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REVIEW

Advances in systemic treatment for recurrent metastatic cervical cancer

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Abstract

Cervical cancer remains a leading cause of cancer-related mortality among women worldwide, particularly in underdeveloped nations. Despite advances in standard therapies, patients with recurrent metastatic cervical cancer face a poor prognosis and limited treatment options. This study aims to evaluate the efficacy and safety of emerging therapeutic approaches in managing this challenging condition, including immunotherapy, targeted medicines, and chemotherapy.

Our review of recent literature and clinical trials highlights the significant progress made in the systematic treatment of metastatic cervical cancer. While each treatment modality has its strengths and limitations, the collective data suggest a trend towards improved patient outcomes with the adoption of these novel therapies. However, the heterogeneity of patient responses underscores the need for personalised treatment strategies. In conclusion, improvements in medical technology and the adoption of tailored treatment approaches have led to promising advancements in the management of recurrent metastatic cervical cancer. To further enhance patient care, there is an urgent need for more extensive clinical trial data and the development of more efficient personalised treatment plans. This study aims to contribute to this effort by comprehensively analysing current therapeutic strategies and identifying areas for future research.

Key words: Cervical cancer; Chemotherapy; Immunotherapy; Systemic therapy; Targeted therapy

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Introduction

Following lung cancer, colon cancer, and breast cancer in women, cervical cancer ranks fourth globally in terms of incidence (Arbyn et al, 2020), and the lives of women are seriously threatened by it. Over 600,000 new cases and over 300,000 fatalities globally each year, according to data from the World Health Organization (WHO) (Grau et al, 2023). High-income countries have far greater rates of HPV (human papillomavirus) vaccination and cervical cancer screening than low-income countries, and new cases of cervical cancer show a positive correlation with HPV vaccination and cervical cancer screening. Consequently, developing nations account for the majority of newly diagnosed cases of cervical cancer (Schubert et al, 2023; Yu et al, 2023). Socioeconomic factors also impact the cervical cancer screening rate as well as the patient survival rate (Stefanoudakis et al, 2024). The Food and Drug Administration approved pabolizumab plus chemotherapy as the first-line treatment of advanced cervical cancer at the end of 2022, based on KEYNOTE-826 research (Xia et al, 2023). Besides the first-line treatment, however, the treatment options are limited, leading to a poor prognosis. The systemic therapies for metastatic cervical cancer, such as systemic chemotherapy, targeted therapy, and immunotherapy, are considered in this review. It discusses innovative approaches for treating metastatic cervical cancer and provides clarity on the future course of treatment through an analysis and synopsis of the existing treatments.

Immunotherapy

The distinct tumour microenvironment allows cancer cells to escape detection by immune cells, leading to immunosuppression and immune evasion. This ultimately culminates

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in the growth of tumour cells (Khalaf et al, 2021). The primary factors responsible for cervical cancer and immune system escape are the oncoproteins generated following HPV infection (Mikuličić et al, 2024). Immunotherapy involves activating the immune system to destroy cancer cells (Li et al, 2023), and currently, several immunotherapies are in clinical trials. Cardonilizumab, which was developed in China, was approved as the first programmed death protein 1/cytotoxic T lymphocyte-associated antigen 4 (PD-1/CTLA-4) double immune checkpoint inhibitor (ICI) in 2022, making it the first dual immunotherapy (Wu et al, 2022). Additionally, anti-PD-1 therapy has been tested combined with targeted therapy, chemotherapy, and radiotherapy. Other options for preventing HPV infection and treating metastatic cervical cancer include vaccine therapy, adoptive cellular immunotherapy, checkpoint inhibitor therapy, oncolytic virus therapy, and antitumor-drug conjugations (Dyer et al, 2019; Kalafati et al, 2023).

