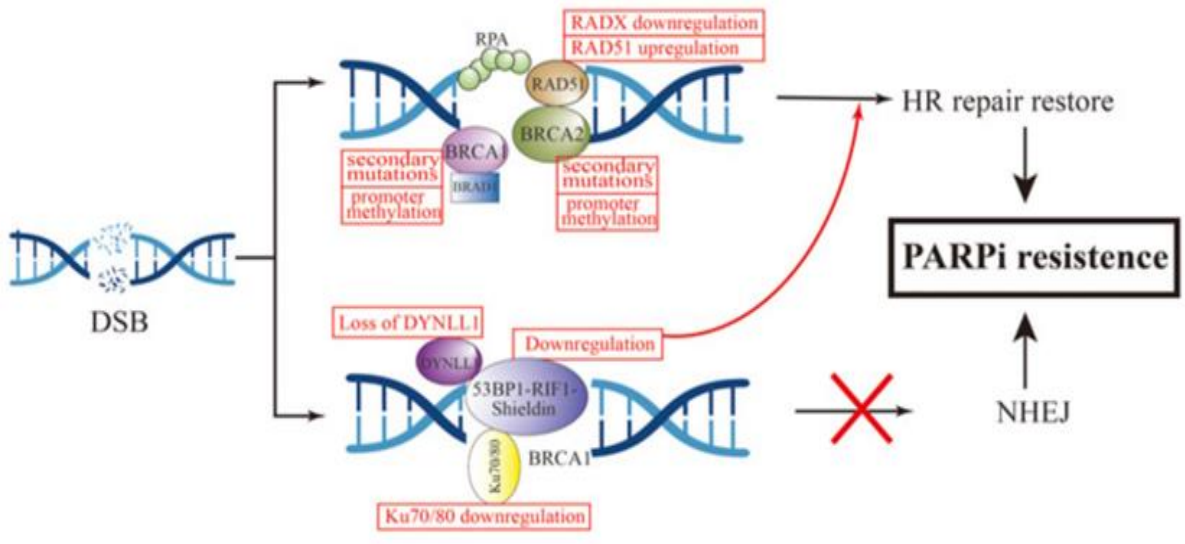

Figure 1: Mechanisms of resistance to PARP inhibitors (PARPi) in cells with double-strand breaks (DSBs). Alterations such as secondary mutations, promoter methylation, and the regulation of RAD51 and RADX restore homologous recombination (HR), leading to treatment resistance. Additionally, the loss of DYNLL1 and inhibition of key proteins in the non-homologous end joining (NHEJ) repair pathway, such as Ku70/80, favor repair through HR, resulting in resistance to PARP inhibitors.

