Postprint: Advances in Pharmacotherapy for Recurrent or Metastatic Cervical Cancer

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Date: 2025-07-21T00:00:00+00:00

Abstract

Cervical cancer ranks first in incidence among the three major gynecological malignant tumors, with its incidence and mortality rates ranking fourth among female malignant tumors and continuing to rise. Early-stage cervical cancer is primarily treated with surgery, mid-to-late stage with concurrent chemoradiotherapy, and recurrent or metastatic disease with systemic therapy. Patients with recurrent or metastatic cervical cancer have low survival rates, poor prognosis, and limited treatment options. The drug therapy for recurrent or metastatic cervical cancer has evolved through stages including cisplatin monotherapy, platinum-based doublet chemotherapy, targeted therapy represented by bevacizumab, immunotherapy, and antibody-drug conjugates. Although relatively systematic treatment selection criteria have been established, therapeutic drugs have been continuously developed iteratively in recent years, clinical trial results are constantly updated, and combination therapy regimens involving drugs with different mechanisms of action are under active investigation. Therefore, it is necessary to summarize the advances in drug therapy for recurrent or metastatic cervical cancer for clinicians to understand, thereby providing more treatment options for patients.

Full Text

Preamble

Advances in Pharmacological Treatment of Recurrent or Metastatic Cervical Cancer

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Abstract: Cervical cancer has the highest incidence among the three major gynecological malignancies and ranks fourth in both incidence and mortality among female cancers, with its incidence continuing to rise. Early-stage cervical cancer is primarily treated with surgery, while concurrent chemoradiotherapy is the main treatment for advanced stages. For recurrent or metastatic cervical cancer, systemic treatment is the primary approach. The survival rate of patients with recurrent or metastatic cervical cancer is low, prognosis is poor, and treatment options are limited. The pharmacological treatment of recurrent or metastatic cervical cancer has evolved through several stages, including cisplatin monotherapy, platinum-based doublet chemotherapy, targeted therapy represented by bevacizumab, immunotherapy, and antibody-drug conjugates. While a relatively systematic treatment guideline has been established, recent advancements in drug development, the continuous updating of clinical trial results, and the exploration of combination therapies with different mechanisms of action underscore the need for an updated summary of the progress in pharmacological treatments for recurrent or metastatic cervical cancer to help clinicians expand therapeutic options for patients.

Key words: Uterine cervical neoplasms; Recurrent or metastatic cervical cancer; Chemotherapy; Targeted therapy; Immunotherapy; Antibody-drug conjugates

Cervical cancer (CC) is the fourth most common cancer among women worldwide. According to the latest GLOBOCAN data, an estimated 661,021 new CC cases and 348,189 deaths occurred globally in 2022. In developing countries, CC ranks second in both incidence and mortality among female cancers, posing a significant threat to women' s health. The 5-year overall survival (OS) rates for early-stage, locally advanced, and metastatic CC are approximately 92%, 65%, and 17%, respectively, with recurrent patients having an estimated median OS (mOS) of less than one year, indicating poor prognosis and limited treatment options. The primary treatment modalities for CC are surgery or definitive radiotherapy; however, most patients with recurrent disease are not amenable to these treatments or respond poorly, making pharmacological therapy a common treatment approach. In recent years, drug development for CC has progressed rapidly, particularly with the emergence of novel targeted and immunotherapeutic agents, necessitating a comprehensive review of advances in pharmacological treatments for recurrent or metastatic (R/M) CC to inform clinical practice.

