OncoTargets and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

CASE REPORT

Clinical effects of autologous cytokine-induced killer cell-based immunotherapy in the treatment of endometrial cancer: a case report and literature review

This article was published in the following Dove Press journal:
OncoTargets and Therapy
22 September 2017
Number of times this article has been viewed

Yong Zhang*
Yalong Qi*
Axiang Wang
Baozhen Ma
Xiaomin Fu
Lingdi Zhao
Quanli Gao

Department of Biotherapy, Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital, Zhengzhou, Henan, People's Republic of China

*These authors contributed equally to this work

Abstract: Endometrial cancer is the most prevalent gynecological malignancy in the USA, and its treatment involves surgery, chemotherapy, and radiotherapy. Cytokine-induced killer (CIK) cell-based treatments have shown antitumor activity against several solid tumors. However, to the best of our knowledge, there are no reports yet of CIK immunotherapy in the treatment of endometrial cancer, and consequently, little is known about its efficacy and safety. Here, we report a case of an endometrial cancer patient receiving a combination treatment with CIK cells immunotherapy and chemotherapy. Assessment for clinical features was carried out after every two cycles of CIK immunotherapy and chemotherapy. No severe toxicity was observed after infusion of CIK cells. After 4 cycles of treatment, the patient achieved complete response and showed elevated Karnofsky Performance Status scores with an overall survival time of 13.6 months. The combination therapy improved the quality of life and prolonged patient survival time, which suggested that CIK cell therapy might be a potentially beneficial option for endometrial cancer.

Keywords: cytokine-induced killer cells, endometrial cancer, immunotherapy, combination therapy

Introduction

Endometrial cancer arises from the endometrium and is the most prevalent gynecological malignancy and the fourth most common cancer in women in the USA.[1] It is caused by cascading molecular mutations, and its incidence is steadily increasing.[2,3] There will be approximately 61,380 new endometrial cancer cases and 10,920 deaths in the USA in 2017.[1] Generally, standard treatment is composed of surgery, radiotherapy, and chemotherapy based on histology. Surgery is the cornerstone of treatment and is typically advocated in the low-risk endometrial cancer disease.[4] In the early stage, external radiation therapy is considered as the optimal adjuvant treatment.[5] Though radiation therapy seems to reduce the incidence of locoregional recurrence, it is still questionable in preventing metastatic tumor formation.[6] Systemic chemotherapies are used in advanced or recurrent endometrial cancer.[7,8] Paclitaxel has been reported to be the most active single agent in advanced or recurrent endometrial cancer, leading to a median overall survival (OS) ranging from 9.5 to 10.3 months.[8–10] In recent years, tumor immune therapy has become an important part of cancer treatment, and cytokine-induced killer (CIK) cell-based treatments play an important role in tumor immune therapy.[11]

Correspondence: Quanli Gao
Department of Biotherapy, Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital, 127 Dong Ming Road, Jin-Shui District, Zhengzhou, Henan 450003, People's Republic of China
Tel +86 371 6558 7187
Email gaoquanli2015@126.com

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/OTT.S147714

CIKs are a group of heterogeneous cells stimulated by multiple cytokines with antitumor activity, and its lytic activity is primarily due to the CD3 and CD56 double-positive T lymphocytes.[12] CIK cells with non-major histocompatibility complex recognize target cells without depending on T-cell receptors.[13] CIK cells can rapidly proliferate in vivo with strong antitumor activity and improve clinical outcomes in several solid cancers with minor adverse reactions.[12,14] Increasing studies have shown that CIK immunotherapy could provide encouraging positive clinical outcomes in cancer treatment, including in lung and renal cancers and malignancies of hematological system.[15–17]

However, the efficacy and safety of CIK cells immunotherapy in endometrial cancer are still unknown. Here, we report a case of endometrial cancer in a patient who received the combination CIK immunotherapy and chemotherapy, and thus provide insights into the clinical application in endometrial cancer.

