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Case report

Complete remission of relapsed cervical cancer through immunochemoradiotherapy: Two case reports and three proposed mechanism

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ABSTRACT

Background: In current practice, immunotherapy has been established as an adjuvant rescue therapy for cervical cancer treatment after standard concurrent chemoradiotherapy (CCRT) with tumor recurrence. Carcinoma of the cervix is a relatively chemotherapy-resistant disease. Patients with recurrent cervical cancer have significantly reduced life expectancy, and fewer than 20% of patients survive for 1 year. Therefore, we tried using CCRT after priming and booster immunomodulatory therapy [i.e., immunochemoradiotherapy, (ICRT)].

Case reports: In the first report, a 34 year-old female diagnosed with International Federation of Gynecology and Obstetrics (FIGO) stage IIA cervical cancer with pathological proof of poorly differentiated squamous cell carcinoma was treated with radical surgery. Two years later, she experienced progressive weakness and numbness in her right leg. Computed tomography showed a mass of 8 cm × 7 cm in her right lower pelvis and presacral area with encasement of the right middle ureter. In addition, right hydronephrosis and a metastatic lymph node were suspected in the right iliac vessels. She received standard CCRT with "add on" immunomodulatory agents as a radiosensitizer to augment ICRT. The priming immunomodulatory agents included picibanil [O (i.e., OK-432)], mixed Cervarix (GlaxoSmithKline, London, England) or Gardasil (Merck and Co., Inc., Kenilworth, NJ, USA) viral-like particle vaccine (V) on day 1, and aldesleukin [A (i.e., interleukin-2)] on Day 2. She also started concurrent radiotherapy and palcitaxol (80 mg/m^2) on Day 2 and boostered OVA (i.e., picibanil, viral-like particle vaccine, and aldesleukin) again on Day 4 and Day 5. After the ICRT treatment, remarkable improvements occurred by lower sacral pain, regression of the pelvic tumor, and decreased squamous cell carcinoma antigen (SCC-Ag) levels from 33.8 ng/mL to normal. The second case report is a 66-year-old female with FIGO stage IIA cervical adenocarcinoma. She underwent staging surgery, followed by CCRT. She first had a relapse on the supraclavicle node 2 years before receiving CCRT. A left axilla mass was noted 6 years before she started the priming and booster ICRT treatment. Both patients have been disease-free for > 5 years since receiving CCRT.

Conclusion: We reported two patients with cervical cancer recurrence after conventional therapy. We combined CCRT and ICRT to augment the host cells' immunosurveillance and reach durable response more than 5 years mimic long-term progression-free survival. These two patients showed promising results.

Introduction

Recurrent cervical cancer after surgery and/or radiotherapy has a high rate of mortality and morbidity. The 5-year survival rates reported in patients with relapsed cervical cancer after radical surgery or radiotherapy range between 3.2% and 13%. Tumor

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recurrence is limited to the pelvis,[1] which occurs in approximately one-half of patients. Curative options for these patients are either high-dose radiotherapy or pelvic exenteration.[2,3] Compared to pelvic exenteration, high-dose radiotherapy or concurrent chemotherapy (CCRT) may be more suitable for younger patients. Treatment of advanced or persistent cervical cancer includes radiotherapy and chemotherapy. However, at the present time, there is no effective treatment for metastatic disease and recurrences. Experimental data from multiple cancer models have provided sufficient evidence that the effects of ionizing radiation may contribute to systemic antitumor immunity.[4] Therefore, we attempted to use standard CCRT after priming and boosting with immunomodulatory therapy [i.e., immunochemoradiotherapy, (ICRT)] as a combination therapy to augment host cells' immunosurveillance in patients with relapsed cervical cancer. We present two patients in whom this innovative approach was successful. It may become a novel treatment option for advanced cervical cancer or recurrent cervical cancer in the future.