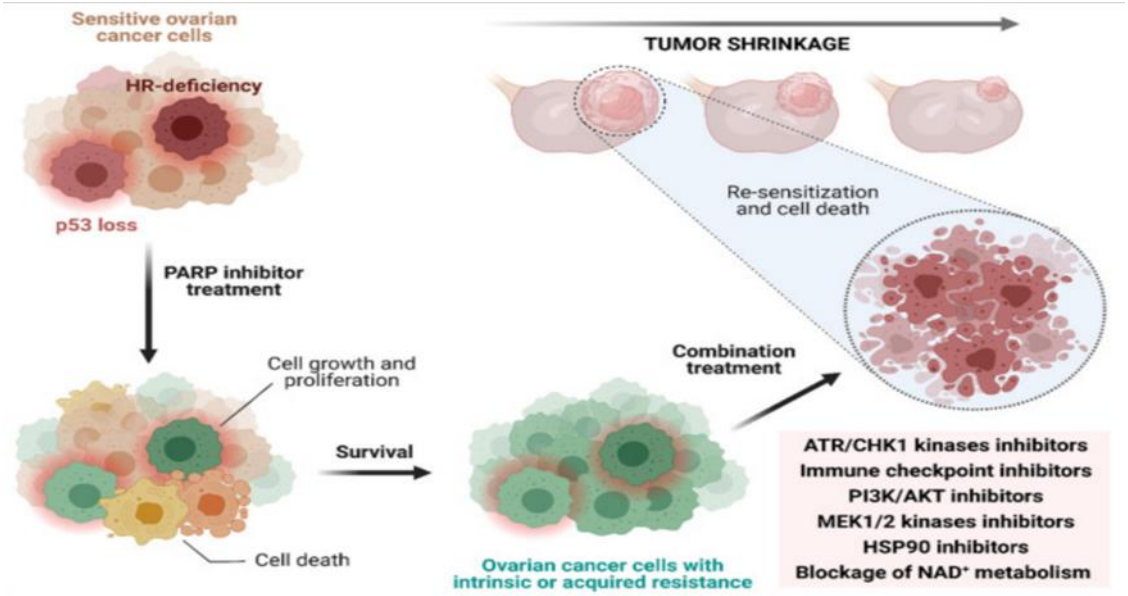

Figure 2: Process of resistance to PARP inhibitors in ovarian cancer cells and strategies to overcome this resistance. Initially, sensitive ovarian cancer cells with homologous recombination (HR) deficiency and p53 loss respond to PARP inhibitor treatment, leading to cell death in some cells while others survive and proliferate, developing resistance. These surviving cells, either with intrinsic or acquired resistance, continue to grow despite treatment. To combat this resistance, combination therapies are proposed, involving inhibitors of various pathways such as ATR/CHK1 kinases, PI3K/AKT, MEK1/2 kinases, immune checkpoints, HSP90, and NAD+ metabolism. These combination treatments aim to re-sensitize resistant cells, promoting further tumor shrinkage and enhancing cell death.
Source: https://www.sciencedirect.com/science/article/pii/S0304419X21001311

Poly (ADP-ribose) polymerase inhibitors (PARPi) have markedly transformed the therapeutic landscape of ovarian cancer, offering a targeted approach for patients harboring mutations in BRCA1/2 genes or demonstrating homologous recombination deficiency (HRD) [10,70-72].

The core mechanism of PARPi is based on synthetic lethality, wherein the inhibition of PARP, a key enzyme involved in DNA repair, results in the accumulation of DNA damage that HR-deficient cancer cells cannot repair. This leads to the accumulation of double-strand DNA breaks (DSBs), genomic instability, and ultimately, cancer cell death [35,73-75].

Despite the initial clinical success of PARPi in the treatment of ovarian cancer, resistance to these agents has emerged as a significant clinical challenge, limiting their long-term efficacy and profoundly affecting patient outcomes [17,76-78]. Understanding the multifaceted nature of PARPi resistance is critical to optimizing their use, developing strategies to counter resistance, and improving the selection of patients most likely to benefit from therapy [36,79-81].

Resistance to PARPi is a complex phenomenon driven by multiple mechanisms, including genetic mutations that restore HR function, activation of alternative DNA repair pathways, epigenetic alterations, and changes in the tumor microenvironment [37,82].

The most prominent mechanism of PARPi resistance is the restoration of HR. In ovarian cancer, the initial sensitivity to PARPi is often due to BRCA1/2 mutations, which result in an HR deficiency, rendering tumor cells particularly vulnerable to PARPi-induced DNA damage. However, secondary reversion mutations in BRCA1/2 can restore functional protein expression, effectively reversing the HR-deficient phenotype [14,38].

This restoration of HR enables efficient DSB repair, significantly reducing the sensitivity of tumor cells to PARPi and ultimately leading to diminished treatment efficacy [6,83]. The clinical impact of BRCA reversion mutations is substantial, as they are associated with shorter progression-free survival and poorer overall outcomes. Detecting these mutations early through techniques such as circulating tumor DNA (ctDNA) analysis is crucial, as it monitors emerging resistance and enables timely therapeutic adjustments [24,39,84].

Beyond genetic reversion, tumors may develop resistance to PARPi by activating alternative DNA repair pathways. When HR is compromised, tumor cells may upregulate non-homologous end joining (NHEJ), microhomology-mediated end joining (MMEJ), or the Fanconi anemia (FA) pathway to compensate for DNA damage [85]. NHEJ is an error-prone repair mechanism that can facilitate DSB repair without HR, contributing to resistance in HR-deficient tumors[8,40].