Case report

A 74-year-old woman was admitted to our hospital with endometrial cancer in October, 2011. The patient was diagnosed with endometrioid carcinoma by histopathology at the Henan Province People's Hospital in March 2008. Then, the patient was treated with total abdominal hysterectomy with bilateral salpingo-oophorectomy and was diagnosed with stage IIIa cancer according to International Federation of Gynecology and Obstetrics staging (1988 version). Following surgery, the patient received six cycles of chemotherapy (paclitaxel + oxaliplatin). Between October 20, 2011, and December 12, 2011, the patient received pelvic radiotherapy and brachytherapy at the Henan Cancer Hospital, owing to disease recurrence. However, liver and pelvic metastases were detected by magnetic resonance imaging (MRI) (Figure 1) on June 13, 2012, and the Karnofsky Performance Status score of the patient was 60. The patient was in the high-risk stage with refractory and relapsed disease, and despite previous treatment with surgery, chemotherapy, and radiotherapy, the outcome was unsatisfactory. Therefore, CIK immunotherapy was considered. Written informed consent has been provided by the patient's son to have the case details and any accompanying images published.

Peripheral mononuclear cells were collected from 50 mL of the patient's blood and cultured in GT-T551 medium (Cat #KB551/KB551S, Takara, Tokyo, Japan) containing anti-CD3 antibody (1:300 dilutions, mouse-anti-human monoclonal IgG2a, sc-19590, Santa Cruz Biotechnology, Inc, Dallas, TX, USA), recombinant human interleukin-1α (IL-1α, 1,000 U/mL), and interferon-γ (IFN-γ, 1,000 U/mL) at 37°C with 5% CO_2 for 24 hours. Then, recombinant human IL-2 (rhIL-2, 1,000 U/mL) was added to the medium. The medium was replaced with fresh IL-2- and IFN-γ-containing medium every 5 days. At day 10, CIK cells were harvested and analyzed for phenotype. All products were free of mycoplasma, bacterial, and fungal contamination. The endotoxin was less than 5 EU. Phenotypic analysis of autologous CIK cells in the patient before culture and after 10 days of culture showed that percentages of $CD3^+$, $CD3^+CD4^+$, $CD3^+CD8^+$, $CD3^+CD56^+$, and CD25+ cell subsets increased from 43.78%±5.98%, 29.88%±4.57%, 18.06%±6.44%, 3.56%±1.53%, and 12.08%±4.01% to 92.06%±8.59%, 46.03%±7.40%, 37.77%±3.99%, 18.03%±3.85%, and 33.07%±5.82%, respectively, with *P*-values <0.05 (*t*-test, SPSS software 11.0, SPSS company, Chicago, IL, USA). Our results indicate that the percentages of $CD3^+$, $CD3^+/CD4^+$, $CD3^+/CD8^+$, and $CD25^+$ cells were significantly increased after stimulation and expansion in culture, which is crucial to tumor immunity. The cytotoxicity of CIK cells was detected in vitro. At an effector-to-target cell (K562 cell) ratio of 40:1, 20:1, and 10:1, the median level of cytotoxicity

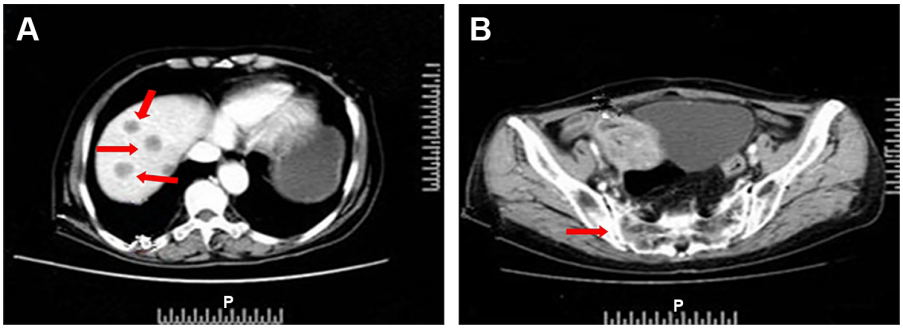

Figure 1 MRI findings of distant metastasis.
Notes: MRI carried out before the patient received CIK cells. (**A**) MRI shows liver metastasis, and red arrows indicated metastatic focus. (**B**) Pelvic metastasis was detected by MRI (red arrows).
Abbreviations: CIK, cytokine-induced killer; MRI, magnetic resonance imaging.

