Clinical and Experimental Obstetrics & Gynecology

Clin. Exp. Obstet. Gynecol. **2024**; 51(7): 155
https://doi.org/10.31083/j.ceog5107155

Review

Immunotherapy for Recurrent and Metastatic Cervical Cancer: A Review

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Academic Editor: Valerio Gaetano Vellone
Submitted: 15 January 2024 Revised: 13 March 2024 Accepted: 29 March 2024 Published: 11 July 2024

Abstract

Objectives: This review aims to summarize the current literature on recurrent and metastatic (r/m) cervical cancer, especially first-line and second-line immunotherapy. Clinical benefits including efficacy and safety of new therapeutic options are also reviewed. **Mechanism**: The published relevant articles were searched from multiple databases, including PubMed, Ovid, and Scopus. The key terms included recurrent cervical cancer, advanced cervical cancer, metastatic cervical cancer, and immunotherapy. The data of the latest clinical trials was retrieved from ClinicalTrials.gov (https://clinicaltrials.gov). **Findings in Brief**: In late 2021, pembrolizumab in combination with chemotherapy with or without bevacizumab was approved as the first-line treatment for recurrent and metastatic cervical cancer. Also tisotumab vedotin was approved as the second-line immunotherapy for r/m cervical cancer. Moreover, a plethora of clinical immunotherapy trials were approved in different countries, and some received as breakthrough therapy designations. Pembrolizumab, cemiplimab, atezolizumab, cadonilimab, zimberelimab, balstilimab and zalifrelimab, nivolumab, and tisotumab vedotin were reviewed with overall survival, progression-free survival, rate of objective response and adverse effects in order to review the efficacy and safety of different therapeutic option. **Conclusions**: The majority of trials indicated that immunotherapy can significantly improve the overall survival (OS) and progression-free survival (PFS) of r/m cervical cancer patients without negatively affecting health-related quality-of-life (HRQoL), and demonstrated that immunotherapy is an effective and safe treatment for r/m cervical cancer.

Keywords: recurrent and metastatic cervical cancer; advanced cervical cancer; first-line immunotherapy; second-line immunotherapy

1. Introduction

Even though cervical cancer is preventable and easy to detect, it remains a high burden on global health. Cumulatively, 604,000 new cases and 342,000 deaths from cervical cancer occurred worldwide in 2020, with it having the fourth highest incidence and resulting in it being the fourth leading cause of death of cancer in women [1]. Almost all patients with cervical cancer are due to persistent infection with the human papilloma virus (HPV). Other risk factors include early onset of sexual activity, multiple sexual partners, cigarette smoking, multiparity, and long-term contraceptive use.

The staging of cervical cancer is based on the 2018 recommendations of the International Federation of Gynecology and Obstetrics (FIGO) [2]. As HPV vaccination and cervical cytology screening become more available, new cases of cervical cancer are gradually reducing, which allows patients to be detected and treated at earlier stages [3]. It remains that there is still a large population of women who do not have access to vaccines or cervical cytology screening, especially in developing countries [1], who are often first diagnosed as being stage III–IV [4–6]. Within the first two years after diagnosis, approximately 15% to 61% of cervical cancer patients will develop recurrent and metastatic (r/m) disease [7]. The prognosis of cervical cancer is closely related to the histological type and FIGO stage. Early-stage cervical cancer has a 5-year survival rate of more than 90%, while advanced, metastatic, and recurrent cervical cancer has a 5-year survival rate of approximately 17% [8].

The initial therapeutic choice is based on the FIGO stage and histological type of cervical cancer. For early-stage patients, surgery might be the first choice, and for advanced and metastatic patients, a combination of chemotherapy and radiation is often be a better choice. However, systemic chemotherapy has limitations, like severe adverse effects (AEs) and a limited therapeutic window. Conversely, r/m cervical cancer has limited curative options.

In recent years, the research in molecular biology and tumor-host immune system reaction has rapidly increased, which has resulted in novel therapeutic strategies, especially immunotherapy for advanced and r/m cervical cancer (CC) patients. The main immunotherapy methods include immune checkpoint inhibitors (ICIs), cancer vaccines, adoptive cell transfer (ACT), and lymphocyte-promoting cytokines [9,10].