Case Reports

Case 1

A 34 year-old female with no known systemic disease was diagnosed with cervical cancer. She underwent type III radical surgery. The pathological examination revealed poorly differentiated squamous cell carcinoma, International Federation of Gynecology and Obstetrics (FIGO) stage IIA (i.e., T2aN0M0). Two years later, she was experiencing progressive weakness and numbness in her right leg. Computed tomography (CT) showed a pelvic mass, 8 cm × 7 cm, in the right lower pelvis and presacral area with encasement of the right middle ureter. In addition, right hydronephrosis and a metastatic lymph node were suspected in the right iliac vessels. The patient received standard CCRT with the prime-boost “add on” immunomodulatory agents picibanil (i.e., OK-432), aldesleukin [i.e., interleukin-2 (IL-2)], levamisole, and human papillomavirus (HPV) 6, 11, 16, 18 recombinant vaccine (Gardasil; Merck and Co., Inc., Kenilworth, NJ, USA) or HPV 16, 18 (Cervarix; GlaxoSmithKline, London, England) were initiated as one vial subcutaneous administered the immunomodulatory therapeutic regimen, respectively. Picibanil (OK-432) and aldesleukin (IL-2) are well-studied immunomodulators for treating melanoma, gastric cancer, and many other cancers.[5] Levamisole and HPV 6, 11, 16, 18 recombinant vaccine (i.e., Gardasil) and/or HPV 16, 18 recombinant vaccine (i.e., Cervarix) have been used for adjuvant therapeutic vaccination. The use of levamisole as an immunostimulant has been successful in controlling certain diseases. Levamisole is used in combination with a vaccine to improve its immunogenic effect in inducing dendritic cell maturation and the secretion of IL-12 and IL-10.[6] External radiation therapy (RT) was also administered in the first 2 months with subsequent integrated chemotherapy, after two cycles of paclitaxol (80 mg/m^2) and/or cisplatin (40 mg/m^2). After completing treatment, remarkable improvements in sacral pain, regression of the pelvic tumor, and decrease in SCC-Ag levels were observed (Figure 1).

Figure 1 shows the SCC-Ag level of the first patient. Her SCC level remained elevated until the completion of the immunotherapy. The patient also received a series of CT scans to evaluate the severity and progression of the tumor. Images of the recurrent tumor were compared before ICRT. Three months after the treatment, a cystic change and a decrease in the size of the tumor had occurred (Figures 2A and 2B, respectively). Two years after she had been treated with ICRT, the masses totally regressed to achieve durable response and there was no definite metastasis to the soft tissues of the neck, lung, chest wall, ribs, lymph nodes, or any part of intestines or bony structure (Figure 2C). These findings suggest that she had achieved a complete remission of cervical cancer, after undergoing priming and booster ICRT.

Case 2

A 66-year-old female was diagnosed with cervical adenocarcinoma, FIGO stage IIA (i.e., T2aN1M1). She underwent surgery and CCRT. Three years before she received CCRT, supraclavicular node and axilla lymph node metastatic carcinoma was noted. Metastatic nodes and a movable mass at the left axilla were noted 6 years before she was administered the immunotherapies OK-432 and HPV 6, 11, 16, 18 or HPV 16, 18 recombinant vaccines (i.e., Gardasil or Cervarix, respectively). Two months later, she received another immunotherapy treatment with OK-432 and IL-2. She is stable now and has been disease-free for > 5 years. Because of successful durable response in relapse of cervical cancer after standard CCRT, our team was approved to complete preclinical model prime-boost vaccination to obtain promising results.

Thus, we reported two retrospective cases of patients who received CCRT with mixed prime-boost “add on” OK-432 and HPV 6, 11, 16, 18 or HPV 16, 18 recombinant vaccines (i.e., Gardasil or Cervarix, respectively) immunomodulatory agents. Figure 3 shows a shrunken metastatic axillary mass at 3 months after additional CCRT, following ICRT in the second patient.

The Institutional Review Board of Chang Gung Memorial Hospital (Taoyuan, Taiwan) understood and approved our overall treatment (approval number, 97-0505B). The patients have given their consent for their case reports to be published.

