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Case Report

Combined Immune Checkpoint Inhibitors, Immunotherapy with Picibanil-based Intraperitoneal Imiquimod, and Chemotherapy in Cases of Advanced Cervical Cancer and Failure of Concurrent Chemoradiation Therapy: A New Clinical Paradigm

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Abstract

This is a case of cervical cancer stage IIB according to the International Federation of Obstetrics and Gynecology Staging who initially presented with abnormal vaginal bloody discharge noted in August 2018. A cervical biopsy showed poorly differentiated squamous cell carcinoma, and pelvic magnetic resonance imaging revealed a 4.3-cm cervical mass involving the anterior lip, upper third of the vagina, and right parametrium without nodal or distant lesions. Although she underwent concurrent chemoradiotherapy, a residual cervical tumor was noted in April 2019. She then underwent salvage radical hysterectomy, bilateral pelvic lymph node dissection, and hyperthermic intraperitoneal chemotherapy with cisplatin in May 2019, followed by immunotherapy (picibanil-based intraperitoneal imiquimod), immune checkpoint inhibitors (pembrolizumab, atezolizumab, ipilimumab, and nivolumab), and concurrent chemoradiotherapy until March 2020. The immune risk profile showed T cell proliferation and alteration of Th1/Th2 activation after immunotherapy and immune checkpoint inhibitor therapy. There was significant increase in natural killer (NK) T cells (3.9-fold) and CD4+CD25 (4.25-fold). CD3, CD4, CD8, CD19, CD8+CD28−, and CD4/CD8 cells were increased, while CD2+CD279+ and NK cells were decreased. She received eight cycles of adjuvant chemotherapy (cisplatin, paclitaxel) and bevacizumab in June 2020 for local tumor recurrence in the pelvis which was found in April 2020. Unfortunately, she died in November 2020 due to septic shock.

Keywords: Advanced cervical cancer, immune checkpoint inhibitor, immunotherapy

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Introduction

Cervical cancer is one of the most common gynecologic cancers in developed countries. The most common clinical feature in this disease is abnormal vaginal bleeding. In the advanced stage, the prognosis of cervical cancer is very poor regardless of treatment.

Therapeutic strategies are decided according to the risk of disease recurrence. In patients with advanced cervical cancer, adjuvant chemotherapy and radiation therapy are thought to be beneficial to prevent distant metastases. There are current and emerging add-on treatment options including immunomodulating agents and/or immune checkpoint inhibitors. Checkpoint inhibitor (anti-PD-1) immunotherapy appears promising in the treatment of advanced cervical cancer. The U.S. Food and Drug Administration (FDA) approved pembrolizumab for the treatment of recurrent or metastatic cervical cancer in 2018. The checkpoint inhibitor Opdivo (nivolumab) has also been reported to produce similar responses.[1]

Our case reveals the potential effects of "ZIPON" therapy (atezolizumab, ipilimumab, pembrolizumab, OK-432, and nivolumab) in advanced cervical cancer. We also report the effect on activated immune cell populations such as CD4+ and CD8+ T cells with this combination therapy.

Case Report

A 43-year-old woman, gravida 3, para 2, presented with abnormal vaginal bloody discharge in August 2018. We performed a cervical biopsy, and the pathology showed poorly differentiated squamous cell carcinoma (SCC). A serological examination showed SCC antigen of 5.72 ng/mL and cancer antigen 125 (CA-125) level of 42.9 U/mL. Pelvic magnetic resonance imaging showed a 4.3-cm mass in the cervix involving the anterior lip, upper third of the vagina, and right parametrium without nodal or distant lesions, at stage International Federation of Obstetrics and Gynecology IIB (pT2bN0). She received concurrent chemoradiotherapy in December 2018, including cisplatin 40 mg/m^2 intravenous injection every week, with external radiation therapy of 4500 cGY/25 fx to the whole pelvis and 5400 cGY/30 fx to the lower pelvis using RapidArc. Intracavitary brachytherapy was delivered to point A for a total of 2000 cGy/5 fx. Although she received concurrent chemoradiotherapy for 5 months, a residual cervical tumor was noted in April 2019. She underwent salvage radical hysterectomy, bilateral pelvic lymph node dissection (pathology showed poorly differentiated squamous carcinoma of the cervix and left parametrium lymph node metastasis), and hyperthermic intraperitoneal chemotherapy with cisplatin in May 2019, followed by immunotherapy (picibanil-based intraperitoneal imiquimod), immune checkpoint inhibitors (pembrolizumab, atezolizumab, ipilimumab, and nivolumab), and concurrent chemoradiotherapy until February 2020. Her immune risk profiles were checked before and after combined "ZIPON" therapy (atezolizumab, ipilimumab, pembrolizumab, OK-432, and nivolumab), which showed significant increases in natural killer (NK) T cells (3.9-fold) and CD4+CD25 cells (4.25-fold). We found an increase in CD3, CD4, CD8, CD19, CD8+CD28−, and CD4/CD8 cells and a decrease in CD2+CD279+ and NK cells [Table 1]. Tumor necrosis factor-alpha (TNF-α) increased significantly from 6.4 pg/mL to 31.1 pg/mL.

Due to recurrent pelvis tumors in April 2020, she underwent eight cycles of adjuvant chemotherapy (cisplatin, paclitaxel) and bevacizumab in June 2020. Unfortunately, she died in November 2020 from septic shock.