2. First-Line Immunotherapies for Recurrent and Metastatic Cervical Cancer

Gynecologic Oncology Group (GOG) 240 is a phase III trial. It demonstrated that the combination of standard chemotherapy and bevacizumab can significantly improve overall survival (OS), which has resulted in the use of bevacizumab with chemotherapy as a standard first-line treatment for r/m CC [11,12].

Several trials have evaluated the efficacy and safety of adding ICIs into the standard therapy in r/m CC [13]. Tumor cells express immune checkpoints, and ICIs can block the interaction between immune cells and tumor cells, thus blocking the inhibitory effect of tumor cells on immune cells [14–16]. The programmed cell death protein 1 (PD-1) axis is the most well-known immune checkpoint pathway, which can inhibit immune response in cervical cancer [17–21].

2.1 Pembrolizumab

Prolonging survival while improving quality of life is the goal of treatment for patients with cervical cancer. The first-line therapy for r/m cervical cancer is pembrolizumab plus platinum chemotherapy (cisplatin or carboplatin) with or without bevacizumab [22]. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks the interaction with programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2), thereby blocking the inhibiting effect of tumor cells on immune cells. Pembrolizumab has been approved by the US Food and Drug Administration (FDA) as a first-line therapy for r/m cervical cancer, especially for PD-L1-positive cervical cancer.

The KEYNOTE-826 study is a multicenter, randomized, double-blind, placebo-controlled phase III trial that has generated a body of published literature demonstrating the importance of pembrolizumab in persistent and r/m CC [23–25].

Patients were enrolled with persistent, recurrent, or metastatic cervical cancer. They were randomized 1:1 to receive pembrolizumab or placebo every 3 weeks with platinum-based chemotherapy with or without bevacizumab (based on the investigator's choice).

A total of 548 patients with a PD-L1 combined positive score (CPS) $\geq$1 were enrolled. The trial reported some statistics in 2021. Median progression-free survival (PFS) in the pembrolizumab group was 10.4 months and placebo group was 8.2 months (hazard ratio (HR) for disease progression or death = 0.62; 95% confidence interval (95% CI): 0.50–0.77; $p < 0.001$). In 317 patients with a PD-L1 CPS $\geq$10, PFS was 10.4 months in the pembrolizumab group and 8.1 months in the placebo group (HR = 0.58; 95% CI: 0.44–0.77; $p < 0.001$). The 24-month OS in pembrolizumab group and placebo group was 53% and 41.7% respectively (HR = 0.64; 95% CI: 0.50–0.81; $p < 0.001$) [23].

The final data of KEYNOTE-826 was reported in 2023 [25]. The median follow-up time was 39.1 months (range, 32.1–46.5 months). The results demonstrated that the combination of pembrolizumab with chemotherapy, with or without bevacizumab, can significantly improve the OS for patients [25].

To evaluate the change in health-related quality-of-life (HRQoL) while OS and PFS have been improved between the pembrolizumab group and placebo group, more work was done in KEYNOTE-826. Approximately 617 patients were enrolled in the study, while 587 (95%) patients received at least one dose of study treatment, and also accomplished at least one post-baseline patient-reported outcome (PROs) and PRO analyses. The median follow-up time was 22.0 months. Results demonstrated that the pembrolizumab group did not negatively affect HRQoL compared with the placebo group [26]. The efficacy, safety, and benefits of pembrolizumab in patients with persistent and r/m cervical cancer are strongly supported. The clinical significance of the OS and PFS improvements has been enhanced with the value of immunotherapy being demonstrated [11,25–27].

