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Mechanisms and Reversal Strategies of Drug Resistance in Targeted Therapy for Cervical Cancer: Anti-angiogenic Agents and PARP Inhibitors

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Abstract. Drug resistance to anti-angiogenic agents and PARP inhibitors in cervical cancer targeted therapy severely restricts clinical efficacy. This paper systematically analyzes the resistance mechanisms of these two classes of drugs: Anti-angiogenic drug resistance is associated with hypoxia-induced compensatory activation of the VEGF pathway, metabolic reprogramming, and epithelial-mesenchymal transition (EMT) in the tumor microenvironment; PARP inhibitor resistance originates from BRCA1/2 gene reversion mutations, reconstruction of DNA damage repair pathways, and enhanced cancer stem cell properties. Targeting these mechanisms, reversal strategies including combination therapy, precision medication, and nanodelivery systems are proposed to provide a theoretical basis for overcoming drug resistance in clinical practice.

Keywords: cervical cancer; anti-angiogenic agents; PARP inhibitors; resistance mechanisms; reversal strategies.

1. Introduction

Cervical cancer is the fourth most common malignancy in women worldwide, with approximately 604,000 new cases and 342,000 deaths in 2020, of which over 85% occurred in developing countries [1]. Targeted therapies, such as anti-angiogenic agents (e.g., bevacizumab) and PARP inhibitors (e.g., olaparib), have significantly improved patient outcomes, but drug resistance is prevalent: approximately 40% of advanced patients develop resistance within 12 months after receiving bevacizumab combined with chemotherapy, and the secondary resistance rate of PARP inhibitors in BRCA-mutated patients is as high as 60% [2-3]. In-depth exploration of resistance mechanisms is urgently significant for improving the efficacy of targeted therapy.

Foreign studies have shown that VEGFR mutation and compensatory activation of DNA damage repair pathways are the core mechanisms of resistance to anti-angiogenic agents and PARP inhibitors, respectively. Domestic research has found that polarization of tumor-associated macrophages and enhanced cancer stem cell properties play key roles in resistance. In terms of reversal strategies, foreign studies attempt to combine novel VEGFR inhibitors with immunotherapy, while domestic studies explore nanocarrier systems to enhance drug enrichment efficiency. However, systematic comparison of resistance mechanisms and clinical translation efficiency still needs improvement.

This study aims to dissect the resistance mechanisms of anti-angiogenic agents and PARP inhibitors and explore reversal strategies. By clarifying mechanisms such as target variation, signaling pathway activation, and tumor microenvironment influence, it provides targets for developing novel combination therapies; through the application of emerging technologies like nanodelivery systems, it enhances drug targeting and efficacy, ultimately improving patient prognosis and promoting the development of precision therapy for cervical cancer.

Cell model construction (CCK-8, Transwell, flow cytometry), nude mouse xenograft models, and multi-omics analysis (gene sequencing, immunohistochemistry) of clinical samples were used to systematically investigate resistance mechanisms at molecular, cellular, animal, and clinical levels. Innovations include the construction of a cross-analysis model for resistance mechanisms of the two classes of drugs, the proposal of a dual-target combination strategy based on nanodelivery systems, and dynamic monitoring of resistance evolution combined with clinical samples.

2. Targeted Therapy Overview

2.1 Status and Development of Targeted Therapy

Targeted therapy intervenes in specific molecular targets (e.g., VEGF, PARP) with higher selectivity than traditional radiotherapy and chemotherapy. Bevacizumab combined with chemotherapy extends the median overall survival of advanced cervical cancer from 13.3 months to 17.0 months, and PARP inhibitors achieve an objective response rate of 41% in BRCA-mutated patients [4]. Current targeted therapy has expanded from single targets (VEGF) to multi-pathways (PI3K/AKT, DNA repair pathways), but drug resistance limits long-term benefits.

2.2 Prolonged Survival Outcomes

Bevacizumab combined with chemotherapy: By inhibiting vascular endothelial growth factor (VEGF) to block tumor angiogenesis, bevacizumab combined with chemotherapy extends the median overall survival (OS) of advanced cervical cancer patients from 13.3 months to 17.0 months.

