Clinical Case Reports

Open Access

CASE REPORT

Recurrent peritoneal serous carcinoma that was unmanageable with paclitaxel–carboplatin therapy responded to autologous formalin-fixed tumor vaccine

Jui-Tung Chen[1] & Tadao Ohno[2]

[1]Jui-Tung Chen Clinic, Akasaka 2-13-5-B1F, Minato-ku, Tokyo 107-0052, Japan
[2]Cell-Medicine, Inc., Sengen 2-1-6-C-B-1, Tsukuba Science City, Ibaraki 305-0047, Japan

Correspondence
Jui-Tung Chen, Jui-Tung Chen Clinic, Akasaka 2-13-5-B1F, Minato-Ku, Tokyo 107-0052, Japan. Tel: +81 3 5856 0015; Fax: +81 3 5856 0016;
E-mail: chin-cl@m.jcnnet.jp

Funding Information
No sources of funding were declared for this study.

Received: 22 February 2015; Revised: 25 April 2015; Accepted: 1 August 2015

Clinical Case Reports **2015; 3(10): 823–826**

doi: 10.1002/ccr3.353

Key Clinical Message

Paclitaxel–carboplatin therapy (TC) usually controls primary peritoneal serous carcinoma (PPSC) but not recurrent disease. In this case, PPSC recurred after three courses of TC, responded dramatically to additional autologous formalin-fixed tumor vaccine (AFTV), and resulted in prolonged, progression-free survival without visible lesions detected by positron emission tomography–computed tomography.

Keywords

Autologous formalin-fixed tumor vaccine, chemoresistance, peritoneal serous carcinoma.

Introduction

Primary peritoneal serous carcinoma (PPSC) has a clinical profile similar to ovarian cancer [1]. Adjuvant paclitaxel–carboplatin therapy (TC) showed almost identical, favorable results regarding survival rates in patients with PPSC and ovarian cancer [2]; however, once recurrence happens, PPSC becomes difficult to manage with TC alone.

Active, specific immunotherapy using the patient's tumor cells can elicit a long-term cell-mediated immune response and succeeds in treating melanoma and colon cancer [3, 4]. Formalin-fixed cells and paraffin-embedded tumor tissues are also good sources of alternative tumor-associated antigens for autologous cytotoxic T-cell induction [5, 6]. Autologous formalin-fixed tumor vaccine (AFTV) was developed on the basis of this principle [7, 8]. A prospective randomized clinical trial showed that AFTV significantly decreased the incidence of early recurrence in patients with hepatocellular carcinoma who had undergone hepatic resection alone [9]. Other pilot and phase I/IIa studies for glioblastoma multiforme indicated that such therapy was effective without notable complications [10, 11]. Therefore, AFTV has been considered to be applicable to many types of solid tumors, such as high-grade malignant fibrous histiocytoma in combination with radiotherapy [12]. In this background, we tried to treat a case of tertiary-recurrent PPSC with TC and AFTV, which seemed difficult to manage with TC alone.

Case Report

A 57-year-old woman presented an abnormal endometrial pap smear, which was suspicious for adenocarcinoma and was systemically explored. However, no malignant lesion was confirmed by total endometrial curettage or computed tomography. The CA125 level was within the normal range. She underwent laparoscopic laparotomy, which identified adenocarcinoma on the surfaces of her ovary, omentum, and peritoneum. After undergoing a total abdominal hysterectomy, bilateral salpingo-oophorectomy, total omentectomy, pelvic lymphadenectomy, and exploratory excision of the right crus of diaphragm, she was histologically diagnosed with PPSC.

She had an elevated CA125 level (1335 U/mL) after 26 months of time to progression (TTP) by the first postoperative paclitaxel (180 mg/m^2) plus carboplatin (CBDCA; area under the curve [6]) therapy (TC) comprising six courses. Positron emission tomography-computed

tomography (PET-CT) showed recurrence at the small bowel, which was observed only on the surface of the ileum. As a result, a 3-cm ileostomy was performed. A second TC comprising six courses was administered; however, after 20 months of TTP, the CA125 level was elevated again (84 U/mL). She underwent TC a third time, which comprised five courses. After resulting 8.3 months of TTP, the CA125 level continuously increased from 17.9 U/mL (day 0) to 2586 U/mL (day 91) (see Fig. 1). PET-CT revealed multiple hot spots around the right crus of the diaphragm, liver, and mesentery (day 85) (see Fig. 2, left). TC was again attempted; however, after initiation of the fourth TC (day 97), the CA125 level increased to 3571 U/mL (day 105). At that point, a decision was made to combine TC and AFTV.