2.2 Atezolizumab

The phase III BEATcc/ENGOT-Cx10/GEICO-68-C/JGOG-1084/GOG-3030 study is ongoing [28]. It evaluating atezolizumab (1200 mg) versus placebo in combination with platinum-based chemotherapy for patients with persistent or r/m cervical cancer. The number of 410 patients were included from 8 October 2018, to 20 August 2021. Median PFS in the atezolizumab group and placebo group was 13.7 months (95% CI: 12.3–16.6) and 10.4 months (95% CI: 9.7–11.7), respectively (HR = 0.62; 95% CI: 0.49–0.78; $p < 0.0001$). At the interim OS analysis, the median OS was 32.1 months (95% CI: 25.3–36.8) and 22.8 months (95% CI: 20.3–28.0), respectively (HR = 0.68; 95% CI: 0.52–0.88; $p < 0.005$). Mild adverse effects such as diarrhea, arthralgia, pyrexia, and rash were increased in the atezolizumab group. Grade 3 or worse adverse effects were found in 79% of patients in the atezolizumab group and 75% of patients in the placebo group. The combination of atezolizumab with platinum-based chemotherapy plus bevacizumab has been demonstrated to significantly improve PFS and OS in r/m cervical cancer [28].

3. Second-Line Immunotherapies for Recurrent and Metastatic Cervical Cancer

Multiple other immunotherapies are evaluated for r/m cervical cancer and the FDA has approved some combinations as second-line therapies.

3.1 Cadonilimab

Cadonilimab (AK104) is a bispecific PD-1/cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody, which shows potential clinical benefits in treating malignant tumors. It is approved as a breakthrough therapy des-

ignation by China's National Medical Products Administration (NMPA). A multicenter, open-label, phase II trial was conducted in 30 hospitals across China between 2019 and 2021, NCT03852251, and primary findings were published [29]. The trial included 111 cervical cancer patients. In phase II, the median follow-up time was 14.6 months, while the objective response rate was 32.3% (32/99, 95% CI: 23.3–42.5). Results showed an encouraging tumor response rate to cervical cancer, demonstrating that cadonilimab is a potential treatment for r/m cervical cancer.

3.2 Cemiplimab

Cemiplimab is a PD-1-blocking monoclonal antibody [30]. EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9 is a phase III, randomized study of cemiplimab. This trial enrolled patients who had received first-line platinum-based therapy followed by progression of their cervical cancer with investigators choosing cemiplimab or chemotherapy as therapeutic choices. Cemiplimab has shown a significant benefit in global health status (GHS), quality of life (QoL), and physical functioning (PF) in recurrent and metastatic cervical cancer [31].

There were 608 patients assigned in a 1:1 ratio to the open-label cemiplimab group (350 mg intravenously every 3 weeks) and the chemotherapy group (based on the investigator's choice in 6-week cycles). The median OS in the cemiplimab group was 12.0 months and 8.5 months in the chemotherapy group (HR = 0.69; 95% CI: 0.56–0.84; $p < 0.001$). Median OS was significantly longer with cemiplimab rather than the chemotherapy group in the squamous-cell carcinoma (SCC) patients (11.1 months (95% CI: 9.2–13.4) and 8.8 months (95% CI: 7.6–9.8)), respectively. Median OS was also significantly longer in the cemiplimab group rather than the chemotherapy group in adenocarcinoma (AC) and adenosquamous carcinoma (ASC) patients (13.3 months (95% CI: 9.6–17.6) and 7.0 months (95% CI: 5.1–9.7)) [32].

In the overall population, the median PFS of the cemiplimab group and chemotherapy group was 2.8 months and 2.9 months (HR = 0.75; 95% CI: 0.63–0.89; $p < 0.001$). HR indicated that the cemiplimab group had a significantly longer median PFS as compared to the chemotherapy group [32].

Eighty eight percent of cemiplimab group patients suffered treatment-related adverse events while those who received chemotherapy had a rate of 91.4%. AEs of grade 3 or higher were lower for cemiplimab than chemotherapy (45% *vs.* 53.4%). Adverse events leading to death in cemiplimab group and chemotherapy group was 1.7% *vs.* 0.7%, respectively. None of the AEs leading to death were considered to be related to cemiplimab [32]. Research demonstrated that cemiplimab can significantly improve OS as compared to single-agent chemotherapy in r/m cervical cancer patients, and could be an alternative choice after first-line platinum-containing chemotherapy.