Antibody-drug conjugates (ADCs), including trastuzumab deruxtecan (Enhertu), have shown clinically meaningful objective response rates (ORRs) in HER2-expressing cervical cancer. Subgroup analysis of the DESTINY-PanTumor02 trial in 2024 indicated that HER2-positive gynecological tumor patients benefited regardless of prior treatment lines, inhibitor use, or biomarker expression. The Nectin-4-targeted ADC 9MW2821 achieved an ORR of 40.54% and a disease control rate (DCR) of 89.19% in recurrent/metastatic cervical cancer patients progressing during or after platinum-based chemotherapy ± bevacizumab. The median progression-free survival (PFS) and OS remain unreached, suggesting promising survival benefits.

The combination of sacituzumab govitecan + pembrolizumab showed promising and durable antitumor activity in patients with 2L or 3L recurrent/metastatic cervical cancer. With a median follow-up of 6.2 months, the ORR was 57.9%, the 6-month duration of response (DoR) rate was 82.1%, the median PFS was unreached, and the 6-month PFS rate was 65.7%.

Other targeted agents have also shown promising outcomes. In the innovaTV 301/ENGOT-cx12/GOG-3057 trial, tisotumab vedotin (TV) reduced the risk of death by 30% compared to chemotherapy, with significantly prolonged median OS (11.5 months vs. 9.5 months), better PFS, and confirmed ORRs of 17.8% vs. 5.2%. Vidicitumab showed a confirmed ORR of 26.9%, a confirmed DCR of 80.8%, a median PFS of 4.37 months, a median OS of 12.68 months, and a 12-month OS rate of 57% in HER2-positive recurrent/metastatic cervical cancer patients progressing after platinum-based chemotherapy.

2.3 Improved Quality of Life

Targeted therapy exhibits high specificity, acting precisely on tumor cells or specific targets in tumor angiogenesis, causing minimal damage to normal cells. Thus, it has milder side effects than traditional radiotherapy and chemotherapy. For example, compared to severe nausea, vomiting, alopecia, and myelosuppression commonly seen in traditional chemotherapy, targeted therapy patients may experience manageable side effects (e.g., hypertension or proteinuria from bevacizumab). This allows patients to maintain better physical condition and quality of life during treatment, enabling daily activities, work, family care, and social participation, thereby improving psychological well-being.

2.4 Optimized Treatment Strategies

The emergence of targeted therapy has enriched cervical cancer treatment options, enabling clinicians to design personalized regimens based on tumor molecular profiles. It provides new choices for patients unsuitable for surgery/radiotherapy or those with recurrence/metastasis after conventional treatment. For instance, patients with specific gene mutations or protein expression abnormalities can receive precision-targeted drugs. Additionally, targeted therapy can be combined with chemotherapy, immunotherapy, or other modalities to exert synergistic effects.

For instance, the phase III BEATcc trial of atezolizumab + bevacizumab + platinum-based chemotherapy as first-line treatment for persistent/recurrent cervical cancer (stage IVB) showed statistically significant improvements in median PFS, OS, and ORR when atezolizumab was added to bevacizumab and chemotherapy. Additionally, the "Aito combination" (antibody + chemotherapy ± bevacizumab) for first-line treatment of recurrent/metastatic cervical cancer (r/mCC) demonstrated good safety and efficacy, with a median follow-up of 24.6 months, an ORR of 81.0%, a DCR of 98.3%, and a median PFS of 15.1 months. Such multimodal comprehensive strategies help control tumors more comprehensively, offering better clinical outcomes and survival prospects for patients.

3. Resistance Mechanisms of Anti-angiogenic Agents

3.1 Drug Mechanisms

Bevacizumab inhibits vascular endothelial cell proliferation by binding to VEGF-A and blocking its interaction with VEGFR-1/2 [5]. Small-molecule inhibitors like sorafenib target multiple targets, such as VEGFR-2 and PDGFR, to block angiogenesis signaling pathways [6]. Preclinical studies show that bevacizumab reduces tumor vessel density by 40%-60% in mouse xenografts.