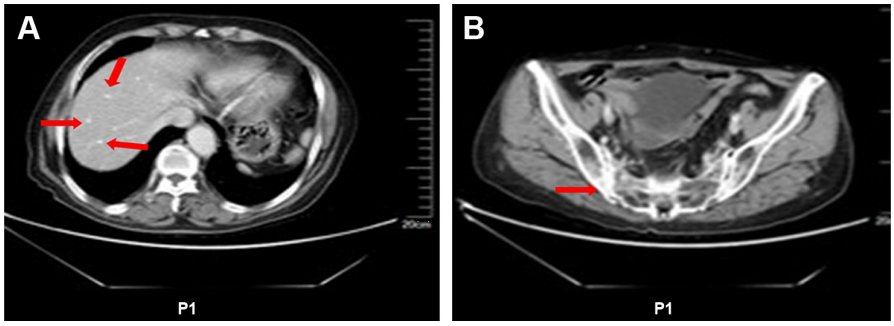

Figure 2 MRI findings after 4 cycles of CIK cells plus chemotherapy.
Note: Liver (**A**) and pelvic (**B**) metastasis showing significant improvement (red arrows).
Abbreviations: CIK, cytokine-induced killer; MRI, magnetic resonance imaging.

was 42% (range, 36%–48%), 52% (range, 48%–58%), and 35% (range, 28%–40%), respectively, which demonstrated that CIK cells generated from peripheral mononuclear cells had strong antitumor activity. The total numbers of CIK cells from one cycle were about 5×10^9.

From June 17, 2012 to August 25, 2012, the patient received chemotherapy (paclitaxel, 240 mg Day 1, every 3 weeks for four cycles) given as adjuvant therapy. Simultaneously, 4 cycles of CIK cells immunotherapy (Day 10) and 2 million units of IL-2 from Day 10 to Day 14 per infusion of CIK cells were administered to the patient. During the first cycle of CIK cells infusion, the patient developed fever (38°C); fortunately, the fever subsided without antibiotic treatment. Other adverse reactions were not observed. After 4 cycles of combined CIK cells immunotherapy with chemotherapy, MRI showed that the liver and pelvic metastases were significantly reduced (Figure 2). According to the RECIST 1.1 criteria,[18] the patient obtained complete response. Her physical strength and appetite increased, and her sleep quality improved. Importantly, the OS time reached 13.6 months.

Discussion

CIK cells are a group of heterogeneous cells with antitumor activity and are stimulated by multiple cytokines.[12] During the past two decades, CIK immunotherapy has been confirmed to be effective and safe in several types of cancers without notable toxic and/or adverse reactions.[19–21] CIK cells have a similar tumor-killing effect as natural killer cells, and a strong antitumor activity similar to T lymphocytes, without the restriction of major histocompatibility complexes.[22] CIK cells could effectively destroy malignant cells by direct disintegration and induce apoptosis in malignant cells by secreting different types of cytokines.[23–25] In addition, these cells could also eradicate the remaining drug-resistant malignant cells.[26] NKG2D, a receptor molecule, strongly expressed on the membrane of CIK cells, is considered the main mediator of antitumor activity.[27] It is a member of the c-type lectin activating receptor family, and its functional activity could be upregulated by the IL-2 in the culture medium.[28]

Initially, CIK cells were reported to effectively kill lymphoma and leukemia.[12] Then, the antitumor activity of CIK cells was also confirmed against several types of solid tumors, including lung cancer, renal cancer, ovarian cancer, and pancreatic cancer.[15,16,29,30] In the treatment of hepatocellular carcinoma, CIK immunotherapy has been explored primarily as adjuvant therapy following surgical resection, and systemic infusion of CIK cells could significantly improve the patients' disease-free survival.[31] CIK immunotherapy has been used in advanced lung cancer as an alternative therapeutic strategy to improve disease control rates, either alone or in combination with chemotherapy.[32] Similar benefits were reported in gastric cancer.[33] However, the application of CIK immunotherapy in the treatment of endometrial cancer has not yet been reported, and hence the efficacy and safety are still unknown. Here, we reported a case of endometrial cancer in a patient who received a combination of CIK immunotherapy and chemotherapy. After 4 cycles of CIK immunotherapy plus chemotherapy, the patient's physical strength, appetite, and sleep quality improved greatly; liver and pelvic metastases regressed significantly; and the patient obtained complete response, with an OS of 13.6 months.