Discussion

We reported two cases of local advanced cervical cancer with recurrence after conventional therapy by either surgery and/or CCRT. We combined CCRT and/or ICRT to augment the host cells' immunosurveillance. These two patients overall show promising results, and both patients are free of disease and mimic progression-free survival for more than 5 years. We currently do not know to rescue the standard treatments and/or “add on” prime-boost immunotherapy for recurrent and/or metastatic cervical cancers have focused on pelvic exenteration. This approach, although morbid, remains the only curative option for locally isolated recurrent disease. When pelvic exenteration is not generally appropriate because of metastatic disease, palliative radiation has been used. However, more novel discoveries about tumor immunity and experimental data from multiple cancer models have provided sufficient evidence that the effects of ionizing radiation may contribute to systemic antitumor immunity.[4] Previous reports have shown consistent promising results in preclinical models of cervical cancer therapeutic vaccines.[7–12] To date, even in an adjuvant setting, the efficacy of radioimmunotherapy for recurrent local invasive cervical cancer has not been well determined and the concept of immunotherapy combined with chemotherapy was also halted at the preclinical stage.[7] These results prompted us to initiate the current study. However, these results are preliminary and further studies are needed to substantiate the clinical utility of these methods. We propose three mechanisms.

First mechanism: radiation therapy converts the tumor into an in situ vaccine

“Abscopal effects” may explain the lasting effect in reducing the possibility of recurrence. Mole[13] emphasize that all cells in the body are interdependent and damage to one cell affects the organism as a whole. Therefore, local radiation has an effect, and other local

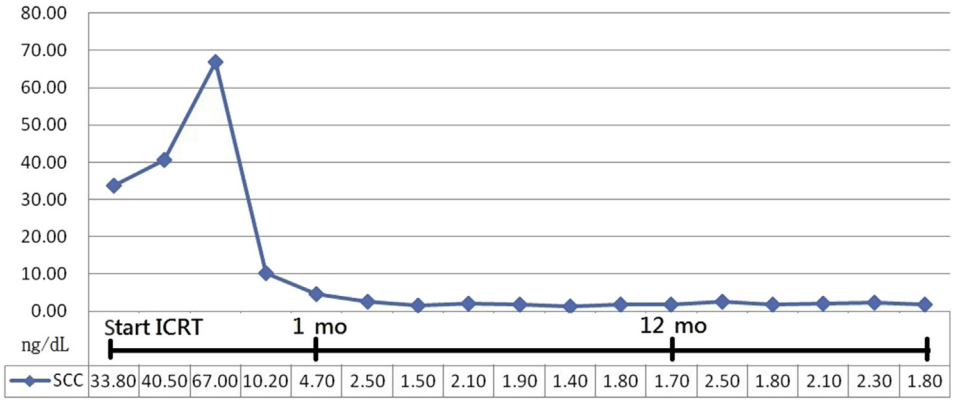

Figure 1. The graph shows the change in the squamous cell carcinoma (SCC) tumor marker level in the first patient. Immunochemoradiotherapy (ICRT) was initiated, and the SCC marker level remained elevated until the end of immunotherapy.