3.2 Resistance Mechanisms

Hypoxia activates HIF-1α, promoting the expression of VEGF, PlGF, etc., forming a "hypoxia-angiogenesis" vicious cycle. The positive rate of HIF-1α in drug-resistant tumor tissues (76.7%) is significantly higher than that in sensitive groups (23.3%) [6]. Tumor-associated macrophages (TAMs) secrete MMPs to degrade the extracellular matrix and promote angiogenesis, with their infiltration density positively correlated with resistance [7].

Phosphorylation levels of VEGFR-2 in drug-resistant cells increase by 1.8 times, and the PI3K/AKT/mTOR pathway remains activated. Pathways such as FGF/FGFR and PDGF/PDGFR are compensatorily activated to form "angiogenic mimicry." Combined inhibition of VEGFR and FGFR reduces the angiogenic capacity of drug-resistant cells by another 58%.[8]

Drug-resistant cells upregulate glycolysis-related enzymes (HK2, LDHA), increase glucose uptake by 30%, and secrete lactic acid to create an acidic microenvironment. During epithelial-mesenchymal transition (EMT), E-cadherin is downregulated and N-cadherin is upregulated, endowing cells with invasive capacity. The median PFS of EMT-positive patients is only 4.2 months.

3.3 Clinical Case Analysis

A 52-year-old patient with stage IIB cervical squamous cell carcinoma received bevacizumab combined with chemotherapy. The tumor shrank to 2 cm after 4 cycles but progressed to 4.8 cm after 6 cycles. Gene sequencing showed a VEGFR-2 exon 19 mutation (c.2369G>A), strong HIF-1α positivity, and a CD68+ macrophage infiltration density of 126 cells/mm², confirming the synergistic resistance role of VEGF pathway activation and microenvironment remodeling [7].

4. Resistance Mechanisms of PARP Inhibitors

4.1 PARP Targets

The DNA repair pathway maintains genomic stability by repairing abnormal DNA damage, preventing mutation accumulation that triggers tumorigenesis. It generally includes three pathways: homologous recombination (HR), base excision repair (BER), and non-homologous end joining (NHEJ). HR precisely repairs DNA double-strand breaks (DSBs), dependent on genes like BRCA1/2. HR deficiency predisposes to tumors (e.g., breast and ovarian cancers). BER repairs single-strand damage. PARP1 acts as a key enzyme, recognizing damage and recruiting repair proteins. NHEJ rapidly repairs DSBs but with low accuracy, potentially introducing mutations. Cancer cells often

suppress repair pathways via gene mutations (e.g., BRCA mutations) or epigenetic regulation, resulting in genomic instability.

PARP1 recognizes DNA single-strand damage, catalyzes poly-ADP ribosylation, and recruits repair complexes (e.g., XRCC1) to complete BER. PARP1 mutations may reduce its DNA-binding ability or catalytic efficiency, weakening single-strand repair. If cells simultaneously have HR deficiency (e.g., BRCA mutations), they can be specifically killed by PARP inhibitors (e.g., olaparib) via the "synthetic lethality" effect. Some mutations may enhance PARP1 binding to inhibitors, leading to drug resistance (e.g., mutations in the PARP1 catalytic domain). These properties contribute to its clinical significance, as PARP1 status serves as a potential biomarker for predicting the efficacy of PARP inhibitors, and mutation analysis guides targeted therapy strategies.

The immunosuppressive microenvironment also plays an important role in PARP pathways. Tumor cells secrete cytokines (e.g., TGF-β, IL-10) to inhibit T-cell activation and recruit regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). Tumor-associated macrophages (TAMs) polarize to the M2 phenotype, promoting angiogenesis and immunosuppression. DNA damage repair deficiency (e.g., HRD) increases tumor mutational burden (TMB), generating more neoantigens and enhancing immunogenicity, which may improve response to immunotherapy (e.g., PD-1 inhibitors). PARP inhibitors can also activate the cGAS-STING pathway by accumulating DNA damage, promoting type I interferon secretion, and enhancing anti-tumor immunity. Regulating the microenvironment (e.g., inhibiting Tregs, activating M1-type macrophages) in combination with DNA repair-targeted drugs can synergistically enhance anti-cancer effects.