Conclusion

The combination of CIK therapy with chemotherapy improved the clinical outcome without notable side effects in our patient who failed surgery, radiotherapy, and chemotherapy. This indicates that CIK therapy may be a potential candidate for treatment of endometrial cancer. However, further studies are necessary to verify these findings.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics. *CA Cancer J Clin*. 2017;67(1):7–30.
2. Straubhar A, Soisson AP, Dodson M, Simons E. Successful treatment of low-grade endometrial cancer in premenopausal women with an aromatase inhibitor after failure with oral or intrauterine progesterone. *Gynecol Oncol Rep*. 2017;21:10–12.
3. Skrzypczak M, Merx I, Schüler-Toprak S, et al. Molecular profiling of estrogen receptor α and progesterone receptor transcript variants in endometrial cancer. *Steroids*. 2015;104:122–128.
4. Look K. Stage I–II endometrial adenocarcinoma evolution of therapeutic paradigms: the role of surgery and adjuvant radiation. *Int J Gynecol Cancer*. 2002;12(3):237–249.
5. Creutzberg CL, van Putten WL, Koper PC, et al. Surgery and post-operative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. *Lancet*. 2000; 355(9213):1404–1411.
6. Maggi R, Lissoni A, Spina F, et al. Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: results of a randomised trial. *Br J Cancer*. 2006;95(3):266–271.
7. Dunton CJ, Pfeifer SM, Braitman LE, Morgan MA, Carlson JA, Mikuta JJ. Treatment of advanced and recurrent endometrial cancer with cisplatin, doxorubicin, and cyclophosphamide. *Gynecol Oncol*. 1991;41(2):113–116.
8. Bestvina CM, Fleming GF. Chemotherapy for endometrial cancer in adjuvant and advanced disease settings. *Oncologist*. 2016;21(10): 1250–1259.
9. Ball HG, Blessing JA, Lentz SS, Mutch DG. A phase II trial of paclitaxel in patients with advanced or recurrent adenocarcinoma of the endometrium: a Gynecologic Oncology Group study. *Gynecol Oncol*. 1996;62(2):278–281.
10. Lincoln S, Blessing JA, Lee RB, Rocereto TF. Activity of paclitaxel as second-line chemotherapy in endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2003;88(3):277–281.
11. Yang L, Ren B, Li H, et al. Enhanced antitumor effects of DC-activated CIKs to chemotherapy treatment in a single cohort of advanced non-small-cell lung cancer patients. *Cancer Immunol Immunother*. 2013;62(1):65–73.
12. Schmidt-Wolf I, Lefterova P, Mehta B, et al. Phenotypic characterization and identification of effector cells involved in tumor cell recognition of cytokine-induced killer cells. *Exp Hematol*. 1993;21(13):1673–1679.
13. Schmidt-Wolf I, Negrin RS, Kiem HP, Blume KG, Weissman IL. Use of a SCID mouse/human lymphoma model to evaluate cytokine-induced killer cells with potent antitumor cell activity. *J Exp Med*. 1991; 174(1):139–149.
14. Chung MJ, Park JY, Bang S, Park SW, Song SY. Phase II clinical trial of ex vivo-expanded cytokine-induced killer cells therapy in advanced pancreatic cancer. *Cancer Immunol Immunother*. 2014;63(9):939–946.
15. Liu L, Zhang W, Qi X, et al. Randomized study of autologous cytokine-induced killer cell immunotherapy in metastatic renal carcinoma. *Clin Cancer Res*. 2012;18(6):1751–1759.
16. Zhu X, Xu Y, Zhou J, Pan X. A clinical study evaluating dendritic and cytokine-induced killer cells combined with concurrent radiochemotherapy for stage IIIB non-small cell lung cancer. *Genet Mol Res*. 2014; 14(3):10228–10235.