The FA pathway, which plays a role in the repair of interstrand crosslinks, has been implicated in PARPi resistance. The dynamic ability of tumor cells to switch between different DNA repair mechanisms underscores their adaptability to therapeutic pressure [86]. It emphasizes the need to target these pathways as part of a comprehensive approach to overcome resistance [37,41].

Epigenetic modifications, such as DNA methylation and histone acetylation, significantly influence PARPi resistance by affecting gene expression and chromatin structure. These modifications can regulate the expression of genes involved in DNA repair and modulate the accessibility of repair proteins to damaged DNA [20,42,87].

The loss of methylation in the BRCA1 promoter region can restore the expression of functional BRCA1 protein, thereby reestablishing HR activity and leading to resistance to PARPi [4,5,88]. The complexity of epigenetic regulation presents an opportunity for therapeutic intervention; agents such as histone deacetylase (HDAC) inhibitors and DNA methyltransferase (DNMT) inhibitors can alter the epigenetic landscape, potentially restoring PARPi sensitivity in resistant cells by modulating chromatin structure and gene expression [31,43,89].

The tumor microenvironment (TME) also plays a pivotal role in modulating the response to PARPi and the development of resistance. Factors within the TME, such as hypoxia, immune cell infiltration, and stromal interactions, can influence therapy response [90]. A notable contributor to PARPi resistance is the efflux of drugs

mediated by ATP-binding cassette (ABC) transporters, particularly ABCB1 (MDR1) [44,45].

These transporters reduce the intracellular concentration of PARPi, leading to decreased therapeutic efficacy. Furthermore, immune cells within the TME, such as tumor-associated macrophages and regulatory T cells, may establish an immunosuppressive milieu that impairs the effectiveness of PARPi and supports tumor cell survival [18,32]. Strategies to overcome this include targeting the TME, inhibiting drug efflux transporters, and modulating the immune response to enhance the efficacy of PARPi in resistant ovarian cancer [46,91].

The multifactorial nature of PARPi resistance has led to the development of combination therapies designed to enhance treatment efficacy and counteract resistance mechanisms [29,43]. Co-treatment with agents targeting pathways such as PI3K/AKT/mTOR, angiogenesis inhibitors, or immune checkpoint inhibitors has shown promise in preclinical models [2,92].

The combination of PARPi with PI3K inhibitors has demonstrated synthetic lethality, as this disrupts critical cellular survival pathways and amplifies DNA damage. Combining PARPi with anti-angiogenic agents like bevacizumab has improved outcomes in specific subgroups of ovarian cancer patients by affecting both the tumor vasculature and immune response [93-95]. Synthetic lethality, which involves inhibiting two complementary pathways to induce cell death, has been a guiding principle for developing combination strategies to overcome resistance [47,48].

Another promising approach is targeting key regulators of the DNA damage response. Co-inhibition of PARPi with agents such as ATR/CHK1 inhibitors enhances cytotoxicity by disrupting critical DNA repair and cell cycle checkpoints [96]. Similarly, inhibiting WEE1 kinase, which regulates the G2/M checkpoint, has been found to potentiate PARPi efficacy [26,49].

These approaches exploit the concept of synthetic lethality to maximize the cytotoxic effects of PARPi and prevent or delay the development of resistance, offering a roadmap for future therapeutic interventions and improving clinical outcomes [50,97].

Identifying predictive biomarkers is essential for optimizing the use of PARPi, improving patient stratification, and enhancing personalized therapy. Beyond BRCA1/2 mutations, other biomarkers are being evaluated to predict PARPi sensitivity, including HR deficiency scores, RAD51 foci formation, and gene expression profiles [15,44].

HRD is characterized by genomic instability and a specific mutational signature, which correlates with better responses to PARPi. Moreover, functional assays that directly assess HR repair competency, such as measuring RAD51 foci formation following DNA damage, offer real-time functional insights into HR status, providing a more precise stratification of patients likely to benefit from PARPi therapy compared to genetic tests alone [30,51].