The AFTV was prepared as has been described [10]. First the formalin-fixed, histologically confirmed neoplastic tissue was thoroughly fragmented and centrifuged. Then, an alcohol extract preparation of freeze-dried Bacillus Calmette–Guérin vaccine (Japan BCG Laboratory, Tokyo. Tokyo, Japan) was added, washed, and suspended in 1 ml of saline with 250 ng of tuberculin microparticles and 250 ng of soluble tuberculin (Japan BCG Laboratory, Tokyo).

After obtaining informed consent from the patient, AFTV were initiated (day 116). She received three intradermal injections of AFTV at 2-week intervals. The day after the third AFTV injection, skin erythema and induration were observed, suggesting delayed-type hypersensitivity reaction around inoculated points; this finding persisted for only 7 days.

The blood CA125 levels dramatically decreased to 244 U/mL (day 133), 53.6 U/mL (day 161), 20.4 U/mL (day 224), 17.9 U/mL (day 251), and 15.8 U/mL (day 281) (Fig. 1). PET-CT revealed no visible mass (day 189) (Fig. 2, right). However, CA125 levels dramatically increased again from 24.8 U/mL (day 310) to 830 U/mL (day 344). Because the entire specimen was used to prepare the three AFTV, additional chemotherapy without AFTV was performed with TC (only one course; no response), followed by gemcitabine monotherapy (no response), and finally, topotecan (no response). The patient died 16.5 months after undergoing TC and AFTV treatment.

Discussion

When comparing clinical profiles of PPSC and ovarian cancer, many similarities exist. For example, TC affects patient survival rates in a similar and favorable manner [2]. A traditional phase II study evaluating the efficacy of TC for platinum-sensitive recurrent ovarian cancers demonstrated an observable response in 75.6% (26.8% complete response, 48.8% partial response) of cases [13], but incidence of the response to TC decreased in the context of PPSC recurrence.

In this case study, the patient's TTP was 26, 20, and 8.3 months after the first, second, and third TC, respectively. When PPSC recurred after the third TC, the CA125 level continued to elevate to 3571 U/mL even after initiating a fourth TC; this response pattern differed from those of the former TC applications in which the CA125

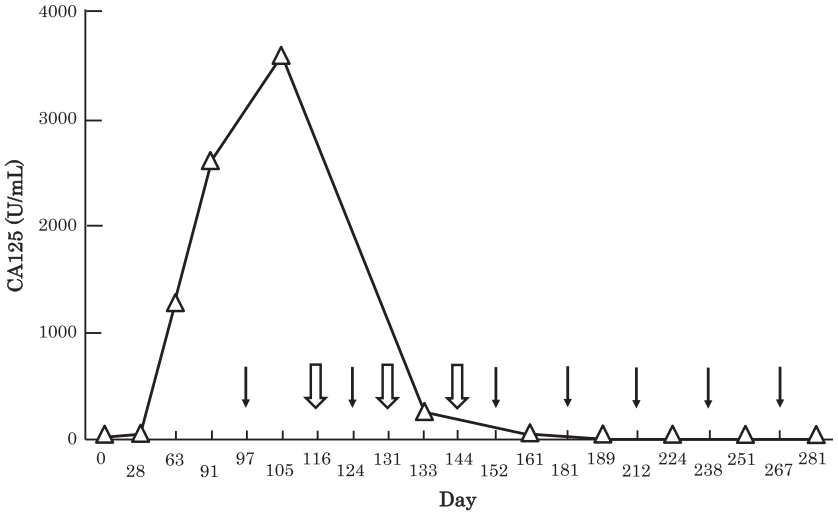

Figure 1. Changes in CA125 levels after TC and AFTV therapy. The CA125 level continuously increased from 17.9 U/mL (day 0) to 2586 U/mL (day 91). TC (solid arrows) began on day 97, and intradermal injections of AFTV (open arrows) commenced on day 116. Following initiation of this therapy, CA125 levels dramatically decreased from 3571 U/mL (day 105) to 244 U/mL (day 133). Levels continued to decrease from 53.6 U/mL (day 161) to 29.3 U/mL (day 189) to 15.8 U/mL (day 281). AFTV, autologous formalin-fixed tumor vaccine; TC, paclitaxel–carboplatin therapy.