Immune checkpoint inhibitors

To induce the body's self-protective function, immune cells have immunological checkpoints on their surface that serve to make the body self-tolerant in the event of infection and to shield normal cells from immune cell recognition and attack (Fife and Bluestone, 2008). Immune checkpoint inhibitors obstruct immunosuppressive signals, enabling immune cells to specifically target cancer cells. Programmed death protein 1 and its ligands (PD-L1 and PD-L2), as well as CTLA-4, are the primary ICIs (Mauricio et al, 2021). Thus, the immune system's ability to efficiently combat tumour cells is enhanced by these two proteins.

Programmed death protein 1 and its ligands

Programmed death protein 1, a type of immune checkpoint receptor, is expressed on the surface of T cells (Pang et al, 2018). Tumour cells often express a ligand that binds to PD-1 known as programmed cell death receptor ligand 1, and both ligand and receptor mediate immune system escape (Kalim et al, 2020). By inhibiting T cell activity and producing adaptive immune resistance, PD-1 and its ligands play a significant role in establishing immune privilege for the initiation and continuation of HPV infection (Chitsike and Duerksen-Hughes, 2020; Grau et al, 2023). Consequently, inhibiting PD-1 or PD-L1 can enhance T cell function, mitigate T cell exhaustion, and modify the tumour immunological milieu, all of which contribute to enhancing the body's Defence against tumour cells (Mauricio et al, 2021).

When it comes to treating cervical cancer, several clinical trials have confirmed and improved the targeted inhibition of PD-1 or PD-L1 (Salani et al, 2024). The first anti-PD-1 medication to be added to the KEYNOTE-028 and KEYNOTE-158 trials was pabolizumab (Chung et al, 2019). Pembrolizumab, an anti-PD-1 monoclonal antibody, was added to chemotherapy with or without bevacizumab to improve the overall survival (OS) and progression-free survival (PFS, primary endpoints) of patients with persistent, recurrent, or metastatic cervical cancer compared to placebo plus chemotherapy with or without bevacizumab, with tolerable toxicity (Salani et al, 2024). According to their findings, at any point during the study, 42% (122 of 290) patients in the pembrolizumab group and 29% (85 of 297) patients in the placebo group had improved GHS-QoL (General Health Status-Quality of Life) ($p = 0.0003$). These findings validate the usefulness of pembrolizumab in patients with metastatic, recurring, or persistent cervical cancer.

The first-line treatment for recurrent or metastatic cervical cancer is bevacizumab plus prior chemotherapy. Programmed death protein 1 was added to standard chemotherapy in accordance with the results of the KEYNOTE-028, KEYNOTE-158, and KEYNOTE-826 trials (Chung et al, 2019), and palizumab plus platinum-based chemotherapy, either with or without bevacizumab, can significantly increase PFS and OS in PD-L1 positive patients (García et al, 2024). Palizumab in combination with platinum/paclitaxel and bevacizumab was approved as the first-line treatment for recurrent/metastatic cervical cancer based on the outcomes of KEYNOTE-826. It was also recommended as a class I treatment in the 2023 NCCN (National Comprehensive Cancer Network) cervical cancer and CACA (Chinese Anti-Cancer Association) diagnosis and treatment guidelines (Xu and Liu, 2022; Xia et al, 2023).

Cytotoxic T lymphocyte antigen 4

Cytotoxic T lymphocyte-associated antigen 4 is a checkpoint protein that inactivates the immune system and is expressed on the surface of T lymphocytes (Mauricio et al, 2021). To prevent overactivation of the immune system, CTLA-4 attaches to the B7 molecule on the surface of antigen-presenting cells to prevent T lymphocyte proliferation (Skafi et al, 2020). Increased expression of CTLA-4 in cancer cells inhibits immune cells from attacking tumour cells. Although ipilimumab is a member of the CTLA-4 family, findings from clinical trials indicate that ipilimumab monotherapy is not effective in the treatment of cervical cancer. However, when used with chemoradiotherapy, it can increase treatment efficacy. Future research may continue to explore the optimal dosage, long-term efficacy, and safety of CTLA-4 in the treatment of recurrent metastatic cervical cancer.

