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Case report

A case of advanced ovarian cancer effectively treated with a combination of multi-peptide dendritic cell immunotherapy, surgery, and chemotherapy

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1. Introduction

Ovarian cancer is the most common cause of death among gynecological cancers and the fifth most common cause of death due to cancer for women in developed countries [1]. The standard treatment for advanced stage ovarian cancer is cytoreductive surgery integrated with platinum-based chemotherapy, although most patients experience relapse and the 5-year survival rate is only 30–55%. Most patients who achieve complete responses with frontline standard therapies relapse within 2 years. Therefore, alternative treatment strategies are needed.

Immunotherapy has emerged as a novel strategy for cancer therapy. Among immune cells, dendritic cells (DCs) are key regulators of both T- and B-cell immunity. They are major antigen-presenting cells (APCs) that are capable of capturing and processing tumor antigens, expressing lymphocyte co-stimulatory molecules, and secreting cytokines to initiate immune responses. DC vaccine immunotherapy is an antigen-specific adaptive immunotherapy that aims to induce the production of tumor specific cytotoxic T lymphocytes (CTLs) and tumor-specific memory T cells. CTLs recognize tumor antigens and attack tumor cells, and memory T cells can control tumor relapse. DCs also activate natural killer (NK) cells. NK cell immunotherapy is a form of antigen-non-specific innate immunotherapy, which has direct cytotoxic activity against tumor cells and stimulates cytokines such as IL-1 and IFN-γ [2]. DCs also have an important role in the maintenance of B-cell function and memory during the immunological response.

Tumor-related antigens are a key factor in the design of DC vaccine immunotherapies, and artificial tumor antigens are utilized when a patient's own cancer cells are not available. Multiple peptides such as Wilms tumor 1(WT1), mucin 1 (MUC-1), cancer antigen 125 (CA125), NY-ESO1, and telomerase have been proposed as potential ovarian cancer antigens for DC vaccine immunotherapy. DC-based multi-peptide immunotherapy is feasible and generates efficient cellular antitumor responses [3].

Malignancies frequently develop resistance to standard therapies and these are often responsible for considerable morbidity and death. This has shifted the focus to more specific targeted immunotherapy. There is increasing evidence from animal studies and clinical trials showing that DC vaccine immunotherapy may be a viable option in cancer treatment.

In this case study, a DC vaccine targeting multi-tumor antigens and NK immunotherapy were combined with surgery and chemotherapy for the treatment of advanced ovarian cancer. The patient was then surgically treated and achieved complete remission.

2. Case presentation

A 74-year-old woman was admitted to a hospital with abdominal fluid retention. Abdominal magnetic resonance imaging revealed massive ascites and large masses in the left ovary and peritoneum. She underwent bilateral salpingo-oophorectomy and omentectomy, as the peritoneal mass was too large to resect. According to histopathologic examination, she was diagnosed with stage IIIc serous adenocarcinoma of the left ovary with metastasis to the greater omentum and peritoneum.

After surgery, she received chemotherapy with docetaxel hydrate and carboplatin every 4 weeks.

During chemotherapy, she visited our clinic to receive DC and NK cell immunotherapy every 2 weeks for a total of 5 treatments. Before starting immunotherapy, the diameter of the metastatic mass in the peritoneum was 6 cm and slight ascites was detected on computed tomography (CT) (Fig. 1). Elevation of tumor markers (CA125: 749.7 U/mL, standard level <35.0; tissue polypeptide antigen [TPA]: 124.7 U/L, standard level <38.0; Sialyl SSEA-1 Antigen (SLX): 47.2 U/mL, standard level <38.0) was also noted.