3.3 Zimberelimab

Zimberelimab is a fully human monoclonal immunoglobulin G4 (IgG4) against the PD-1 receptor, with high affinity and selectivity, which was investigated as an immunotherapy for patients with PD-L1-positive r/m cervical cancer that failed 1 or more prior chemotherapy regimens [33]. A phase II, single-arm, open-label registrational study enrolled a total of 105 r/m cervical cancer PD-L1-positive patients who had progressed after chemotherapy. Patients were treated with zimberelimab (240 mg intravenously every 2 weeks) for 2 years until disease progressed, adverse effects became unacceptable, or withdrawal from the trial. The mean duration of follow-up time was 16.9 months (range, 16.3–18.4). The rate of objective response was 27.6%, and the rate of disease control was 55.2%. Median OS and PFS were 16.8 months and 3.7 months. Treatment-related adverse events occurred in 78.1% of all patients [34].

The study demonstrated that zimberelimab monotherapy has a durable anti-tumor activity, and the safety is also acceptable which supports that it could be an optimal treatment choice for r/m cervical cancer patients.

3.4 Balstilimab + Zalifrelimab

Balstilimab (bal) is a fully-human monoclonal antibody, that binds with PD-1 and prevents the interaction with its ligands PD-L1 and PD-L2, thereby blocking the inhibiting effect of tumor cells on immune cells [35]. The efficacy and safety of balstilimab was evaluated in patients with previously treated r/m CC [36]. A trial enrolled 161 patients treated with balstilimab (3 mg/kg intravenously once every two weeks). The rate of objective response in patients with PD-L1-positive tumors was 20%, while the rate was 7.9% in PD-L1-negative tumors. The rate of disease control was 49.3%. Balstilimab demonstrated meaningful response rates with manageable safety [37].

Zalifrelimab (zal) is a fully-human anti-CTLA-4 antibody. The combination of bal with zal has received FDA fast-track designation for r/m CC. NCT03495882 is a phase II trial evaluating the combination of bal + zal in patients with r/m cervical cancer who recurred after one prior platinum-based treatment. One hundred fifty five patients were enrolled in the trial and treated with a combination of balstilimab (once every 2 weeks) with zalifrelimab (once every 6 weeks). The overall rate of objective response was 25.6% (95% CI: 18.8–33.9). The rate of objective response was 32.8% and 9.1% in patients with PD-L1-positive and PD-L1-negative tumors. The rate of overall disease control was 52% (95% CI: 43.3–60.6) [38,39]. The median follow-up time was 21 months, the median PFS was 2.7 months, and overall survival was 12.8 months. The 6-month overall survival was 69.2% (95% CI: 60.1–76.7) and the 12-month overall survival was 53.3% (95% CI: 43.8–61.9). Severe AEs were observed in 16 patients (10.3%).

3.5 Tisotumab Vedotin

Tisotumab vedotin (TV) is an antibody-drug conjugate (ADC) medication, which comprises a monoclonal antibody against tissue factor and monomethyl auristatin E (MMAE), which leads to apoptotic cell death.

NCT03438396 is a multicenter, single-arm, open-label, phase II trial, which was conducted across 35 academically-based centers. The patients included had r/m SCC, AC, or ASC of the cervix. A total of 102 patients were enrolled, 101 of them received at least 1 dose of TV (up to a maximum of 200 mg, intravenously once every 3 weeks) until progression or intolerable toxicity. The median follow-up time was 10.0 months. The rate of confirmed objective response was 24%. Thirteen patients suffered serious treatment-related AEs. One death was considered related to the therapy because of septic shock, while 3 death were considered to be unrelated to the treatment [40].

3.6 Nivolumab

Nivolumab is a human monoclonal antibody against the PD-1. A phase II trial evaluated the clinical activity of nivolumab in patients with advanced or recurrent cervical cancer. The rate of objective response of nivolumab was 25%. The 6-month OS was 84%, and the median PFS was 5.6 months. Results demonstrated that those patients who were PD-L1-positive (33%) had a better objective response rate versus PD-L1-negative patients (0%), and PD-L1 expression and microsatellite-instability status might be potential efficacy biomarkers [41].