Adoptive cell therapy

The antigen-specific immune cells known as adoptive cell therapy (ACT) have been isolated from tumour tissues using immune cells or genetic engineering, amplified or activated thousands of times *in vitro*, and shown to have high tumour reactivity, allowing them to identify and kill tumour cells efficiently (Zhu et al, 2022), upon infusion into patients. The body's normal cells are not harmed by the increased number of specialised T cells, which are capable of eliminating tumour cells (Zhang et al, 2021; Waldman et al, 2020). Chimeric antigen receptor T cells (CAR T cells), T cell receptor modified T cells (TCR-T) therapy, and tumour infiltrating lymphocytes (TIL) therapy are the three primary treatments (Pang et al, 2018). Autologous TILs have attracted the interest of many researchers in adoptive cellular immunotherapy for cervical cancer. Natural T cells of a specific sort called TILs are harvested from the patient's tumour. Because they are able to identify many immunological sites on tumour cells, they are multiplied and activated thousands of times *in vitro* before being reinjected into the body. Immunotherapy for cervical cancer has been approved because of its potent ability to invade immune cells and kill tumour cells (Ferrall et al, 2021; Zhu et al, 2022).

Adoptive cell therapy treatment is not currently recommended as an immunotherapy for cervical cancer, according to the NCCN recommendations. However, a highly anticipated direction of ongoing research in treating patients with recurrent, metastatic, or persistent cervical cancer by using autologous TIL manufacturing processes originally developed by the National Cancer Institute (NCT03108495) (Yu et al, 2023). Furthermore, several small-scale clinical studies have been carried out to validate the efficacy of TCR-T treatment and TIL therapy in the management of patients with HPV-related cervical cancer (Doran et al, 2019; Xu and Liu, 2022).

Oncolytic virotherapy

Naturally occurring or genetically modified viruses that have a great affinity for certain receptors produced by tumour tissues but do not harm normal tissues are known as oncolytic viruses (Áyen et al, 2020). Once they have gained access to cancer cells, oncolytic viruses can partially replicate themselves in tumour tissues. This causes tumour cells to lyse, which in turn releases certain antigens. These specific antigens help the immune system boost antigen-presenting cell function and trigger an immunological response (Lawler et al, 2017; Áyen et al, 2020). According to (Kalafati et al, 2023), oncolytic viruses mostly comprise adenoviruses, vaccinia viruses, herpes simplex viruses, Newcastle disease viruses, reoviruses, and vesicular stomatitis viruses. According to recent developments in oncolytic virus research, the virus's ability to cause cancer can be further enhanced by genetic engineering techniques such as gene knockout, insertion, or transfer of foreign genes (Bai et al, 2019). There have been few clinical trials to date, despite the fact that numerous preclinical studies have assessed the therapeutic benefit of oncolytic viruses in cervical cancer. Currently, clinical trials are testing the oncolytic properties of these viruses in the treatment of different malignant tumours, and oncolytic viruses are anticipated to emerge as a novel treatment for recurrent and metastatic cervical cancer (Kalafati et al, 2023).

Human papillomavirus therapeutic vaccine

There is an important distinction between the HPV therapeutic vaccine and the HPV preventive vaccine, with the HPV therapeutic vaccine administered to patients with an HPV

infection. Based on the close relationship between persistent infection of high-risk HPV and the occurrence of cervical cancer (Hancock et al, 2018), HPV E6/E7 cancer proteins are the target antigens of therapeutic vaccines. After delivering E6 and E7 antigens to antigen-presenting cells, HPV antigen-specific T lymphocytes are activated. Thus, HPV-infected cells and cancer cells with target genes E6 and E7 are killed (Hancock et al, 2018; Grau et al, 2023). However, the development of HPV therapeutic vaccines is limited, and there are no approved therapeutic HPV vaccines available for use. Additionally, there are still numerous challenges in developing an effective and safe HPV therapeutic vaccine. One of the biggest challenges is the Viral Diversity and Targeting, HPV consists of over 200 types, with about 14 types identified as high-risk for causing cancers. Developing a vaccine that targets multiple HPV types simultaneously while maintaining effectiveness is challenging.