Clinical trials exploring strategies to improve PARPi efficacy and overcome resistance are ongoing. These trials include evaluating next-generation PARPi agents with distinct pharmacokinetic properties, assessing combination regimens with targeted therapies or chemotherapy, and exploring sequential treatment approaches [8,23,52].

Developing new PARPi with improved ability to penetrate the tumor microenvironment and reduced susceptibility to drug efflux mechanisms holds promise for overcoming current treatment limitations. Furthermore, integrating molecular diagnostics to monitor real-time resistance mechanisms will be critical for adapting treatment approaches and improving patient outcomes [37,53].

Future research directions should also focus on the role of the TME in modulating the response to PARPi. The interactions between tumor cells, immune cells, and stromal components may significantly influence drug sensitivity and resistance, offering novel therapeutic targets [35,54].

Exploring non-BRCA mechanisms of HRD, such as alterations in other HR-related genes and replication stress pathways, will be crucial in broadening the application of PARPi beyond BRCA-mutant cancers [52]. The goal is to refine personalized treatment approaches informed by the molecular characterization of individual tumors, enabling the dynamic adaptation of therapeutic strategies based on real-time monitoring of resistance profiles [55].

Restoration of HRR and Reversion Mutations

The most significant contributor to PARPi resistance in ovarian cancer is the restoration of homologous recombination repair (HRR) through reversion mutations in BRCA1/2. These mutations, which restore the wild-type function of BRCA genes, negate the synthetic lethality exploited by PARP inhibitors [39,98].

Despite being a well-recognized mechanism, there is still a limited understanding of the prevalence and dynamics of reversion mutations across different patient populations. Recent studies have suggested that the frequency of BRCA1/2 reversion mutations may be higher than initially believed, especially in patients who have undergone multiple lines of therapy [36].

Liquid biopsy techniques, particularly the analysis of circulating tumor DNA (ctDNA), have emerged as potential tools for the early detection of reversion mutations, enabling real-time monitoring of treatment resistance. Incorporating ctDNA analysis into clinical practice could revolutionize how we track and manage resistance in ovarian cancer, although further validation in large clinical cohorts is required [99-101].

Alternative DNA Repair Pathways and PARPi Resistance

The reliance on alternative DNA repair mechanisms, such as non-homologous end joining (NHEJ) and microhomology-mediated end joining (MMEJ), has been increasingly recognized as a compensatory strategy employed by HRR-deficient tumors. In the context of PARPi resistance, these pathways can effectively "rescue" the cell by repairing DNA double-strand breaks without functional HRR [44,72].

However, these repair mechanisms are error-prone, leading to increased genomic instability, which may further drive tumor evolution and heterogeneity. Targeting these alternative pathways, particularly MMEJ, with small molecule inhibitors in combination with PARPi could provide a novel therapeutic strategy [19,28].

For instance, inhibitors of DNA ligase III, a key component of MMEJ, are currently under investigation for their potential to sensitize cancer cells to PARPi. Early preclinical data indicate that dual inhibition of PARP and MMEJ may enhance therapeutic efficacy, although this approach has yet to be tested in large-scale clinical trials [68,76].

Tumor Microenvironment (TME) and Its Role in Resistance

The role of the tumor microenvironment (TME) in PARPi resistance is a relatively underexplored area. Hypoxia within the TME can induce HRR activity even in HR-deficient cells, possibly explaining the observed resistance in some cases. Hypoxia-driven upregulation of hypoxia-inducible factor 1-alpha (HIF-1α) has been shown to promote DNA repair pathways, allowing tumors to evade the cytotoxic effects of PARPi [40,57].

The immunosuppressive nature of the TME, characterized by an influx of regulatory T cells and myeloid-derived suppressor cells, further complicates therapeutic responses. Integrating immune checkpoint inhibitors, such as anti-PD-1 or anti-PD-L1 antibodies, with PARPi has shown promise in preclinical models by enhancing

the immune response against HR-deficient tumors [34]. However, clinical data on the efficacy of this combination in ovarian cancer are still limited, and further studies are needed to determine the optimal timing and patient selection for this approach [23,102].