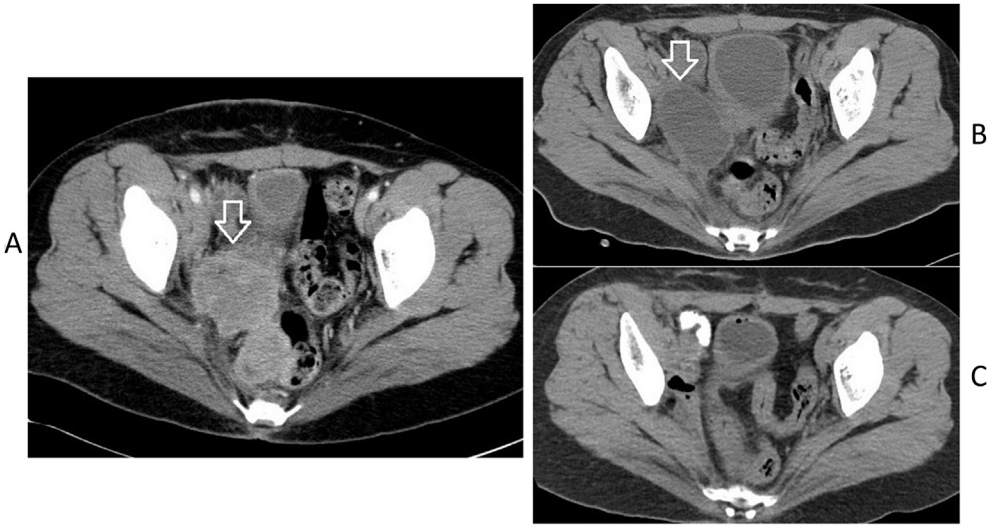

Figure 2. (A) Before beginning immunochemoradiotherapy (ICRT), recurrent cervical cancer is visible in the patient's right lower pelvis and presacral space. The transverse view of the pelvis on the computed tomography (CT) image shows two large tumor masses, the sizes of which are 5.00 cm × 5.50 cm and 3.64 cm × 4.44 cm. (B) The recurrent tumor mass, after priming and boosting every 3 days with OA-OA and concurrent chemoradiotherapy (CCRT). The treatment-mediated cystic change by the 3rd month after initiating ICRT and CCRT. The transverse view of the pelvis on the CT image shows that two tumor masses remain. One tumor, 6.90 cm × 4.29 cm, is a cystic mass with an irregular wall and engorged vessels. It is in the right pelvis and has invaded the urinary bladder and rectum. The other tumor has atrophied to 3.37 cm × 4.40 cm. (C) The transverse view of the pelvis on the CT image shows that the tumor masses have vanished. OA = picibanil/aldesleukin.

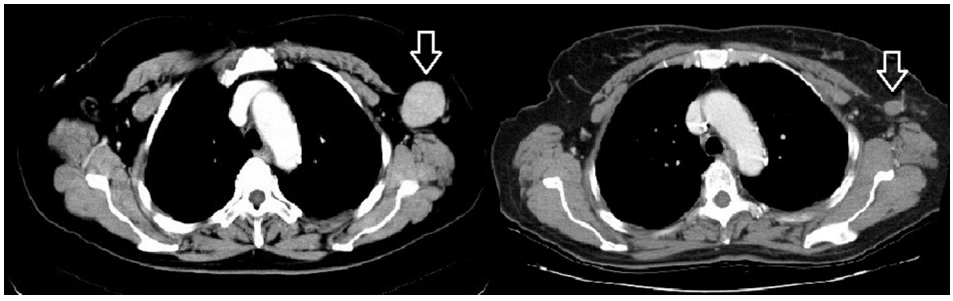

Figure 3. The computed tomography (CT) image of a shrunken metastatic axillary mass after additional concurrent chemoradiotherapy (CCRT), following ICRT with picibanil (OK-432) and human papillomavirus (HPV) 6, 11, 16, 18 recombinant vaccine (Gardasil; Merck and Co., Inc. Kenilworth, NJ, USA).

therapies could influence other aspects of the body; this phenomenon could be called an "abscopal effect."[13,14] Many mechanisms of abscopal effects have been discussed. The most accepted mechanism is related to the immune system, especially the "danger" model of immunity originally proposed by Matzinger in 1994.[15,16] Matzinger postulated that the immune system—rather than differentiating "self" from "nonself"—responds to "danger signals" that occur as a consequence of tissue damage. Apoptosis and necrosis induced by environmental stress, pathogens, chemotherapy, and radiation can create a milieu that elicits "danger

signals." Based on this theory, radiation may induce cancer apoptosis and/necrosis, which releases exosomes and elicit an inflammatory response locally and thereby induce T-cell activation against tumor antigens. These antigens then circulate and may be responsible for the abscopal effects seen during RT. A similar hypothesis has also been described by Demaria et al[17] who demonstrated that the abscopal effect induced in tumors treated by radiation appears to be immune-mediated, and that T-cells are required for the distant effects. Dewan also found in two preclinical carcinoma models that fractionated radiotherapy, instead of single-dose radiotherapy, induces an abscopal effect when combined with anti-CTLA-4 antibody.[18]

Second mechanism: the combination of immunotherapy and chemotherapy may cause a synergistic therapeutic effect

Cytotoxic chemotherapy remains one of the most widely available treatment options for cancer. The efficacy of chemotherapy is unfortunately limited; in particular, cures are rarely achieved for solid tumors. Immunotherapy is a more experimental treatment method aimed at mobilizing the body's immune cells to attack tumor cells; however, it is also rarely curative. Few studies have investigated combining chemotherapy and immunotherapy, largely because the two forms of treatment are considered antagonistic in the standard regimen.

