

Immunotherapy with Subcutaneous Injection of Immunomodulatory Agent (OK-432) Elicits Durable Response in Locally Advanced or Relapsed Cervical Cancer

Quenny Michelle Dyan A. Alas^{1,2,3#}, Cheng-Tao Lin^{4,5**}

¹Department of Obstetrics and Gynecology, Adventist Medical Center, Iligan, ²Department of Obstetrics and Gynecology, Amai Pakpak Medical Center, Marawi, Philippines, ³Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital at Linkou, ⁴Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Chang Gung Memorial Hospital and Chang Gung University, ⁵Chang Gung Immunology Consortium, Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Linkou Medical Center, Taoyuan, Taiwan

#Both authors contributed equally to this work

Abstract

Immunotherapy (IT) has been studied as a new and alternative treatment option for locally advanced, persistent, recurrent, or relapsed cervical cancer in an effort to extend the life and possibly cure patients with advanced stage disease. Targeted immune checkpoint inhibitors augment anticancer immunity and prolong patient's life span without immune-related adverse events (irAEs). Here, we present a case of a 56-year-old woman, gravida 2 para 0, diagnosed with squamous cell carcinoma of the cervix stage IVB who received IT coupled with subcutaneous injection of immunomodulatory agent (OK-432) during her standard treatment of concurrent chemoradiation therapy (CCRT) and as a maintenance therapy after CCRT due to relapsed cervical cancer. This form of treatment strategy showed good response as reflected by a decrease in tumor biomarker with no notable serious irAEs.

Keywords: Cervical cancer, immunomodulatory agent, immunotherapy

INTRODUCTION

A great benefit in harnessing host factors against cancer is endowed in the triggering innate and adaptive immune cells interaction. To generate optimal potent anticancer immunity, antigen-presenting cells—most notably dendritic cells (DCs) must undertake some processes. We used adjuvant picibanil (OK-432) to trigger skin naïve DCs transform to immature DCs that presents major histocompatibility complex Class I and/or Class II, toll-like receptors, or Fc receptors to capture tumor-associated antigens and/or neoantigens, which achieve *in situ in vivo* immunization. Mature DCs recruit various immune cells that orchestrate immunosurveillance for cervical cancer therapy.^[1]

Matured DCs secrete multiple chemokines and/or cytokines such as interleukin 2, 12 (IL-2, 12) to recruit innate and adaptive immune cells, eliciting robust CD4+ or/and CD8+ T-cells anticancer response. The CD8+ T-cell is a major antitumor effector cell in cervical cancer. Maintaining long-term host immunosurveillance efficacy of CD8+ T-cells requires help from CD4+ T-cells.^[2,3]

We used immunomodulatory agents through subcutaneous administration rendering *in vivo* antigen-presenting cells' host immune function. DCs have been a major key player in orchestrating innate and/or adaptive immune cells to

Address for correspondence: Dr. Cheng-Tao Lin,

Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Linkou Medical Center and Chang Gung University College of Medicine, 5, Fu-Hsin Street, Kwei-Shan Taoyuan, Taiwan.
E-mail: 51424@adm.cgmh.org.tw

Article History:

Received 12 December 2018
Received in revised form 17 December 2018
Accepted 9 January 2019
Available online 29 April 2019

Access this article online

Quick Response Code:



Website:
www.e-gmit.com

DOI:
10.4103/GMIT.GMIT_1_19

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Alas QM, Lin CT. Immunotherapy with subcutaneous injection of immunomodulatory agent (OK-432) elicits durable response in locally advanced or relapsed cervical cancer. *Gynecol Minim Invasive Ther* 2019;8:80-2.

generate a boost anticancer response. OK-432 is a useful adjuvant cancer therapies' drug to trigger *in vivo* DCs to achieve the anticancer effect. This OK-432 processes and presents mimic of signal 1 and 2 pathway thus can enhance host immunity against tumor cells. Our protocol regimens, "OBKyZiPanc" cluster immunotherapy (IT) with immunomodulatory adjuvant agents, represent IO (IT mixed OK-432) subcutaneous priming and booster to trigger host immune cells secreting IL-12 (Th1 pathway) to achieve immunosurveillance and anticancer activity.