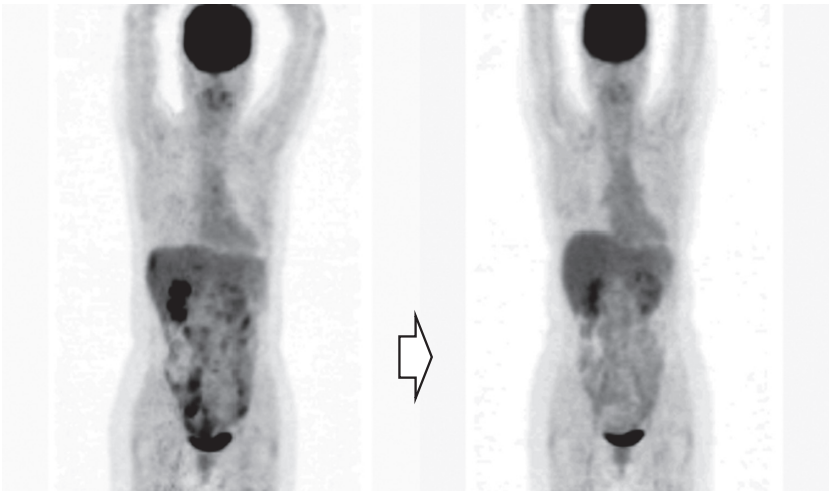

Figure 2. Response to TC and AFTV therapy assessed by PET-CT. PET-CT images before and after TC and AFTV. Left: Multiple hot spots around the right crus of the diaphragm, liver, and mesentery are visible. Right: No recurrent hot spots detected after TC and AFTV. AFTV, autologous formalin-fixed tumor vaccine; TC, paclitaxel–carboplatin therapy; PET-CT, positron emission tomography-computed tomography.

level decreased in response to therapy. Thus, TC alone could not manage the fourth recurrent PPSC in this case.

When TC was combined with AFTV, the patient responded dramatically to the additional AFTV and did not develop severe adverse effects. In addition, the patient showed a TTP of 11.5 months, which was longer than that of the third TTP. Because formalin fixation preserves the specific antigenicity of tumor cells [5] and preparation of AFTV from resected and fixed tumor tissues [10, 11] is simple, AFTV therapy is a viable option for clinical applications. Furthermore, after the patient received TC and AFTV, no visible lesions were detected by PET-CT. These findings suggest that TC and AFTV could serve as a new strategy for recurrent PPSC, which is unmanageable with TC alone.

The feasibility and efficacy of complete laparoscopic staging was demonstrated in early stage ovarian cancer [14]; however, in advanced stage, the role of laparoscopy has been limited in cytoreductive procedures. In this case, cancer mass was observed on the surfaces of the ovary, omentum, peritoneum, and right crus of diaphragm, and laparotomy was rationally indicated for optimal maximum cytoreduction. The efficacy of intraperitoneal (IP) chemotherapy preceded by cytoreductive surgery was reported in advanced ovarian cancer [15]. In this case, consecutive cytoreductive laparotomy after laparoscopic survey was seemed to be appropriate, and we do not adopt IP chemotherapy due to the possibility in severe adverse events, such as grade 3–4 pain, ileus, diarrhea, or an associated complication of IP catheter, which might worsen quality of life in spite of the expected promising survival by IP [16]. Latest immunotherapeutic advancements in the treatment of tumors [17–19] should be taken in consideration for this type of patients.

Conclusion

In this case study, the patient gained approximately a year of progression-free survival time after the recurrence of TC-resistant PPSC, which implies that this type of immunotherapy may be a viable treatment option for chemo-refractory recurrent PPSC.

Patient Consent

Written informed consent was obtained from the patient for publication of this Case report and accompanying images.

Acknowledgment

None.

Conflict of interest

The authors declare that they have no conflict of interest, except that TO works at a private company known as Cell-Medicine, Inc.

References

1. Muto, M. G., W. R. Welch, S. C. Mok, C. A. Bandera, P. M. Fishbaugh, S. Tsao, et al. 1995. Evidence for a multifocal origin of papillary serous carcinoma of the peritoneum. Cancer Res. 55:490–492.