Antibody-drug conjugate

Antibody-drug conjugates (ADC) are novel anticancer therapies, which bind cytotoxic drugs to antibodies targeted by monoclonal receptors on the tumour surface, thereby delivering cytotoxic drugs directly to cancer cells and resulting in cancer cell apoptosis (McNamara et al, 2023). These conjugates enable the precise delivery of drugs to tumour tissues, thus increasing their efficacy (Drago et al, 2021), and minimising cytotoxicity to healthy tissues (McNamara et al, 2023). The only anti-drug conjugate approved for cervical cancer as of, 2023 is Tivdak (tisotumab vedotin-tftv), which is also the first ADC-approved drug in the field of gynaecology in the United States (Xia et al, 2023). Tivdak, developed by Genmab and Seageng, covalently binds a microtubule destructor (monomethyl auristatin E or MMAE) to an antibody by targeting tissue factors using a proteinase-cleavable joint (Heitz et al, 2023). Tivdak has shown a manageable and tolerable safety in clinical trials, the tisotumab vedotin-tftv FDA (Food and Drug Administration) approval for recurrent or metastatic cervical cancer was based on the innovaTV 204 clinical trial showing 24% objective response rates and 72% disease control rate (Heitz et al, 2023). Overall, ADC appear to have a promising future in the treatment of cervical cancer; however, additional clinical trials are required to confirm their safety and efficacy.

Targeted therapy

Targeted therapy refers to a molecular-level therapeutic approach that specifically targets genes or proteins within the body that are implicated in the development of cancer. Tumour cells express a number of cytokines, such as vascular endothelial growth factor (VEGF) and its receptor as well as epidermal growth factor (EGF) and its receptor, that are linked to tumour growth and metastasis when the tissue containing the cervical cancer tumour grows (Bhatla et al, 2021). Currently, targeted therapies for cervical cancer mainly include anti-angiogenic drugs, poly ADP-ribose polymerase (PARP) inhibitors, and small molecule tyrosine kinase inhibitors (TKIs). These three targeted therapies have achieved significant efficacy in the treatment of recurrent and metastatic cervical cancer, the specific details are as follows.

Anti-angiogenic drugs

Vascular endothelial growth factor is a multifunctional factor that promotes angiogenesis. Proliferating tumour cells abnormally secrete VEGF (Ghalehbandi et al, 2023). Bevacizumab is a monoclonal antibody, which can inhibit the activity of VEGF and is an anti-angiogenic drug (Méndez-Valdés et al, 2023). When used in conjunction with chemotherapy, bevacizumab can enhance blood vessel permeability, enhance immune cell invasion of tumour cells more effectively, and raise the body's susceptibility to chemotherapy (Áyen et al, 2020; Dastidar et al, 2020).

Bevacizumab was added to standard chemotherapy based on the Gynecologic Oncology Group (GOG)-240 (NCT 00803062). As per García et al (2024), the response rate, PFS, and OS were considerably enhanced by the combination of bevacizumab with chemotherapy (paclitaxel + cisplatin, topotecan + cisplatin). Bevacizumab was therefore added to the NCCN guidelines in, 2014 as a first-line treatment for recurrent cervical cancer; however,

because of the drug's high cost, bevacizumab's clinical use is restricted (Méndez-Valdés et al, 2023).

Inhibitors

A class of enzymes known as PARP is involved in several biological processes, such as apoptosis, gene transcription, and DNA damage repair (Ashworth, 2008). Niraparib and Olaparib, two of the main PARP inhibitors currently licenced by the FDA (Food and Drug Administration) and the European Medicines Agency, are used to treat ovarian cancer recurrence (Franzese et al, 2019; Nakai and Matsumura, 2023).

In a study of cervical cancer, the activity of PARP in the nucleus was about twice that of normal cervical cells (Mauricio et al, 2021), so PARP may be a treatment target for recurrent and metastatic cervical cancer. Trials investigating the role of veliparib, rucaparib, or niraparib in advanced cervical cancer (NCT03795272, NCT03644342, and NCT03476798) are currently underway due to the lack of valid data on the efficacy of these drugs in the treatment of recurrent and metastatic cervical cancer (Áyen et al, 2020).