Ferroptosis as a Novel Therapeutic Target

Ferroptosis, a form of programmed cell death distinct from apoptosis, has recently gained attention as a potential mechanism for overcoming resistance to cancer therapies, including PARPi. Unlike apoptosis, ferroptosis is driven by iron-dependent lipid peroxidation, making it an attractive target in cancers with altered iron metabolism, such as ovarian cancer [57,70].

Preclinical studies have demonstrated that inducing ferroptosis can enhance the sensitivity of HR-deficient tumors to PARPi. Specifically, the combination of PARPi with ferroptosis inducers, such as erastin or RSL3, has shown synergistic effects in experimental models of ovarian cancer [18]. However, translating these findings into clinical practice remains in its early stages. Clinical trials investigating the safety and efficacy of ferroptosis inducers in combination with PARPi are needed to determine the therapeutic potential of this approach [39,103].

Immune Modulation and PARPi Efficacy

The interaction between the immune system and DNA damage response pathways is an emerging area of interest in cancer therapy. PARPi have been shown to increase tumor mutational burden (TMB), which can enhance the presentation of neoantigens and stimulate an immune response [44,96].

This provides a rationale for combining PARPi with immunotherapies, remarkably immune checkpoint inhibitors. Clinical trials combining PARPi with anti-PD-1/PD-L1 therapies are underway, with early results showing promising responses in patients with HR-deficient tumors [88,104].

However, the immunosuppressive effects of the TME, including the recruitment of regulatory T cells and myeloid-derived suppressor cells, may limit the efficacy of these combinations. Strategies to modulate the TME, such as using TGF-β inhibitors or myeloid cell-targeting therapies, could enhance the effectiveness of PARPi-immunotherapy combinations [14,56].

Biomarkers for Early Detection of Resistance

One of the significant challenges in managing PARPi resistance is the lack of reliable biomarkers for early detection. While BRCA1/2 mutations are established predictors of PARPi sensitivity, they are insufficient for predicting resistance. Emerging biomarkers, such as RAD51 foci formation and genomic scars indicative of HRR deficiency, promise to improve patient stratification [65,97].

Moreover, liquid biopsy technologies, particularly the analysis of ctDNA, have shown potential for real-time monitoring of tumor evolution and resistance development. Incorporating these biomarkers into clinical practice could allow more personalized treatment approaches and timely intervention to prevent resistance[26,68].

Combination Therapies Beyond PARPi

Although PARPi have transformed the treatment of HRR-deficient ovarian cancer, their long-term efficacy is limited by resistance. Combination therapies targeting multiple pathways involved in DNA repair and tumor survival are being explored to overcome this. ATR, CHK1/2, and WEE1 inhibitors, which regulate the DNA damage response, have shown synergistic effects when combined with PARPi in preclinical models [33,49].

Combining PARPi with antiangiogenic agents, such as bevacizumab, has demonstrated enhanced efficacy in clinical trials, although the mechanisms underlying this synergy are not fully understood. Expanding the use of combination therapies in clinical trials, particularly in earlier lines of treatment, could improve outcomes for patients with ovarian cancer [17,105].

Epigenetic Modulation and Resistance Reversal

Epigenetic changes, including DNA methylation and histone modifications, play a significant role in developing resistance to cancer therapies. PARPi resistance has been linked to the reactivation of HRR through epigenetic mechanisms [6,22]. Combining PARPi with epigenetic modulators, such as HDAC or DNMT inhibitors, has shown promise in reversing resistance and enhancing therapeutic efficacy. Preclinical studies have demonstrated that epigenetic modulation can re-sensitize HR-deficient tumors to PARPi, providing a rationale for further clinical investigation of these combinations [87,91].

Clinical Application of Liquid Biopsy in Resistance Monitoring

The implementation of liquid biopsy for the real-time monitoring of treatment resistance is an exciting development in the field of oncology. By analyzing ctDNA, clinicians can detect genetic changes that confer resistance to PARPi, such as BRCA1/2 reversion mutations or alterations in other DNA repair genes [63,90].

