Alloreactive cytotoxic T lymphocyte immunotherapy treatment of a patient with metastatic prostate cancer

A case report

Junfeng Shi, PhD\textsuperscript{a,b}, Yi Chen, MS\textsuperscript{c}, Yuetong Chen, MS\textsuperscript{a}, Yunzhu Shen, PhD\textsuperscript{a,b}, Huanyu Zhao, MD\textsuperscript{a}, Hui Sun, MS\textsuperscript{c}, Jinfei Chen, MD\textsuperscript{a,b,d,*}

Abstract

**Rationale:** Cytotoxic T lymphocyte (CTL) immunotherapy is an autologous cellular immune therapy that has been approved for treating patients with malignant tumors. However, there is still limited information regarding the impact of CTL on metastatic prostate cancer (PC) patients with bone metastatic lesions.

**Patient concerns:** An 82-year-old male patient complained of interrupted urination, urination pain, and significant dysuria on November 24, 2014. Transurethral resection of the prostate (TURP) and postoperative pathological examination showed prostatic adenocarcinoma, and a SPECT/CT scan demonstrated multiple bone metastases. In addition, prostate specific antigen (PSA) and free PSA (FPSA) levels were 54.54 μg/mL and 2.63 μg/mL, respectively, at the beginning of treatment.

**Diagnoses:** The man was diagnosed with prostatic adenocarcinoma and multiple bone metastases.

**Interventions:** The patient received 30 cycles of alloreactive CTL (ACTL) immunotherapy regularly.

**Outcomes:** Over the course of the 2-year treatment, the PC patient exhibited diminished bone metastasis accompanied by a marked reduction of serum PSA and FPSA from 54.54 and 2.63 μg/mL to 0.003 and <0.006 μg/mL, respectively.

**Lessons:** Our clinical observations demonstrate that CTL immunotherapy is a viable treatment option for PC patients, particularly those with bone metastatic lesions and high serum levels of PSA and FPSA.

**Abbreviations:** AAV = adenoassociated virus, ACTL = alloreactive CTL, CTL = cytotoxic T lymphocyte, DC = dendritic cells, FPSA = free PSA, GvHD = graft-versus-host disease, PBMC = peripheral blood mononuclear cells, PC = prostate cancer, PSA = prostate specific antigen, TURP = transurethral resection of the prostate.

**Keywords:** alloreactive CTL, bone metastasis, immune therapy, prostate cancer, PSA/FPSA

1. Introduction

Prostate cancer (PC) remains the most common male cancer and the sixth leading cause of cancer-associated deaths in men worldwide.\textsuperscript{[1]} The current treatment options for this disease include surgical removal, endocrine therapy, radiotherapy, and chemotherapy. However, for advanced PC patients with metastatic disease at the time of diagnosis, these treatments appear to have a limited effect. Thus, there is a strong aspiration for developing alternative treatments, including immunity-related or target-based therapy, for use in conjunction with standard treatments.\textsuperscript{[2,3]}

Alloreactive CTL (ACTL) immunotherapy is a promising alternative therapy for PC. This therapy is based on the antitumor effect of a unique form of adoptive T cells. These T cells are initially generated by transferring sensitized peripheral blood mononuclear cells (PBMC) from a healthy donor to a tumor-bearing patient.\textsuperscript{[4,5]} According to Hickey et al, the combination of ACTL-based cellular therapy with prodrug activator gene therapy is highly effective against breast cancer with strong brain metastatic potential.\textsuperscript{[6]} Similarly, immunotherapy has shown great promise in the treatment of PC patients.\textsuperscript{[7–9]} In addition, the generation of robust cytotoxic T lymphocytes (CTLs) against prostate-specific antigen (PSA) through priming dendritic cells (DC) with recombinant adenoassociated virus (AAV) has been explored as an adjuvant immunotherapy for the treatment of PC patients.\textsuperscript{[10]} To our knowledge, however, there has been little information regarding the efficacy of ACTL immunotherapy for patients with bone metastasis.\textsuperscript{[11,12]}

Here, we describe and discuss a case that uses ACTL immunotherapy for the treatment of a patient with advanced...
The patient was highly reactive to this therapy, despite being initially diagnosed with bone metastasis and high levels of PSA/FPSSA. The steady regression of the disease over the course of the treatment highlights the value of the ACTL immunotherapy for overcoming aggressive PC malignancy in the clinic. The treatment was approved by the Institutional Review Board of Nanjing Medical University, and the patient signed an informed consent.