CASE REPORT

This is a case of 56-year-old woman, gravida 2, para 0, who came in at the outpatient clinic on June 2016 with a complaint of a palpable mass between the vagina and the anus associated with contact bleeding. A biopsy was performed which revealed squamous cell carcinoma (SCCA) of the cervix. She was then diagnosed with SCCA of the cervix stage IVB (inguinal node) T4N1M1. She had completed the standard concurrent chemoradiation (CCRT) on September to October 2016. During her CCRT, IT with subcutaneous injection of the immunomodulatory agent (OK-432) given monthly was incorporated into her treatment regimen. Furthermore, IT with subcutaneous injection with the immunomodulatory agent was given after completing her CCRT as part of her maintenance therapy. She received a total of 9 IT from September 2016 to August of 2017 with no known adverse reactions such as fever, nausea, vomiting, cough, abdominal pain, and bowel or urinary disturbances. However, she was lost to follow-up for approximately 6 months. On April 2018, she consulted at the outpatient clinic for anal pain associated with bleeding. Initial consideration was radiation proctitis. Biopsy of the rectum was performed which revealed chronic ulcer with no malignancy. However, during biopsy, she developed acute onset of massive hematochezia, and hence, she was referred for colonoscopy. On colonoscopy, pseudomembranous colitis with blood clots was noted. She was given antibiotics and was advised for a diverting colostomy for palliation. On further workup, her magnetic resonance imaging revealed a lung and liver metastasis. Due to the presence of distant metastases in the liver and lungs, integrated cancer therapy was offered and thoroughly discussed to her under the calculated immune risk profiles to prevent further tumor progression. The integrated cancer therapy offered and discussed were in the form "OBKyZiPanc" which was composed of subcutaneous injection of immunomodulatory agent OK-432, bevacizumab, Keytruda (pembrolizumab), atezolizumab and pamidronate with interferon, and topotecan-based chemotherapy. She agreed and consented to the proposed plan and received the treatment from May 2018 to August of 2018. During her IT, the dramatic response was noted as reflected by a decrease

in tumor biomarker, SCC antigen from 138 to 33.30 ng/mL. During her treatment with immunochemotherapy, no serious immune-related adverse events (irAEs) were noted. This study was approved by the Institutional Review Board (the "IRB") of Chang Gung Medical Foundation on 2017/02/15.

DISCUSSION

IT has revealed the clinical advantages in phase II/III clinical trials for several solid tumors, such as melanoma, lung, and prostate cancer. Since 2010, bevacizumab (Avastin) approved by the US FDA for ovarian cancer first-line clinical cancer therapy to be normalization of vascular within the tumor microenvironment.^[4]

In current, clinician used immune checkpoint inhibitors to abrogate a promising 50%–70% anticancer effect to be a similar percentile immune-related adverse effect. This study, we provide "combination of strategies" to elicit effective anticancer vaccination. There are three programmed death-1 (PD-1)/PD ligand-1 (PD-L1) inhibitors monotherapy approved in the treatment of nonsmall cell lung cancer since 2015, namely, nivolumab (PD-1 inhibitor), pembrolizumab (PD-1 inhibitor), and atezolizumab (PD-L1 inhibitor) to abrogate a promising anticancer effect^[5-7]

Multiple clinical trials are now underway to evaluate local advanced cervical cancer IT, including vaccines such as Z-100 trial or PaxVax vaccines, adjuvants, and checkpoint inhibitors, alone or as multimodality therapy. Successful targeted conventional therapies such as surgery, chemotherapy, and radiotherapy and/or antiangiogenesis agents with IT to release not only the persistent cancer exosome but also the successful the sustained migrating sufficient numbers of cytotoxic T and/or NK lymphocytes to infiltrate cancer mass to eradicate.

This case reported to provide the target immune checkpoint inhibitors with conventional therapy to augment anticancer immunity and prolong patient's life span without irAEs.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Acknowledgment

The study was supported by grant CMRPG3G1831 and IRB201601707B0, and CMRPG3G0631 and IRB1048973B, which was provided by the Chang Gung University Hospital (Taoyuan, Taiwan).

Financial support and sponsorship

The study was supported by grant CMRPG3G1831 and IRB201601707B0, and CMRPG3G0631 and IRB1048973B, which was provided by the Chang Gung University Hospital (Taoyuan, Taiwan).

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Chen IJ, Yen CF, Lin KJ, Lee CL, Soong YK, Lai CH, *et al.* Vaccination with OK-432 followed by TC-1 tumor lysate leads to significant antitumor effects. *Reprod Sci* 2011;18:687-94.
2. Lin CT, Wang CN, Lai CH. Immunotherapy for advanced or relapsed cervical cancer. *Gynecol Minim Invasive Ther* 2013;2:3-7.
3. Wang YL, Peng HH, Su SY, Lin CT. Combined immunotherapy (OK-432, IL-2) with chemotherapy decrease the recurrence rate in advanced ovarian cancer. *Reprod Sci* 2019;26(2):244-9.
4. Carmeliet P, Jain RK. Angiogenesis in cancer and other diseases. *Nature* 2000;407:249-57.
5. Qiao M, Jiang T, Zhou C. Shining light on advanced NSCLC in 2017: Combining immune checkpoint inhibitors. *J Thorac Dis* 2018;10:S1534-46.
6. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, *et al.* Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med* 2015;372:2018-28.
7. Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gümüş M, Mazières J, *et al.* Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med* 2018;379:2040-51.