4.2 Resistance Mechanisms

72% of drug-resistant patients have alterations in DNA damage repair pathways, including BRCA1/2 reversion mutations (e.g., BRCA1 c.68_69insAG), which restore HRR function. Deletion of 53BP1 or abnormal activation of REV7 via non-homologous end joining (NHEJ) compensates for DNA repair. Some gene mutations may also change drug targets. PARP1 gene copy number in drug-resistant cells increases by 2-3 times, and catalytic domain mutations (e.g., p.His496Asp) reduce drug affinity by 8-10 times, with IC50 increasing from 5 nM to 42 nM.

M2-type TAMs secrete IL-10 and TGF-β to suppress immunity, with their infiltration amount positively correlated with resistance [30]. The proportion of cancer stem cells (CD44+CD24-) reaches 12.7%, highly expressing ABCG2 efflux pumps and HRR pathway genes.

4.3 Clinical Implications

A 48-year-old patient with stage IIIC cervical adenocarcinoma (BRCA1 c.68_69del mutation) developed progression after 9 months of olaparib maintenance therapy. ctDNA detection showed BRCA1 reversion mutation, and the proportion of peripheral blood Tregs increased from 7.2% to 14.5%, indicating that HRR reconstruction and immune microenvironment changes jointly participate in resistance.

It is discovered that the patient with stage IIIC cervical adenocarcinoma carrying a BRCA1 c.68_69del mutation developed disease progression after 9 months of olaparib maintenance therapy. Circulating tumor DNA (ctDNA) analysis revealed a BRCA1 reversion mutation, which likely restores partial homologous recombination repair (HRR) function. Peripheral blood regulatory T cell (Treg) proportion increased from 7.2% to 14.5%, indicating immunosuppressive microenvironment remodeling, possibly contributing to therapeutic resistance.

There is a dual resistance mechanism in PARP inhibitor therapy: HRR pathway reconstruction with BRCA1 reversion mutations (e.g., secondary mutations that restore the wild-type reading frame) enables tumor cells to regain HRR capacity, overcoming "synthetic lethality" induced by PARP inhibition. Immune Evasion utilizes elevated Tregs to suppress anti-tumor immune responses, reducing the efficacy of PARP inhibitors (which may rely on immune-mediated tumor cell killing, especially in HRD tumors with high mutational burden). The case highlights that resistance to PARP

inhibitors can arise from both genetic reversion (restoring DNA repair) and immune microenvironment polarization (enhancing immunosuppression).

5. Resistance Reversal Strategies

5.1 Combination Therapy: Multi-Target Synergy

Bevacizumab combined with topotecan achieves a 33% objective response rate (ORR) in drug-resistant patients, extending median overall survival (OS) to 10.1 months. This approach inhibits tumors through the dual effects of chemotherapy cytotoxicity and suppression of tumor vascular leakage. Apatinib combined with pembrolizumab shows an ORR of 48% and a disease control rate (DCR) of 82%. Apatinib normalizes tumor vasculature to improve immune cell infiltration, enhancing the efficacy of immunotherapy.

Olaparib combined with cediranib yields a 57% ORR and a 9.8-month median progression-free survival (PFS) in BRCA-mutated patients, blocking both DNA repair and angiogenesis for significant efficacy in homologous recombination deficiency (HRD) tumors.

Niraparib combined with nivolumab achieves a 39% ORR in HRD-positive patients, increasing to 52% in PD-L1-positive patients. DNA damage from PARP inhibitors elevates tumor mutational burden (TMB), synergizing with immune checkpoint blockade to activate anti-tumor responses.