2. Case presentation

An 82-year-old male patient was originally admitted to the hospital for difficulty in urinating spontaneously on November 24, 2014. The patient was diagnosed with prostatic adenocarcinoma after transurethral resection of the prostate (TURP) and postoperative pathological examination (Fig. 1). In addition, a SPECT/CT scan revealed multiple bone metastases (Fig. 2). Initial PSA and free PSA (FPSA) levels were 54.54 and 2.63 μg/mL, respectively (Fig. 3A). The patient exhibited poor tolerance to radiotherapy and chemotherapy, possibly due to advanced age or pacemaker implantation; therefore, immune therapy of allorreactive CTL was selected as a treatment option.

![Figure 1. The H&E analysis of postoperative prostate tumors.](image1)

![Figure 2. SPECT/CT scans show multiple bone metastases.](image2)

![Figure 3. PSA (A and C) and FPSA (B and D) levels during the course of therapy.](image3)
The patient received the first two cycles of ACTL treatment from December 16, 2014 to February 10, 2015. His PSA levels significantly decreased from 54.54 to 1.35 µg/mL after 28 cycles of continuous ACTL immunotherapy, to undetectable levels of <0.003 µg/mL on May 12, 2016; similarly, immediately after completion of ACTL therapy the FPSA levels were down from 2.63 µg/mL to undetectable levels of <0.01 µg/mL. The PSA and FPSA level remained stable in subsequent days. All the changes in PSA and FPSA are plotted in Fig. 3B, and each test was performed in the same laboratory. Importantly, there were few bone metastatic lesions detected by the SPECT/CT scan in December 2016 (Fig. 4). Similarly, no metastatic lesions were detected in other organs, including the lung, liver, and the brain, by the PET-CT scan. Importantly, the patient remains alive after receiving 2 years of immunotherapy, despite being initially diagnosed with metastatic lesions at multiple sites of the body (Fig. 5).
of the effect of bicalutamide,[17] an antiandrogen drug. However, the doses of bicalutamide, given only once or twice a month, were insufficient. Thus, administration of bicalutamide should have limited interference on our assessment of the association between the ACTL immunotherapy and metastatic progression of the disease. Meanwhile, there is lack of evidence in the link between zoledronic acid treatment and disruption of metastatic lesions in PC patients.[18–20] This is also consistent with the current literature, where zoledronic acid treatment is associated with changes in the degree of bone metastasis but not a complete inhibition of metastasis.[21] Thus, the inhibition of tumor metastasis in the PC patient, at its best, is likely attributed to the combined treatment of the immunotherapy and bicalutamide.

4. Conclusion
Our observation demonstrates a strong effect of ACTL cellular immunotherapy in inhibiting metastatic PCs and expands the therapeutic window of the therapy.

Acknowledgment
Written consent was taken from the patient for publishing his clinical details and histopathological photomicrographs.

Author contributions
Data curation: Yuetong Chen.
Methodology: Yi Chen.
Resources: Yunzhu Shen.
Supervision: Jinfei Chen.
Validation: Huanyu Zhao, Hui Sun.
Writing – original draft: Junfeng Shi.