1 Literature Search Strategy

A computerized search was conducted across multiple databases including CNKI, Wanfang Data, PubMed, Web of Science, and the Cochrane Library, as well as conference abstracts from ASCO and SGO, and government announcements. The search timeframe spanned from database inception to December 2024. Chi-

nese search terms included "recurrent or metastatic cervical cancer," "pharmacological treatment," "chemotherapy," "targeted therapy," "immunotherapy," and "antibody-drug conjugates." English search terms included "Recurrent or metastatic cervical cancer," "Pharmacological treatment," "chemotherapy," "Targeted therapy," "Immunotherapy," and "Antibody-drug conjugates." Additionally, specific clinical trial names and drug names mentioned in the articles were searched. Inclusion criteria comprised studies and clinical trials related to pharmacological treatment of R/M CC. Exclusion criteria included articles not relevant to the topic or those without available full text. A total of 49 articles were ultimately included.

2 Chemotherapy

Since the publication of results from the phase II clinical trial GOG-26 by the Gynecologic Oncology Group (GOG), cisplatin monotherapy at 50 mg/m^2 every three weeks has been considered the standard chemotherapy regimen for CC, with an objective response rate (ORR) and median OS (mOS) of 38% and 9 months, respectively. Building upon single-agent studies, GOG investigated several combination chemotherapy regimens, comparing ifosfamide plus cisplatin (GOG-110), paclitaxel plus cisplatin (TP, GOG-169), and topotecan plus cisplatin (GOG-179) against established cisplatin monotherapy. Based on these results, particularly from GOG-204, the TP regimen emerged as superior. Subsequently, the Japan Clinical Oncology Group (JCOG) evaluated the paclitaxel plus carboplatin (TC) regimen in the JCOG-0505 study, which demonstrated non-inferiority to the TP regimen in terms of progression-free survival (PFS) and OS, with significantly reduced toxicity. However, post-hoc analysis revealed that the TP regimen offered advantages in the subgroup of patients who had not previously received cisplatin. Consequently, both TP and TC regimens are considered first-line chemotherapy options for R/M CC.

3 Targeted Therapy

Current understanding suggests that solid tumor growth depends on two cell populations: tumor cells and tumor vascular endothelial cells. Inhibiting the growth of either population exerts anti-tumor effects. The former is primarily targeted by cytotoxic chemotherapy, while the latter represents the newly developed anti-angiogenic therapies. Platinum-based chemotherapy demonstrates some efficacy in R/M CC, but the duration of effective response is short, with mOS of approximately one year, prompting increased focus on developing angiogenesis inhibitors. Vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF) are overexpressed in various tumors including CC and represent major drug targets. VEGF receptors (VEGFR) and EGF receptors (EGFR) are predominantly expressed on vascular endothelial cells and tumor cells, respectively. Both belong to the receptor tyrosine kinase family and mediate signaling through common downstream pathways (Ras/Raf/MAPK and PI3K/Akt/mTOR), promoting tumor angiogenesis, cell proliferation, growth,

metastasis, and adhesion. Therefore, angiogenesis inhibitors mainly comprise two categories: monoclonal antibodies (MoAbs) that bind extracellularly to prevent ligand binding, and small-molecule tyrosine kinase inhibitors (TKIs) that bind intracellularly to the tyrosine kinase domain.

3.1 Monoclonal Antibodies (MoAb)

Bevacizumab, a humanized MoAb targeting VEGF, is the most extensively studied and widely used anti-angiogenic agent in CC patients. The GOG-227C trial evaluated bevacizumab monotherapy in 46 patients with previously treated R/M CC, reporting PFS and OS of 3.4 months and 7.3 months, respectively, demonstrating notable efficacy. Although the study observed a high incidence of adverse events with bevacizumab, quality of life was not significantly impacted. Consequently, the FDA approved bevacizumab for persistent/R/M CC treatment. Notably, due to its anti-angiogenic properties, bevacizumab is contraindicated in patients with uncontrolled severe hypertension, bleeding tendencies, history of thromboembolism, high risk of gastrointestinal perforation, or severe proteinuria (e.g., nephrotic syndrome). In contrast, the anti-EGFR MoAb cetuximab showed no significant clinical benefit in phase II studies for R/M CC.