DC and NK cells were prepared every 2 weeks from 25 ml of the patient's peripheral blood according to the methods described in Patent Number 5577472. Then, 4 tumor antigens including WT1,

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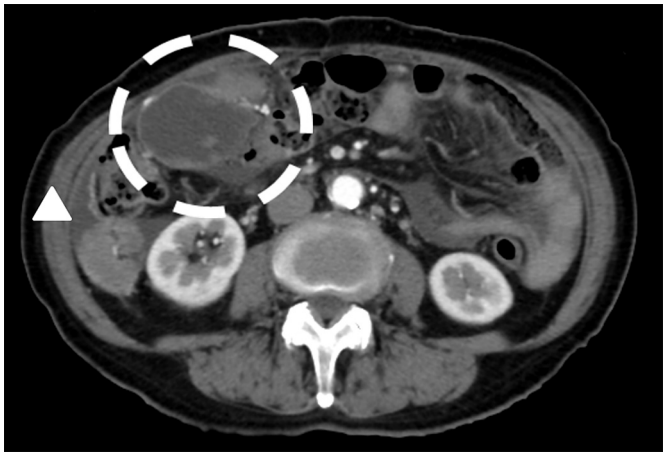

Fig. 1. Abdominal CT was taken just before Patient's first visit to our clinic after the surgery. Metastatic mass in peritoneum and slight ascites (△) was detected.

CA125, NY-ESO1, and telomerase were selected according to the patient's human leukocyte antigen (HLA)-A type and were pulsed onto monocyte-derived DCs and incubated for 24 h. All DC and NK cells were subjected to quality control evaluation, which involved assessing the total number of live cells, monocyte-derived DC and NK characteristics, and percentage of viable cells.

DCs ($>1 \times 10^7$ cells) were administered via intracutaneous injection near both the inguinal lymph nodes, and NK cells ($>1 \times 10^9$ cells) via intravenous drip infusion at 2-week intervals for a total of 5 infusions. During immunotherapy, no adverse reactions were observed.

Three months after DC and NK immunotherapy, CT evaluation showed a decrease in the size of the peritoneal metastatic mass and disappearance of ascites (Fig. 2). Six months after immunotherapy, the levels of the tumor markers were normalized (CA125: 28.3 U/mL, TPA: 22.7 U/L, and SLX: 21.7 U/mL). Fluorodeoxyglucose-positron emission tomography showed no active glucose uptake by the remaining peritoneal mass.

Because the size of the peritoneal metastatic lesion and metabolic function decreased dramatically by a combination of immunotherapy and chemotherapy, the remaining peritoneal mass was then removed completely by laparoscopy, followed by three injections of adjuvant chemotherapy (Fig. 3).

After achieving complete remission, the patient has been free from recurrences for 13 months.

3. Discussion

DCs are considered essential targets for generating therapeutic immunity against various cancers. One of the main aims of DC-based immunotherapy is the generation of antigen-specific CTL responses. DCs and tumor-associated antigens (TAAs) play essential roles in this process. DCs are known to be the most powerful antigen-presenting immune cells. DCs pulsed with various TAAs have been shown to be effective at inducing the production of specific antitumor CTL cells.

In this study, we selected 4 promising peptides, WT1, CA125, NY-ESO1, and telomerase as TAAs for advanced ovarian cancer. WT1 is a transcription factor and has a negative influence on cell differentiation, but promotes proliferation of progenitor cells. It also plays an important role in angiogenesis. Oncogenic properties of WT1 have been demonstrated in various hematological malignancies and solid tumors including high-grade serous ovarian cancer. WT1 is highly immunogenic and has been identified as a molecular target for cancer immunotherapy [4]. A report showed that a WT1-pulsed DC–based vaccine was able to generate specific T cell responses in patients with recurrent ovarian cancer [5]. CA125 is a surface glycoprotein and is usually evaluated in serum samples as a marker of disease progression, although with limited specificity. A study showed more than 90% of ovarian cancers express very high levels of CA125 [6]. Studies have shown functional roles of CA125 in tumorigenesis and metastasis e.g. inducing resistance to TNF-related apoptosis-inducing ligand (TRAIL)-induced apoptosis by reducing the expression of TRAIL receptor-2 and increasing the expression of cellular FLICE inhibitory protein [7], which suggests that CA125 is a potential therapeutic target. NY-ESO1 is a “cancer-testis” antigen frequently expressed in ovarian and other cancers [8]. It is among the most immunogenic tumor antigens, although its function in tumorigenesis is unknown. NY-ESO1 peptide activates both CD8+ and CD4+ NY-ESO1 specific T cells by a number of major histocompatibility complex (MHC) class 1 and class 2 epitopes [9]; therefore, it has been a good TAA candidate in immunotherapy against many malignancies.