Small molecule tyrosine kinase inhibitors

Research has revealed that tyrosine kinases are primarily involved in HPV infection and that the overexpression of ERBB2 (Erythroblastic Leukemia Viral Oncogene Homolog 2) receptor tyrosine kinases is linked to the occurrence of cervical cancer. However, its impact on the stage of HPV infection has not previously been identified (Mikuličić et al, 2024). A TKI with anti-angiogenic activity, nintedanib, is being studied for its potential use in treating patients with advanced or recurring cervical cancer (Luvero et al, 2017). Vergote et al (2023) explored a double-blind phase II randomised study in patients with first-line recurrent or primary advanced cervical cancer (Vergote et al, 2023). Patients received carboplatin-paclitaxel with oral nintedanib 200 mg BID (twice a day) or carboplatin-paclitaxel with placebo. One group had an extended PFS. They established the role of nintedanib in addition to paclitaxel and carboplatin in first-line recurrent/metastatic cervical cancer (Vergote et al, 2023).

Systemic chemotherapy

Chemotherapy is a systemic treatment for cancer and is also the main treatment method for recurrent and metastatic cervical cancer. Chemotherapy is a systemic treatment for recurrent and metastatic cervical cancer. The chemotherapy methods for cervical cancer include single-drug chemotherapy and combination chemotherapy (Zhou et al, 2017), and the standard chemotherapy regimen for recurrent and metastatic cervical cancer is platinum-based combination chemotherapy. Platinum drugs are anti-tumour drugs that can inhibit the DNA replication of tumour cells after binding with their DNA, thus reducing tumour volume (Zhong et al, 2020).

The experimental results of GOG-240 (Tewari et al, 2014) show that platinum combined with paclitaxel has a high effective rate. Although there are many chemotherapy regimens for recurrent and metastatic cervical cancer, the current first-line chemotherapy regimen for recurrent and metastatic cervical cancer is cisplatin/carboplatin + paclitaxel + beizumab as recommended by the NCCN guidelines in 2014. The 2018 NCCN guidelines recommend pabolizumab as a second-line treatment for recurrent and metastatic cervical cancer (Zhou et al, 2017; Koh et al, 2019; García et al, 2024). For recurrent metastatic cervical cancer, chemotherapy is not often used alone and is generally more effective in combination with other drugs. For example, Lorusso et al (2024) recommend pembrolizumab in combination with chemotherapy, which significantly improved PFS in patients with newly diagnosed, high-risk, locally advanced cervical cancer (Lorusso et al, 2024).

Here, we summarised the advantages and disadvantages of the above methods for the treatment of recurrent and metastatic cervical cancer in Table 1.

Conclusion

In recent years, significant progress has been made in the treatment of cervical cancer, especially in the treatment of recurrent and metastatic cervical cancer. The use of