3.2 Tyrosine Kinase Inhibitors (TKI)

The receptor tyrosine kinase family is extensive. Beyond EGFR and VEGFR, other anti-angiogenic targets include fibroblast growth factor receptors (FGFR) and platelet-derived growth factor receptors (PDGFR). These family members often share sequence homology, making TKIs generally multi-target inhibitors. Previous studies of TKIs in R/M CC, including pazopanib, cediranib, lapatinib, and nintedanib, have shown limited activity and may increase adverse event rates. Recently, the phase II SUMMIT trial evaluated neratinib in 16 patients with HER2-mutated R/M CC, demonstrating an ORR of 25%, mPFS of 7.0 months, and mOS of 16.8 months, showing promising efficacy. GOG-227G is investigating the activity of brivanib, a dual VEGFR2/β-FGFR inhibitor, in CC patients who have received at least one prior chemotherapy regimen.

4 Immunotherapy

Human papillomavirus (HPV) infection is the primary etiological factor for CC. Viral antigens produced by HPV infection activate the immune system; however, in the setting of immunodeficiency or long-term persistent high-risk HPV infection, a minority of patients develop immune tolerance leading to CC. CC exhibits characteristics of an "immunologically hot" tumor, providing a foundation for immunotherapy. The advent of immune checkpoint inhibitors (ICIs) represents a major breakthrough in CC immunotherapy.

4.1 ICIs

ICIs are antibodies targeting immune checkpoint molecules that enhance the anti-tumor activity of immune cells. PD-(L)1 and CTLA-4 are the most established targets in cancer immunotherapy. PD-(L)1 inhibitors block the binding of PD-L1 on tumor cells to PD-1 on T cells, releasing the immune "brake" and reactivating T cell recognition and killing of tumors. CTLA-4 inhibitors block the binding of CTLA-4 on T cells to B7 molecules on antigen-presenting cells, enabling efficient B7 binding to CD28 on T cells to activate and promote rapid T cell proliferation, serving as an "ignition" signal. Persistent HPV infection upregulates PD-1 and PD-L1 expression in cervical cells and infiltrating immune cells. Up to 84.7% of CC patients are PD-L1-positive, with even higher PD-L1 expression in tumor tissues of patients with advanced metastatic CC, suggesting that CC patients may be potential beneficiaries of PD-(L)1 inhibitors.

Pembrolizumab, a PD-L1 inhibitor, was the first ICI approved for CC, transforming clinical practice. Two key studies of pembrolizumab monotherapy in advanced CC, KEYNOTE-028 and KEYNOTE-158, achieved ORRs of 13.3%-17% with acceptable safety. However, the latter study found no responses in PD-L1-negative patients. Based on these results, the FDA approved pembrolizumab for R/M CC patients with disease progression during or after chemotherapy, limited to PD-L1-positive patients (CPS $\geq$ 1). Table 1 lists other ICIs that have been validated through clinical trials and are recommended for clinical use. Recently, the anti-PD-L1 monoclonal antibodies socazolimab and enlonstobart, as well as the anti-PD-1 and anti-CTLA-4 bifunctional combination antibody iparomlimab and tuvonralimab (Qibeian), have been sequentially approved by the NMPA for second-line and beyond R/M CC.

4.2 Immune Combination Chemotherapy $\pm$ Targeted Drugs

For patients with R/M CC, system treatment primarily based on chemotherapy yields suboptimal results, with half of patients relapsing within six months after first-line treatment. Both targeted agents and single-agent ICIs provide limited efficacy benefits. The combination of immunotherapy with chemotherapy $\pm$ targeted agents has achieved new breakthroughs in first-line treatment for R/M CC. The phase III GOG-240 study explored the combination of standard chemotherapy with targeted therapy, with final analysis showing that adding bevacizumab to chemotherapy improved mOS compared to chemotherapy alone (16.8 vs. 13.3 months, HR=0.77, 95%CI=0.62-0.95, P=0.0068), representing an approximately 4-month increase in mOS and the first time a biologic agent improved OS in gynecologic cancers. The NCCN guidelines recommend bevacizumab combined with chemotherapy (TC/TP) as a preferred first-line regimen for R/M CC.