2. Ayhan, A., C. Taskiran, N. Yigit-Celik, G. Bozdag, M. Gultekin, A. Usubutun, et al. 2006. Long-term survival after paclitaxel plus platinum-based combination chemotherapy for extraovarian peritoneal serous papillary carcinoma: is it different from that for ovarian serous papillary cancer? Int. J. Gynecol. Cancer 16:484–489.
3. Soiffer, R., F. S. Hodi, F. Haluska, K. Jung, S. Gillessen, S. Singer, et al. 2003. Vaccination with irradiated, autologous melanoma cells engineered to secrete granulocyte-macrophage colony-stimulating factor by adenoviral-mediated gene transfer augments antitumor immunity in patients with metastatic melanoma. J. Clin. Oncol. 21:3343–3350.
4. Vermorken, J. B., A. M. Claessen, H. van Tinteren, H. E. Gall, R. Ezinga, S. Meijer, et al. 1999. Active specific immunotherapy for stage II and stage III human colon cancer: a randomized trial. Lancet 353:345–350.
5. Kim, C., M. Matsumura, K. Saijo, and T. Ohno. 1998. In vitro induction of HLA-A2402-restricted and carcinoembryonic-antigen-specific cytotoxic T lymphocytes on fixed autologous peripheral blood cells. Cancer Immunol. Immunother. 47:90–96.
6. Liu, S. Q., H. Shiraiwa, K. Kawai, H. Hayashi, H. Akaza, B. S. Kim, et al. 1996. Tumor-specific autologous cytotoxic T lymphocytes from tissue sections. Nature Med. 2:1283.
7. Ohno, T. 2003. Autologous cancer vaccine: a novel formulation. Microbiol. Immunol. 47:255–263.
8. Peng, B. G., S. Q. Liu, M. Kuang, Q. He, S. Totsuka, L. Huang, et al. 2002. Autologous fixed tumor vaccine: a formulation with cytokine-microparticles for protective immunity against recurrence of human hepatocellular carcinoma. Jpn. J. Cancer Res. 93:363–368.
9. Kuang, M., B. G. Peng, M. D. Lu, L. J. Lian, J. F. Huang, Q. He, et al. 2004. Phase II randomized trial of autologous formalin-fixed tumor vaccine for postsurgical recurrence of hepatocellular carcinoma. Clin. Cancer Res. 10:1574–1579.
10. Ishikawa, E., K. Tsuboi, T. Yamamoto, A. Muroi, S. Takano, T. Enomoto, et al. 2007. Clinical trial of autologous formalin-fixed tumor vaccine for glioblastoma multiforme patients. Cancer Sci. 98:1226–1233.
11. Muragaki, Y., T. Maruyama, H. Iseki, M. Tanaka, C. Shinohara, K. Takakura, et al. 2011. Phase I/IIa trial of autologous formalin-fixed tumor vaccine concomitant with fractionated radiotherapy for newly diagnosed glioblastoma. J. Neurosurg. 115:248–255.
12. Todoroki, T., T. Kondo, S. Sugahara, Y. Morishita, K. Mori, and T. Ohno. 2011. Long-term survivor of relapsed MFH on the thigh treated with autologous formalin-fixed tumor vaccine (AFTV) combined with limb-sparing surgery and radiotherapy. World J. Surg. Oncol. 9:96–99.
13. González-Martín, A. J., E. Calvo, I. Bover, M. J. Rubio, A. Arcusa, A. Casado, et al. 2005. Randomized phase II trial of carboplatin versus paclitaxel and carboplatin in platinum-sensitive recurrent advanced ovarian carcinoma: a GEICO (Grupo Espanol de Investigacion en Cancer de Ovario) study. Ann. Oncol. 16:749–755.
14. Bogani, G., A. Cromi, M. Serati, E. Di Naro, J. Casari, C. Pinelli, et al. 2014. Laparoscopic and open abdominal staging for early-stage ovarian cancer: our experience, systematic review, and meta-analysis of comparative studies. Int. J. Gynecol. Cancer 24:1241–1249.
15. Grosso, G., D. Rossetti, F. Coccolini, G. Bogani, L. Ansaloni, and L. Frigerio. 2014. Intraperitoneal chemotherapy in advanced epithelial ovarian cancer: a survey. Arch. Gynecol. Obstet. 290:425–434.
16. Crane, E. K., C. C. Sun, P. T. Ramirez, K. M. Schmeler, A. Malpica, and D. M. Gershenson. 2015. The role of secondary cytoreduction in low-grade serous ovarian cancer or peritoneal cancer. Gynecol. Oncol. 136:25–29.
17. Baxevanis, C. N., S. A. Perez, and M. Papamichail. 2008. Combinatorial treatments including vaccines, chemotherapy and monoclonal antibodies for cancer therapy. Cancer Immunol. Immunothe. 58:317–324.
18. Gravitz, L. 2013. Cancer immunotherapy. Nature 504, S1.
19. Chester, C., O. Dorigo, J. S. Berek, and H. Kohrt. 2015. Immunotherapeutic approaches to ovarian cancer treatment. J. Immmunother. Cancer 24:3–7.