



Contents lists available at ScienceDirect

## Gynecology and Minimally Invasive Therapy

journal homepage: [www.e-gmit.com](http://www.e-gmit.com)

## Case report

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

Yi-Hao Lin<sup>1</sup>, Hsin-Hong Kuo<sup>1</sup>, Ling-Hong Tseng, Jian-Tai Qiu, Fu-Shun Chang, Cheng-Tao Lin\*

Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Linkou Medical Center, Chang Gung University College of Medicine, Taoyuan, Taiwan

## ARTICLE INFO

## Article history:

Received 1 December 2015

Received in revised form

14 December 2015

Accepted 20 January 2016

Available online 3 March 2016

## Keywords:

cervical cancer  
chemoradiotherapy  
immunotherapy

## 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 paclitaxol (80 mg/m<sup>2</sup>) on Day 2 and boosted 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.

Copyright © 2016, The Asia-Pacific Association for Gynecologic Endoscopy and Minimally Invasive Therapy. Published by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Conflicts of interest: The authors have no competing interests or conflicts of interests to declare.

\* Corresponding author. Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, 5 Fu-Shin Street, Kwei-Shan, Taoyuan 333, Taiwan.

E-mail address: [51424@cgmh.org.tw](mailto:51424@cgmh.org.tw) (C.-T. Lin).

<sup>1</sup> Yi-Hao Lin & Hsin-Hong Kuo both contributed equally to this paper.

<http://dx.doi.org/10.1016/j.gmit.2016.01.008>

2213-3070/Copyright © 2016, The Asia-Pacific Association for Gynecologic Endoscopy and Minimally Invasive Therapy. Published by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 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

recurrence is limited to the pelvis,<sup>1</sup> which occurs in approximately one-half of patients. Curative options for these patients are either high-dose radiotherapy or pelvic exenteration.<sup>2,3</sup> 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.<sup>4</sup> 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.<sup>5</sup> 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.<sup>6</sup> External radiation therapy (RT) was also administered in the first 2 months with subsequent integrated chemotherapy, after two cycles of paclitaxol (80 mg/m<sup>2</sup>) and/or cisplatin (40 mg/m<sup>2</sup>). 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.<sup>4</sup> Previous reports have shown consistent promising results in preclinical models of cervical cancer therapeutic vaccines.<sup>7–12</sup> 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.<sup>7</sup> 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<sup>13</sup> 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

Download English Version:

<https://daneshyari.com/en/article/3948265>

Download Persian Version:

<https://daneshyari.com/article/3948265>

[Daneshyari.com](https://daneshyari.com)