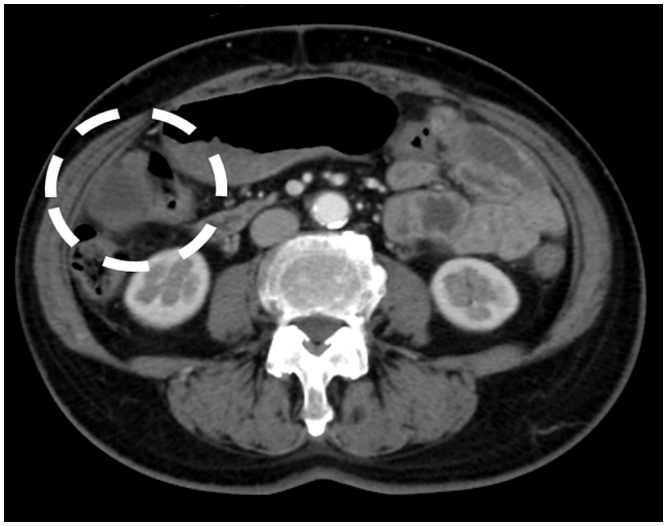

Fig. 2. Abdominal CT 3 months after 5 injections of DCs and NK cells, 1 month after the completion of chemotherapies.

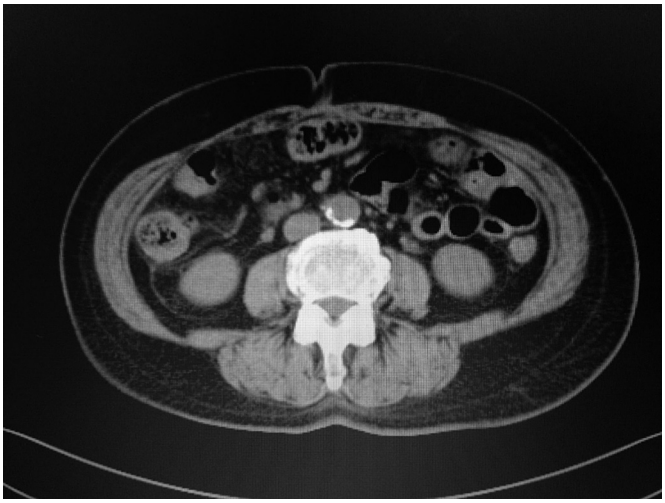

Fig. 3. Abdominal CT after the completion of all the therapies. No malignant masses were detected.

Telomerase is a cellular reverse transcriptase that adds new DNA onto the telomeres that are located at the ends of chromosomes and protect cells from apoptosis, and are thus required for the sustained growth of most advanced cancers. As telomerase is upregulated in most tumors and somatic cells display little or no telomerase activity, inhibition represents a potential therapeutic strategy. The active site of telomerase in cancer cells is a possible target for the development of vaccines. Adoptive cell therapy against telomerase has successfully been used for adenocarcinomas in mice. At least 23 clinical studies have investigated telomerase immunotherapy as an anticancer strategy, with median survival ranging from 88 to 450 days in non-responders and from 216 to >600 days in responders [10].

This report shows promising results using multiple peptides as TAAs for DC immunotherapy, in combination with standard therapy. A multicenter clinical study of advanced cancer patients previously treated with conventional therapy with or without subsequent immunotherapy showed that patients treated with immunotherapy have a significantly better progression-free survival rate. Furthermore, patients with multi-peptide specific CTL responses confirmed by ELISPOT assay have a better overall survival rate. Some chemotherapeutic reagents have been shown to upregulate antigenic peptides on HLA molecules on tumors, increase antigen presentation, and decrease immunosuppressive myeloid-derived suppressive cells and regulatory T-cells, resulting in increased antitumor immunity [11]. A combination of multi-peptide DC immunotherapy and conventional therapy may be a promising strategy to improve prognosis, and may be effective as preoperative therapy for advanced solid cancers, without any severe side effects.

Conflicts of interest

The authors declare no conflicts of interest.

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