Two assumptions contribute to this view. First, most chemotherapies kill the target cells by triggering the process of programmed cell death (i.e., apoptosis). This mode of cell death is regarded as nonstimulatory or tolerogenic (i.e., tolerance inducing). In general, chemotherapeutic agents have an immunosuppressive function; however, they provide an immunomodulatory therapeutic window to elicit tumor-specific T-cells to generate an excellent anticancer response. Thus, apoptosis-inducing chemotherapy would be expected to induce a state of nonresponsiveness in cytotoxic T-lymphocytes that could otherwise potentially destroy tumor cells.

Second, lymphocyte depletion (i.e., lymphopenia) is a common adverse effect of many anticancer drugs and/or radiation, which is assumed to be detrimental to any potential immune response. However, recent studies challenge both of these assumptions, and new mechanisms have been raised.[7]

One mechanism that has been postulated in an attempt to explain the synergistic effects of chemotherapy and immunotherapy is that chemotherapeutic drugs may enhance the antitumor effects of immunotherapy by acting directly on the tumor and host environment, and thereby minimizes the drugs' immunosuppressive effects. Some studies have demonstrated that certain drugs may modify the immunogenicity of tumor cells. Some chemotherapeutic agents may cause tumor cells to become highly immunogenic, while others may directly cause tumor cell death by the release of a multitude of epitopes and exosomes for recognition by the immune system. This factor subsequently incites an immune response against tumor cells such as lysis by cytotoxic T-lymphocytes (CTLs). Moreover, chemotherapy may eliminate or reduce the activity of regulatory T-cells and their tumoricidal activity. Other potential mechanisms include the induction of transient lymphopenia through chemotherapy, which may eliminate the activity of regulatory T-cells and the stimulation of antitumor CTLs.[19]

Third mechanism: immunochemoradiotherapy is the future trend

To study the efficacy of the combination of chemotherapy and radiotherapy, many researchers have developed unique analytical paradigms. We initially used picibanil (OK-432), which triggers dendtritic cells to express many cell surface receptors such as major histocompatibility complex class I (MHC I), MHC II, CD1d, and /or toll-like receptors to carry tumor-derived antigens to tumor-draining lymph nodes to complete effective signal 1 and signal 2 immunization, after ICRT.[8–12] To determine the type of interaction between chemotherapy and radiotherapy within the radiation field (i.e., supra-additivity, additivity, or infra-additivity), Steel and Peckham described isobologram analysis, which is based on the isoeffect concept of chemoradiotherapy interaction. Independent dose–response curves for chemotherapy and radiotherapy are necessary to create a plot (i.e., isobologram).[20] Other methods exist to determine the types of additivity such as the median effect principle and the response surface approach. The concept of additivity unfortunately is of limited use in clinical practice because the preclinical prediction of additivity does not translate well into clinical outcomes. Therefore, the use of this method is limited for forming hypotheses, which need to be confirmed empirically. Shioyama et al[21] used chemoradiotherapy and immunotherapy successfully to treat a patient with a gastrointestinal stromal tumor, and their study is the only clinical study, rather than a preclinical study, to discuss ICRT. Even for preclinical studies, ICRT has been a rare subject in past decades. There are many differences between this report and our report such as the sequence of immunotherapy and CCRT that was administered, the cancer type, and different regimens. However, our report still illustrates the potential of treating cancer by priming and boosting using the ICRT regimen.

We have presented two cases of recurrent cervical cancer that was cured by innovative prime-boost immunochemoradiotherapy. We have demonstrated proof of the concept of concurrent radiotherapy with chemotherapy and/or immunotherapy that links innate and adaptive immune cells to elicit a promising anticancer response.[8–10] Further studies on the efficacy between different combinations of regimens or treatment methods and their mechanisms are nonetheless needed.

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