Discussion

The initial staging of cervical cancer is indicative of its prognosis. For locally advanced cervical cancer, radiation with platinum-based chemotherapy is standard treatment, while immunotherapy can be considered in patients with a poor therapeutic outcome.[2,3] There are current and emerging add-on treatment options including immunomodulating agents and/or immune checkpoint inhibitors.

Concerning immunomodulating agents, picibanil (OK-432) is used subcutaneously as an injected bacterium-extracted material to trigger skin Langerhans cells to recruit T cells and secrete signal 3, such as TNF-α. In our case, TNF-α significantly increased from 6.4 pg/mL to 31.1 pg/mL. When macrophages and dendritic cells are exposed to OK-432, they produce IL-12 and IL-18, which shifts the T and B cell balance to Th1 cell dominant. Theoretically, Th1 activation is more likely to kill tumor cells. OK-432 can also trigger dendritic cells to produce CD80 (B7.1); therefore, targeting this signaling pathway through the inhibition of cytotoxic T lymphocyte activation-4 (CTLA-4) can be useful to treat malignancy.

Table 1: Immune risk profiles before and after combined OK-432 and immune checkpoint inhibitors

	Before-treatment (OK-432 with ICI)	After-treatment (OK-432 with ICI)
Time	20190503	20200207
Lymphocytes subsets		
CD3	79.8	82.3
CD4	23.9	32.4
CD8	38.5	42.4
CD4/CD8	0.6	0.8
NK	8.5	7.0
CD19	7.4	9.6
CD2+CD279+	8.9	1.0
CD152	<0.1	0.1
CD4+CD25+	1.6	6.8
CD11b +	21.9	20.3
CD8+CD28−	32.5	38.8
NKT	1.4	5.5
HLA-DR	46.3	47.9

ICI: Immune checkpoint inhibitors, NKT: Natural killer T cell, OK-432: picibanil

Imiquimod can activate Toll-like receptor 7, which has been shown to induce many kinds of cytokines that shift immune responses to the Th1 pathway. Both OK-432 and imiquimod can efficiently activate the immune system.

Concerning checkpoint inhibitors, ipilimumab is a recombinant human IgG1 monoclonal antibody against CTLA-4.[4] It inhibits the activation of regulatory T cell and antigen-presenting cell pathways. By blocking CTLA-4, activation and proliferation of T cells are enhanced, thereby augmenting cell-mediated immunity. Pembrolizumab is a humanized monoclonal antibody against PD-1.[5] It binds to the PD-1 receptor on T cells to prevent PD-L1 and PD-L2 from binding. Inhibition of the PD-1 pathway results in the reversal of T cell suppression and release of tumor infiltrating lymphocytes. Atezolizumab is a humanized monoclonal antibody that binds to PD-L1.[6] PD-L1 is an immune checkpoint protein that is expressed on tumor cells and downregulates T cell function by binding to PD-1 and B7.1 (CD80). Atezolizumab inhibits the interaction between PD-1 and B7.1 (CD80), thus increasing T cell function. In a previous study, the use of checkpoint inhibitor (anti-PD-1) immunotherapy appeared to be promising in the treatment of advanced cervical cancer. The U.S. FDA approved pembrolizumab for the treatment of patients with recurrent or metastatic cervical cancer in 2018.

The persistence of cervical cancer after concurrent chemoradiation therapy (CCRT) can be due to tolerance in the host immunosurveillance and/or exhausted immune cells. In our case, we used cell flow cytometry analysis of T cells to show CD279 + cells; over 5%–10% of T cells were exhausted during the cancer therapy. Thus, we added immune checkpoint inhibitors including pembrolizumab, nivolumab, atezolizumab, and ipilimumab to orchestrate neoantigens. We also used OK-432-based antigen-presenting cells to uptake these neoantigens and recruit activated and/or co-stimulatory T cells to achieve full activation of cytotoxic lymphocytes for cancer therapy such as CD28+ and HLA-DR immune cells. In our case, we checked the immune risk profiles before and after using immunotherapy and checkpoint inhibitors; this showed activated CD4+ and CD8+ T cells [Table 1].

In the era of immunotherapy-induced antigen spread, researchers have found that CCRT combined with immunotherapy has a better therapeutic outcome and lower recurrence rate compared to CCRT in patients with advanced cervical cancer.[7,8] We used a targeted combination of immunotherapy and checkpoint inhibitors to trigger skin antigen-presenting cells to orchestrate anticancer immunity and prolong the patient's life without immune-related adverse effects. We first combined interruption of PD-L1/PD1 pathways with the release of tumor-associated antigens and then administered OK-432 subcutaneously in a concurrent or sequential manner to trigger antigen-presenting cells to pick up tumor-associated antigens and orchestrate full T cell activation for cancer therapy. We hope for better therapeutic strategies in advanced cervical cancer.

The limitation of this study includes the fact that the immune risk profiles could have been be affected by different physical conditions in the patient, including the status of the disease or different treatment methods (surgery, chemotherapy). However, the benefit of combined immunotherapy and checkpoint inhibitors was still observed. Further development of effective biomarker strategies to identify patients most likely to benefit from immunotherapy and checkpoint inhibitors is necessary. We aim to prolong the patient's life and also strike a balance between life quality, complications, and cost to improve care in advanced cervical cancer patients.

Ethical approval and declaration of patient consent

This study was approved by the CGMH Research Ethics Committee (project number CMRPG3H1771).

The authors certify that they have obtained all appropriate patient consent forms. In the forms, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published, and due efforts will be made to conceal her identity, but that anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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