In December 2023, the final overall survival results from the KEYNOTE-826 study were published, demonstrating that adding pembrolizumab to chemotherapy $\pm$ bevacizumab significantly improved ORR, PFS, and OS in R/M CC

patients, reducing the risk of death with manageable safety. The ORR in the overall population reached 65.9%, reducing death risk by 37% in the overall population, 40% in the PD-L1 CPS $\geq$ 1 subgroup, and 42% in the PD-L1 CPS $\geq$ 10 subgroup. The NCCN guidelines recommend pembrolizumab + TP/TC chemotherapy $\pm$ bevacizumab as the preferred first-line treatment for PD-L1-positive R/M CC patients. Subsequently, the BEATcc study, which used atezolizumab combined with chemotherapy + bevacizumab as first-line treatment for R/M CC patients, confirmed that immune combination chemotherapy + bevacizumab improves survival. However, since all patients in this trial received bevacizumab, the benefit for patients unsuitable for bevacizumab remains unclear. The COMPASSION-16/AK104-303 study, the only phase III CC first-line clinical trial enrolling an all-Chinese population, demonstrated that cadonilimab + chemotherapy $\pm$ bevacizumab provided further improvements over the current standard therapy (pembrolizumab + chemotherapy $\pm$ bevacizumab), independent of bevacizumab combination and PD-L1 expression status.

4.3 Targeted-Immune Combination

Due to mechanisms such as immunosuppression in the tumor microenvironment and resistance mutations during treatment, drug resistance to immunotherapy has become a key factor affecting clinical efficacy. Research indicates that anti-angiogenic agents can enhance ICI efficacy by improving antigen presentation, activating cytotoxic CD8 T cells, and promoting lymphocyte infiltration into tumors. The treatment modality of targeted therapy + immunotherapy without chemotherapy is being actively explored.

The ALTER-GO-020 study investigated the feasibility of penpulimab + anlotinib as first-line treatment for R/M CC. As of December 2023, 17 patients were enrolled and 10 were evaluable for efficacy, showing an ORR of 58.8% (95%CI=32.9%-81.6%), DCR of 88.2% (95%CI=63.6%-98.5%), mPFS of 11.0 months (95%CI=5.4-16.7 months), and mOS not reached. All 17 patients experienced treatment-related adverse events (TRAEs), with 8 (47.1%) being grade $\geq$ 3. Although preliminary results show a high ORR, the small sample size limits the conclusions. A multicohort phase II study (NCT03827837) found that camrelizumab combined with famitinib demonstrated durable anti-tumor activity and manageable safety in the R/M CC cohort. Based on these results, the phase II clinical study SHR-1210-II-217 compared camrelizumab + famitinib, camrelizumab monotherapy, and chemotherapy alone. As of September 25, 2023, the three arms showed ORRs of 42.9%, 22.2%, and 14.3%, and mOS of 20.6, 14.9, and 13.9 months, respectively, with clear benefits from the targeted-immune combination, particularly in patients with cervical squamous cell carcinoma or PD-L1-positive disease. The phase III clinical study SHR-1210-III-329 for this regimen is ongoing.

4.4 Other Immunotherapies

Beyond ICIs, other immunotherapies have been explored, including therapeutic cancer vaccines and adoptive cell transfer therapy (ADCT). ADCT mainly includes CAR-T, TCR-T, and TIL therapies. Since CC is an HPV-related disease, various therapeutic cancer vaccines targeting HPV have been developed and tested in clinical trials, including the synthetic long peptide vaccine ISA101 targeting HPV16 E6 and E7 oncoproteins, the DNA vaccine GX-188, and the attenuated Listeria monocytogenes vaccine ADXS11-001 targeting HPV-16 E7 oncoprotein. However, these have shown limited benefit for R/M CC patients. Among ADCT approaches, TIL therapy appears promising for CC patients. TIL therapy involves isolating tumor-infiltrating lymphocytes from tumor tissue, expanding them ex vivo, and reinfusing them to exert anti-tumor activity. LN145 and GT101 are currently promising TIL therapies for R/M CC treatment.