Table 1. Therapy methods of recurrent metastatic cervical cancer and key points

Therapy methods of recurrent metastatic cervical cancer		Advantages	Disadvantages
Immunotherapy	Immune checkpoint inhibitor (ICI)	1. Breaks immune tolerance, enhancing anti-tumour immune response	1. Relatively low response rate, High cost
		2. Long-lasting efficacy	2. May cause severe immune-related side effects
	Adoptive cell therapy (ACT)	1. Targeted, directly attacking tumour cells	1. Complex preparation process, high cost
		2. Good long-term efficacy, forming long-term immune memory	2. May cause immune-related side effects
	Oncolytic virotherapy (OV)	1. Specifically recognises and infects tumour cells, destroying them	1. Potential for infection of normal cells
		2. Stimulates immune response, attracting more immune cells to kill cancer cells	2. Safety and efficacy require further validation
	Human papillomavirus (HPV) therapeutic vaccine	Manufacturing simplicity, low manufacturing cost, safety, stability, and ease of production	The current therapeutic vaccines mainly target the E6 and E7 antigen genes, while the research on other target antigen gene vaccines is relatively limited
	Antibody-drug conjugates (ADC)	1. Targeted, directly acting on tumour cells	1. High cost
		2. Relatively few side effects	2. Potential for drug resistance
		3. Significant efficacy, suitable for advanced or metastatic cervical cancer	3. Applicable to specific types of cervical cancer, not suitable for all patients
Targeted therapy	Anti-angiogenic drugs	1. High specificity, targeting tumour angiogenesis	1. May cause side effects such as hypertension, proteinuria
		2. Inhibits tumour growth and metastasis	2. Issues of drug resistance
		3. Prolongs patient survival	
	Inhibitors	1. Suitable for patients with specific genetic mutations	1. May cause side effects such as myelosuppression, anaemia
		2. Enhances tumour cells' sensitivity to chemotherapy drugs	2. Gastrointestinal reactions, such as nausea and vomiting
		3. Improves patient survival	3. Relatively expensive
	Small molecule tyrosine kinase inhibitors (TKIs)	1. Convenient oral administration, high patient compliance	1. May cause side effects such as rash, diarrhoea
		2. Inhibits tumour growth and metastasis	2. Issues of drug resistance
		3. Significant effectiveness for some tumour patients	3. May affect cardiac function
Systemic chemotherapy	Systemic chemotherapy	1. Reduces tumour size	1. Chemotherapy drugs may damage normal cells
		2. Eliminates micrometastases and reduces the risk of spread	2. Gastrointestinal side effects, such as nausea, vomiting, loss of appetite, etc.
		3. Increases sensitivity to radiation therapy, synergistic treatment	3. Decreased immunity, prone to infections
		4. Controls cancer spread and metastasis	4. Adverse effects on other systems, such as cardiovascular, liver, kidney toxicity, etc.

pembrolizumab as first-line treatment has achieved better therapeutic efficacy compared to other treatments. In summary, chemotherapy combined with immunotherapy or targeted therapy has made a breakthrough in the treatment of recurrent and metastatic cervical cancer, but there are limitations to current treatments. For instance, some immunotherapy and targeted therapy methods are only effective for specific patient populations. Additionally, the toxic side effects of chemotherapy on the human body remain a significant issue that is currently difficult to address. It is hoped that in future studies, we can further study how to reduce the toxic side effects of these drugs. In conclusion, each modality-immunotherapy, targeted therapy, and chemotherapy-possesses its advantages and disadvantages in managing recurrent and metastatic cervical cancer. Based on our review of the literature, it is recommended that the most suitable treatment plan be selected based on each patient's characteristics as well as the stage of their disease.

Key points

- For patients diagnosed with recurrent metastatic cervical cancer, surgical options are generally limited. Therefore, there is a need for more comprehensive treatment approaches that can enhance both the quality of life and survival time of these patients.
- This article presents a comprehensive overview of treatment options available for individuals with recurrent and metastatic cervical cancer, encompassing three crucial modalities, namely immunotherapy, targeted therapy, and chemotherapy.
- Immunotherapy primarily aims to bolster the patient's immune system and activate it to kill cancer cells.
- Targeted therapy focuses on specific molecules within cervical cancer cells to impede their growth and spread.
- Conversely, chemotherapy employs chemical agents to inhibit or eradicate the proliferation of cervical cancer cells, often serving as an adjuvant therapy.

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Availability of data and materials

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Author contributions

GHK was responsible for collecting data and conducting analysis, as well as preliminary writing and revision of the article. WMD was responsible for writing, revising, and collaborating with the school team, as well as conducting in-depth analysis of the experimental data cited in the article. SZ was responsible for assisting in data collection and analysis, providing strong support for the discussion section of the article, and also responsible for the revision of the article and the school team. XMW was responsible for data collection and analysis, also responsible for article revision and proofreading, strictly monitoring the content of the article to ensure the logical, scientific, and rigorous nature of the paper. XMW was also responsible for article submission and contacting editors. All authors contributed to the important editorial changes in the manuscript. All authors have read and approved the final manuscript. All authors have fully participated in this work and are responsible for it.

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