This non-invasive approach allows for the dynamic tracking of tumor evolution and the timely adjustment of treatment strategies. Several clinical trials are currently investigating liquid biopsy to guide PARPi therapy, and early results suggest that this approach could improve outcomes by enabling more personalized and adaptive treatment strategies [44,83].

Mechanisms of Resistance to PARPi

The primary mechanism of resistance to PARPi is the restoration of HRR function, often mediated by reversion mutations in BRCA1/2. These mutations enable the resumption of effective DNA repair, allowing cancer cells to evade PARP inhibition [27]. Although several studies have reported the occurrence of reversion mutations, their prevalence and impact on clinical outcomes remain underexplored.

Moreover, the molecular markers that could predict early reversion events are poorly defined, making it challenging to tailor treatment strategies for patients at higher risk of developing resistance [15].

Alternative DNA repair pathways, particularly NHEJ and MMEJ, have been implicated in resistance to PARPi. While NHEJ is a well-established pathway that repairs double-strand breaks, its role in PARPi resistance is context-dependent and varies across cancer subtypes. On the other hand, MMEJ, a more error-prone mechanism, has contributed to the survival of BRCA-deficient cells in the presence of PARPi. The interplay between these pathways and their relative contributions to resistance are areas that require further investigation [94,106].

Role of the Tumor Microenvironment in Resistance

TME significantly influences the response to PARPi. Hypoxia, which is a common feature of many solid tumors, can induce a hypoxia-inducible factor (HIF)-mediated suppression of DNA repair pathways, potentially promoting resistance [67].

Immune cell infiltration within the TME, particularly tumor-associated macrophages and T regulatory cells, can create an immunosuppressive milieu that reduces the efficacy of PARPi, especially when combined with immune checkpoint inhibitors. Strategies that modulate the TME, such as targeting HIF or reprogramming immune cells, could enhance the efficacy of PARPi in resistant tumors [30,78].

Ferroptosis, an iron-dependent form of cell death, has recently gained attention as a potential mechanism to overcome drug resistance. Although preclinical studies have shown that inducing

ferroptosis can sensitize tumor cells to PARPi, there is a lack of clinical evidence to support this approach. Further studies are needed to explore the viability of targeting ferroptosis with PARPi as a therapeutic strategy [2,33].

Emerging Biomarkers for Resistance Monitoring

While BRCA1/2 mutations remain the most commonly used biomarkers for predicting PARPi sensitivity, there is a growing interest in identifying additional biomarkers to predict resistance better [94].

One promising avenue is circulating tumor DNA (ctDNA) to monitor the emergence of resistance in real-time. ctDNA provides a non-invasive method to detect genetic alterations associated with resistance, such as BRCA reversion mutations, before they manifest clinically. However, the implementation of ctDNA in routine clinical practice is still limited by technical challenges and the need for standardization [86-88].

Moreover, RAD51 foci formation, which indicates functional HRR activity, has been proposed as a biomarker to predict PARPi resistance. Quantifying RAD51 foci in tumor biopsies could provide insights into the functional status of HRR and help stratify patients for alternative therapies. Despite the promise of these biomarkers, further validation in clinical trials is required to establish their utility in guiding treatment decisions [85,107].

Limitations of Current Therapeutic Strategies

Current therapeutic strategies focus heavily on BRCA1/2 mutations as the primary predictors of PARPi sensitivity. However, this approach overlooks the potential role of other DDR pathways and their interactions with PARPi [1-3]. For example, defects in mismatch repair (MMR) and base excision repair (BER) could also influence the response to PARPi, yet these pathways are rarely considered in clinical decision-making. Expanding the scope of biomarker testing to include other DDR pathways may improve patient selection and treatment outcomes [26,57].

The reliance on clinical trials that predominantly assess BRCA-mutated populations also limits the generalizability of findings to patients with non-BRCA-mutated tumors. More inclusive clinical trials that evaluate the efficacy of PARPi in patients with other genetic backgrounds are necessary to broaden the therapeutic scope of these inhibitors [43,94].