Currently, the DUBHE-C-204 study (iparomlimab and tuvonralimab + TC/TP ± bevacizumab) and the VICT-004 study (zimberelimab + platinum-based chemotherapy ± bevacizumab) are ongoing, with expectations of providing more suitable and cost-effective new treatment options for Chinese R/M CC patients.

5 Antibody-Drug Conjugates (ADC)

ADCs consist of monoclonal antibodies targeting specific antigens linked to small-molecule cytotoxic drugs via linkers, combining the potent killing effect of traditional small-molecule chemotherapy with the tumor-targeting capability of antibody drugs. Tisotumab vedotin (TV) is an ADC targeting tissue factor (TF), which preclinical studies have found to be highly expressed (94%-100%) in CC cells and involved in tumor growth, angiogenesis, and metastasis. The innovaTV 204 trial evaluated TV monotherapy in 102 R/M CC patients, achieving a final ORR of 24%, mOS of 12.1 months, mPFS of 4.2 months, with grade ≥ 3 adverse events occurring in 28% of patients. The innovaTV 205 study explored TV combination regimens: TV + pembrolizumab first-line showed an ORR of 40.6% with mOS not reached; TV + pembrolizumab second-line showed an ORR of 38.2% with mOS of 15.3 months; TV + carboplatin first-line showed an ORR of 54.5% with mOS not reached. The phase III innovaTV 301 trial compared TV monotherapy versus investigator' s choice of chemotherapy (including topotecan, vinorelbine, gemcitabine, irinotecan, pemetrexed) in 502 R/M CC patients who progressed during or after first-line treatment, demonstrating survival benefit with TV over chemotherapy. Since 2023, NCCN guidelines have recommended TV as a preferred second-line treatment for R/M CC, and it has received FDA approval for this indication. Beyond TV, other clinically recognized ADCs include RC48 (disitamab vedotin), T-DXd (trastuzumab deruxtecan), SG (sacituzumab govitecan), and Sac-TMT (sacituzumab tirumotecan). As more clinical trials progress, ADC drugs are expected to become important options for R/M CC, particularly for patients who have progressed after platinum-based chemotherapy and immunotherapy.

6 Summary and Outlook

Treatment options for R/M CC remain limited, but advances in pharmacotherapy have brought new hope. With improved chemotherapy regimens and the application of anti-angiogenic agents, patients' mOS has exceeded 12 months, and the emergence of ICIs has significantly improved outcomes for some patients. Currently, TP/TC chemotherapy ± bevacizumab has become the standard treatment for R/M CC, and pembrolizumab + TP/TC chemotherapy ± bevacizumab is recommended as the first-line preferred treatment for PD-L1-positive R/M CC. Dual immunotherapy combinations and targeted-immune combinations represent future treatment trends for R/M CC. The advent of ADCs has further expanded therapeutic options for R/M CC patients. An increasing number of ongoing and initiated drug clinical trials bring promise to R/M CC patients. In the future, pharmacological treatment for R/M CC will trend toward personalization, using genomic analysis to identify molecular characteristics of CC (such as HPV subtypes, genetic mutations, etc.) to develop tailored treatment strategies. However, corresponding drug toxicities must also be carefully monitored. For example, bevacizumab may cause hypertension, proteinuria, and bleeding, while immunotherapeutic agents can trigger autoimmune reactions affecting multiple organ systems, including thyroid dysfunction and skin disorders. Clinicians must thoroughly understand these medications to improve efficacy and provide better prognoses and quality of life for R/M CC patients.

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Note: Figure translations are in progress. See original paper for figures.