17. Olioso P, Giancola R, Di Riti M, Contento A, Accorsi P, Iacone A. Immunotherapy with cytokine induced killer cells in solid and hematopoietic tumours: a pilot clinical trial. *Hematol Oncol*. 2009;27(3):130–139.
18. Eisenhauer E, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228–247.
19. Marten A, Renoth S, Von Lilienfeld-Toal M, et al. Enhanced lytic activity of cytokine-induced killer cells against multiple myeloma cells after co-culture with idiotype-pulsed dendritic cells. *Haematologica*. 2001;86(10):1029–1037.
20. Zhang Z, Zhao X, Zhang T, et al. Phenotypic characterization and anti-tumor effects of cytokine-induced killer cells derived from cord blood. *Cytotherapy*. 2015;17(1):86–97.
21. Pan K, Guan XX, Li YQ, et al. Clinical activity of adjuvant cytokine-induced killer cell immunotherapy in patients with post-mastectomy triple-negative breast cancer. *Clin Cancer Res*. 2014;20(11):3003–3011.
22. Jiang J, Xu N, Wu C, et al. Treatment of advanced gastric cancer by chemotherapy combined with autologous cytokine-induced killer cells. *Anticancer Res*. 2006;26(3B):2237–2242.
23. Pardoll D. Does the immune system see tumors as foreign or self? *Ann Rev Immunol*. 2003;21(1):807–839.
24. Wongkajornsilp A, Wamanuttajinda V, Kasetsinsombat K, et al. Sunitinib indirectly enhanced anti-tumor cytotoxicity of cytokine-induced killer cells and CD3+ CD56+ subset through the co-culturing dendritic cells. *PLoS One*. 2013;8:e78980.
25. Zou W. Immunosuppressive networks in the tumour environment and their therapeutic relevance. *Nature Rev Cancer*. 2005;5(4):263–274.
26. Yu J, Zhang W, Jiang H, Li H, Cao S, Ren X. CD4+ T cells in CIKs (CD4+ CIKs) reversed resistance to Fas-mediated apoptosis through CD40/CD40L ligation rather than IFN-γ stimulation. *Cancer Biother Radiopharm*. 2008;23(3):342–354.
27. Karimi M, Cao TM, Baker JA, Verneris MR, Soares L, Negrin RS. Silencing human NKG2D, DAP10, and DAP12 reduces cytotoxicity of activated CD8+ T cells and NK cells. *J Immunol*. 2005;175(12): 7819–7828.
28. Jamieson AM, Diefenbach A, McMahon CW, Xiong N, Carlyle JR, Raulet DH. The role of the NKG2D immunoreceptor in immune cell activation and natural killing. *Immunity*. 2002;17(1):19–29.
29. Hongeng S, Pctviscs S, Worapongpaiboon S, Rcrkamnuaychoke B, Pakakasama S, Jootar S. Generation of CD3+ CD56+ cytokine-induced killer cells and their in vitro cytotoxicity against pediatric cancer cells. *Int J Hematol*. 2003;77(2):175–179.
30. Nagaraj S, Ziske C, Schmidt-Wolf IG. Human cytokine-induced killer cells have enhanced in vitro cytolytic activity via non-viral interleukin-2 gene transfer. *Genet Vaccines Ther*. 2004;2(1):12.
31. Hui D, Qiang L, Jian W, Ti Z, DaLu K. A randomized, controlled trial of postoperative adjuvant cytokine-induced killer cells immunotherapy after radical resection of hepatocellular carcinoma. *Dig Liver Dis*. 2009;41(1):36–41.
32. Wu C, Jiang J, Shi L, Xu N. Prospective study of chemotherapy in combination with cytokine-induced killer cells in patients suffering from advanced non-small cell lung cancer. *Anticancer Res*. 2008;28(6B): 3997–4002.
33. Jiang JT, Shen YP, Wu CP, et al. Increasing the frequency of CIK cells adoptive immunotherapy may decrease risk of death in gastric cancer patients. *World J Gastroenterol*. 2010;16(48):6155–6162.