4. Discussion

Despite screening and vaccination, cervical cancer, especially those experiencing r/m disease, remains a major cause of mortality worldwide. As the therapeutic process of r/m cervical cancer is long and complex, a search for novel and safe efficacy prediction markers and precise individualized treatment will become the main direction of clinical research.

PD-L1 expression is commonly found in cervical cancer, and seems to be a biomarker to some ICIs. KEYNOTE-826 demonstrated that the combination of pembrolizumab and chemotherapy with or without bevacizumab can significantly improve OS and PFS of PD-L1 positive r/m cervical cancer. Researchers have shown no evidence to support using pembrolizumab for PD-L1 negative r/m cervical cancer, and even for PD-L1 positive patients, there is no evidence to support pembrolizumab for this population [42]. The results of ENGOT-Cx10–GEICO 68-C–JGOG1084–GOG-3030 demonstrated that the inclusion of atezolizumab significantly enhanced the effectiveness of first-line bevacizumab and chemotherapy for r/m cervical cancer. This benefit was observed in a patient population despite PD-L1 status. These results show that for r/m cervical cancer, especially those with PD-L1 negative status, atezolizumab might be a good choice for immunotherapy.

NCT03852251 showed that the use of cadonilimab revealed an encouraging tumor response rate, but lacked the statistics of OS and PFS. Cemiplimab can significantly improve OS in r/m cervical cancer patients and might be used after first-line platinum-containing chemotherapy. To those PD-L1-positive r/m CC patients who could not accept first-line immunotherapy, zimberelimab demonstrated a durable anti-tumor activity and manageable safety profile and could be an optimal treatment choice for those patients. Bal + zal and nivolumab both show a higher objective response rate in PD-L1-positive tumors and could be used as second-line immunotherapy for PD-L1-positive r/m cervical cancer patients.

Currently there are more available immunotherapeutic options for PD-L1-positive r/m CC, and the improvement for OS, PFS, and objective response rate have been proven. However, for PD-L1-negative r/m CC, there are limited therapeutic options compared with PD-L1-positive r/m CC. It is critical to find more potential efficacy biomarkers to identify those who would receive the greater benefit from all the drugs, especially for PD-L1-negative r/m CC.

After analyzing the latest literature of pharmacotherapy, D'Oria *et al*. [9] stated that besides clinical trials, primary and secondary prevention remains the fundamental goal to reduce the burden of cervical cancer.

In this review, the researches mainly focused on SCC, AC, and ASC histologic types. Therefore, numerous rare histologic types of cervical cancer are more aggressive [43]. There is little guidance on optimal therapy, and for patients who suffer from rare histologic types of cervical cancer, they had a median recurrence of 16 months and 40 months of median OS [43,44]. Some neuroendocrine tumors treated with nivolumab and adoptive immune cell therapy were reported as case reports [45–47]. Further studies of immunotherapy should pay more attention to these rare tumors.

5. Conclusions

Immunotherapy is now a new solution for cancer treatment. Pembrolizumab and atezolizumab are now approved as first-line treatment options and can significantly improve the OS and PFS of r/m CC patients. Some combinations have been approved as second-line therapies, including cemiplimab, cadonilimab, zimberelimab, balstilimab and zalifrelimab, nivolumab, and tisotumab vedotin. Different agents have their own advantages in different aspects. However, limited agents for second-line immunotherapy compared OS and PFS with first-line therapy. Immunotherapy has become a promising avenue for the treatment of r/m cervical cancer. But more work should be done to search for novel and safe efficacy prediction markers and precise individualized treatment. Immunotherapy is and will be new hope for r/m cervical cancer patients.

Author Contributions

YW and XH did the literature searching and screening. YW drafted the manuscript. XH reviewed and revised the draft. Both authors approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

We thank reviewers who contributed to this research topic.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

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