Combination of Therapies and Future Directions

While PARPi has demonstrated significant efficacy as monotherapy, combination therapies are emerging to overcome resistance and enhance treatment outcomes. Combining PARPi with DDR inhibitors, such as ATR or CHK1/2 inhibitors, has shown promise in preclinical studies, particularly in tumors with intact HRR pathways [28]. Additionally, combining PARPi with anti-angiogenic agents, such as bevacizumab, has demonstrated synergistic effects in reducing tumor growth and improving progression-free survival in clinical trials [73].

Another promising strategy is the use of immune checkpoint inhibitors in combination with PARPi. By targeting the immunosuppressive components of the TME, such as PD-1/PD-L1, this approach aims to enhance the immune response against tumor cells while simultaneously inhibiting DNA repair. Ongoing trials are evaluating the efficacy of these combinations, with early results suggesting improved outcomes in patients with platinum-resistant ovarian cancer [96,108].

Current Clinical Trials and Future Research Directions

Several clinical trials are underway to explore novel combination therapies and identify resistance biomarkers. For instance, trials combining PARPi with ATR or CHK1/2 inhibitors investigate these combinations' potential to overcome HRR-independent resistance mechanisms [57]. The endpoints of these trials typically include progression-free survival, overall survival, and the identification of predictive biomarkers, such as RAD51 foci or ctDNA alterations [24].

In addition to combination therapies, ongoing research is focused on understanding the role of epigenetic modifiers, such as HDAC and DNMT inhibitors, in reversing PARPi resistance [31]. These agents target the chromatin structure and gene expression patterns associated with HRR deficiency, potentially restoring sensitivity to PARPi. Early-phase trials are evaluating the safety and efficacy of these combinations in patients with recurrent ovarian cancer [95].

Another promising area of research is using CRISPR-based gene editing to identify novel targets for overcoming PARPi resistance. By systematically knocking out genes involved in DNA repair pathways, researchers aim to uncover new vulnerabilities in PARPi-resistant tumors. These findings could inform the development of next-generation DDR inhibitors that are more effective in targeting resistant cancer cells [48].

Clinical Relevance and Translational Impact

The identification of novel biomarkers and the development of combination therapies have the potential to transform the clinical management of ovarian cancer. By integrating real-time monitoring tools, such as ctDNA, into clinical practice, physicians can more accurately track the development of resistance and adjust treatment strategies accordingly. Personalized treatment approaches guided by biomarker profiling could improve outcomes for patients with heterogeneous tumors [39,80].

However, several challenges remain in translating these findings into clinical practice. The high cost and technical complexity of biomarker testing, particularly for ctDNA, limit its widespread adoption. Furthermore, the safety and efficacy of combination therapies must be rigorously tested in large-scale clinical trials before they can be integrated into standard care [64,106].

Future Directions and Clinical Implications

The future of PARPi therapy in ovarian cancer lies in overcoming the various mechanisms of resistance that have been identified. Ongoing clinical trials investigating combination therapies, biomarker-driven treatment strategies, and novel approaches such as ferroptosis induction and immune modulation hold promise for improving patient outcomes. As our understanding of the molecular and cellular mechanisms of PARPi resistance continues to evolve, new therapeutic strategies will likely emerge, offering hope for patients with HRR-deficient ovarian cancer who develop resistance to current treatments [107-109].

Conclusion

In conclusion, the use of PARPi has significantly advanced the treatment of ovarian cancer, offering targeted therapy for patients with HR-deficient tumors. However, the emergence of resistance, driven by complex genetic, epigenetic, and microenvironmental factors, remains a significant obstacle to the long-term efficacy of these agents.

Continued research is necessary to fully elucidate the mechanisms of resistance, develop predictive biomarkers, and design innovative combination therapies to overcome these challenges. A comprehensive approach that integrates molecular biology, genomics, and clinical data will be critical to enhancing the therapeutic potential of PARPi and improving outcomes for patients with ovarian cancer.

Personalized treatment strategies, informed by molecular diagnostics and tailored to individual tumor characteristics, will likely be vital in achieving long-term clinical benefits and overcoming the complexities of PARPi resistance.

Declarations

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Conflict of interest

The authors declare that there is no conflict of interest.

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