References
[1] Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108.
[2] Gao J, Ward JF, Pettaway CA, et al. VISTA is an inhibitory immune checkpoint that is increased after ipilimumab therapy in patients with prostate cancer. Nat Med 2017;23:551–5.
[3] Ciccarese C, Massari F, Iacovelli R, et al. Prostate cancer heterogeneity: Discovering novel molecular targets for therapy. Cancer Treat Rev 2017;54:68–73.
[4] Kruse CA, Cepeda L, Owens B, et al. Treatment of recurrent glioma with intracavitary alloreactive cytotoxic T lymphocytes and interleukin-2. Cancer Immunol Immunother 1997;45:77–87.
[5] Kruse CA, Beck LT. Artificial-capillary-system development of human alloreactive cytotoxic T-lymphocytes that lyse brain tumours. Biotechnol Appl Biochem 1997;25:197–205.
[6] Hickey MJ, Malone CC, Erickson KL, et al. Combined alloreactive CTL cellular therapy with prodrug activator gene therapy in a model of breast cancer metastatic to the brain. Clin Cancer Res 2013;19:4137–48.
[7] Ragde H, Cavanagh WA, Tjoa RA. Dendritic cell based vaccines: progress in immunotherapy studies for prostate cancer. J Urol 2004;172:2532–8.
[8] Harrington KJ, Spitzweg C, Bateman AR, et al. Gene therapy for prostate cancer: current status and future prospects. J Urol 2001;166:1220–33.
[9] Alberti C. Prostate cancer immunotherapy, particularly in combination with androgen deprivation or radiation treatment. Customized pharmacogenomic approaches to overcome immunotherapy cancer resistance. G Chir 2017;37:223–35.
[10] Mahadevan M, Liu Y, You C, et al. Generation of robust cytotoxic T lymphocytes against prostate specific antigen by transduction of dendritic cells using protein and recombinant adeno-associated virus. Cancer Immunol Immunother 2007;56:1615–24.
[11] Luo G, He Y, Zhao Q, Yu X. Immune Cells Act as Promising Targets for the Treatment of Bone Metastasis. Recent Pat Anticancer Drug Discov 2017;12:221–33.
[12] Eshhar Z, Waks T, Pinthus J. Redirecting immune cells against bone metastases: Immunotherapy of prostate cancer metastases using genetically programmed immune effector cells. Discov Med 2005;5:259–64.

[13] Merad M, Manz MG. Dendritic cell homeostasis. Blood 2009;113:3418–27.

[14] Ferrantini M, Capone I, Belardelli F. Dendritic cells and cytokines in immune rejection of cancer. Cytokine Growth Factor Rev 2008;19:93–107.

[15] Sun JY, Krouse RS, Forman SJ, et al. Immunogenicity of a p210(BCR-ABL) fusion domain candidate DNA vaccine targeted to dendritic cells by a recombinant adeno-associated virus vector in vitro. Cancer Res 2002;62:3175–83.

[16] Sun JY, Senitzer D, Forman SJ, et al. Identification of new MHC-restriction elements for presentation of the p210(BCR-ABL) fusion region to human cytotoxic T-lymphocytes. Cancer Immunol Immunother 2003;52:761–70.

[17] Chow H, Ghosh PM, deVere White R, et al. A phase 2 clinical trial of everolimus plus bicalutamide for castration-resistant prostate cancer. Cancer 2016;122:1897–904.

[18] Lipton A, Cook R, Saad F, et al. Normalization of bone markers is associated with improved survival in patients with 11 bone metastases from solid tumors and elevated bone resorption receiving zoledronic acid. Cancer 2009;113:193–201.

[19] Zullig LL, Wolf S, Vlastelica L, et al. The Role of Patient Financial Assistance Programs in Reducing Costs for Cancer Patients. J Manag Care Spec Pharm 2017;23:407–11.

[20] Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst 2002;94:1458–68.

[21] Vignani F, Bertaglia V, Buttiglieri C, et al. Skeletal metastases and impact of anticancer and bone-targeted agents in patients with castration-resistant prostate cancer. Cancer Treat Rev 2016;44:61–73.