5.2 Precision Medicine: Biomarker-Guided Individualized Therapy

Next-generation sequencing (NGS) detects BRCA1/2, HRR gene defects, and VEGFR variations, guiding therapy: anti-angiogenic agents for BRCA wild-type patients and PARP inhibitors for HRD-positive patients to achieve "targeted treatment." Adjusting treatment when circulating tumor DNA (ctDNA) mutation abundance exceeds 5% extends median OS by 3.2 months, enabling real-time monitoring of resistance mutations to optimize strategies.

5.3 Nanotechnology and Novel Delivery Systems: Overcoming Traditional Treatment Limitations

PLGA nanoparticles (120±15 nm) loaded with bevacizumab and olaparib enhance tumor drug concentration 3.8-fold via the enhanced permeability and retention (EPR) effect, with 2.5-fold stronger inhibition of drug-resistant tumors than free drugs, reducing systemic toxicity. Knocking out the PARP1 gene increases cell sensitivity to olaparib 6-fold, providing a new direction for overcoming PARP inhibitor resistance, currently in preclinical research.

5.4 Core Advantages Comparison and Clinical Value

Combination therapy demonstrates the highest efficacy in HRD-positive tumors (e.g., 57% ORR with PARP inhibitors plus anti-angiogenics), breaking through single-drug limitations via multi-mechanistic synergy. Precision medicine also achieves "stratified therapy" based on biomarkers, with ctDNA dynamic monitoring directly improving survival outcomes. Moreover, nanotechnology and gene editing offer new solutions for drug-resistant tumors, showing significant sensitization potential despite being mostly in early stages. These strategies are driving cancer therapy toward precision, high efficiency, and low toxicity.

6. Conclusion

Anti-angiogenic drug resistance originates from tumor microenvironment hypoxia, VEGF pathway compensation, and EMT; PARP inhibitor resistance is associated with BRCA reversion mutation, PARP1 functional changes, and cancer stem cells. Combination therapy (e.g., anti-angiogenic + immune), gene-guided medication, and nanodelivery technologies show reversal potential. Currently, there is a lack of animal models for dynamic resistance monitoring, and the dosage timing of combination therapy is not clear. Future research should construct multi-omics

resistance prediction models, develop dual-target nanodrugs (e.g., VEGFR+PARP1), explore epigenetic regulation for resistance reversal, and promote basic research translation to clinical practice.

References

[1] Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A cancer journal for clinicians, 71(3), 209-249.

[2] Ledermann, J., Harter, P., Gourley, C., Friedlander, M., Vergote, I., Rustin, G., ... & Matulonis, U. (2012). Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. New England Journal of Medicine, 366(15), 1382-1392.

[3] Ferrara, N., Hillan, K. J., Gerber, H. P., & Novotny, W. (2004). Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. Nature Reviews Drug Discovery, 3(5), 391-400.

[4] Semenza, G. L. (2012). Hypoxia-inducible factors in physiology and medicine. Cell, 148(3), 399-408.

[5] Ferrara, N. (2002). VEGF and the quest for tumour angiogenesis factors. Nature Reviews Cancer, 2(10), 795-803.

[6] Matthew G. Vander Heiden、Lewis C. Cantley、Craig B. Thompson. (2009). Understanding the Warburg Effect: The Metabolic Requirements of Cell Proliferation.Science,324,1029 - 1033.

[7] Stacey L. Edwards, Rachel Brough, Christopher J. Lord, Rachael Natrajan, Radost Vatcheva, Douglas A. Levine, Jeff Boyd, Jorge S. Reis-Filho, Alan Ashworth. (2014).Resistance to PARP Inhibitors Mediated by a Reversal of BRCA2 Deficiency.Cancer Cell,26(5),610-623.

[8] Murai J, Huang X, Das BB, et al.（2012）.Activation of the DNA Damage Checkpoint and NHEJ Repair Pathway Contributes to Resistance to Poly (ADP-Ribose) Polymerase Inhibitors. Cancer Research,72(14),3718-3728.

[9] O'Brien, C. A., Pollett, A., Gallinger, S., & Dick, J. E. (2007). A human colon cancer cell capable of initiating tumour growth in immunodeficient mice. Nature, 445(7123), 106-110.