

A Case of Recurrent Ovarian Cancer Successfully Treated with Adoptive Immunotherapy and Lentinan

KATSUNADA FUJIMOTO¹, MASAMICHI TOMONAGA¹ and SHIGENORI GOTO²

¹Fukuoka Medical Clinic and ²Seta Clinic, Fukuoka, Japan

Abstract. *Background: Immunotherapy is useful for the prevention of the post-operative recurrence of some types of cancer and, in combination with certain anticancer drugs, is expected to prolong survival time. However, the clinical efficacy of immunotherapy alone against advanced cancer has not yet been demonstrated. Case Report: A 67-year-old woman with ovarian cancer who had undergone post-operative adjuvant chemotherapy suffered from recurrent cancer in the lymph nodes. A partial response to adoptive immunotherapy and the administration of the biological response modifier, lentinan containing β -glucan as the principal component, was maintained for five months without the use of chemotherapy. Conclusion: Adoptive immunotherapy with lentinan alone was potentially useful for the treatment of lymph node metastases from ovarian cancer.*

Most cases of ovarian cancer respond well to chemotherapy. However, advanced ovarian cancer recurs in many patients and is often treated by chemotherapy. Chemotherapy may cause adverse reactions that may impair patients' quality of life. CD3-LAK immunotherapy, an adoptive immunotherapy, was employed in our patient. The efficacy of this adoptive immunotherapy as a postoperative adjuvant therapy for hepatocellular carcinoma has been verified in randomized controlled trials and has not been associated with serious adverse reactions (1, 2).

Lentinan contains β -1,3-glucan as the principal component purified from lentinus edodes. Lentinan induces no serious adverse reactions. It was reported that the administration of lentinan in combination with tegafur is clinically efficacious in prolonging the survival time of patients with stomach cancer (3). The combination of CD3-LAK immunotherapy and

lentinan induced significant shrinkage of the lymph nodes with metastatic cancer in this case. Moreover, the shrunken lymph nodes were maintained for a long period.

Case Report

A 67-year-old woman who became aware of abdominal swelling was diagnosed with ovarian cancer (serous papillary adenocarcinoma stage IIIc) in July 2001 and underwent resection of the left ovary. She was subsequently treated with a combination of carboplatin and paclitaxel (TJ therapy) as adjuvant chemotherapy in five cycles starting in September 2001. The patient underwent hysterectomy and the dissection of the omentum and lymph nodes in February 2002. TJ therapy as an adjuvant chemotherapy was started in March 2002. A follow-up operation in August 2002 showed no recurrence of cancer, and five additional cycles of TJ therapy were administered. The patient was subsequently followed up regularly without treatment. In November 2003, the recurrence of cancer was suspected because of increased CA125 levels. Computed tomography (CT) of the chest showed swollen mediastinal lymph nodes. Positron emission tomography (PET) revealed a tumor in the lymph nodes. The patient visited our hospital to receive treatment for adoptive immunotherapy.

The first physical examination showed normal findings. Laboratory data showed that the level of serum CA125 was 101 U/ml. CT showed swollen mediastinal lymph nodes as the metastatic focus (Figure 1).

In adoptive immunotherapy, lymphocytes were collected from the patient, separated, and stimulated with interleukin-2 (IL-2) and an anti-CD3 antibody. Activated and proliferated T lymphocytes (CD3-LAK) were used for the treatment (4). CD3-LAK was administered every two weeks at a dose of 4.3×10^9 per administration on average. The treatment profile and CA125 level are shown in Figure 2.

Serum CA125 level decreased from 101 U/ml to 76.1 U/ml following the administration of CD3-LAK immunotherapy four times. The reduction rate in mediastinal lymph nodes size was 44% (Figure 1). In May 2004, serum CA125 level increased again to 84 U/ml and CT showed swelling of the right cervical

Correspondence to: Katsunada Fujimoto, MD, Fukuoka Medical Clinic, 6-18 Tenya-machi, Hakata-ku, Fukuoka, 812-0025, Japan. Tel: +81 92 281 0511, Fax: +81 92 281 0522, e-mail: fujimoto@j-immunother.com

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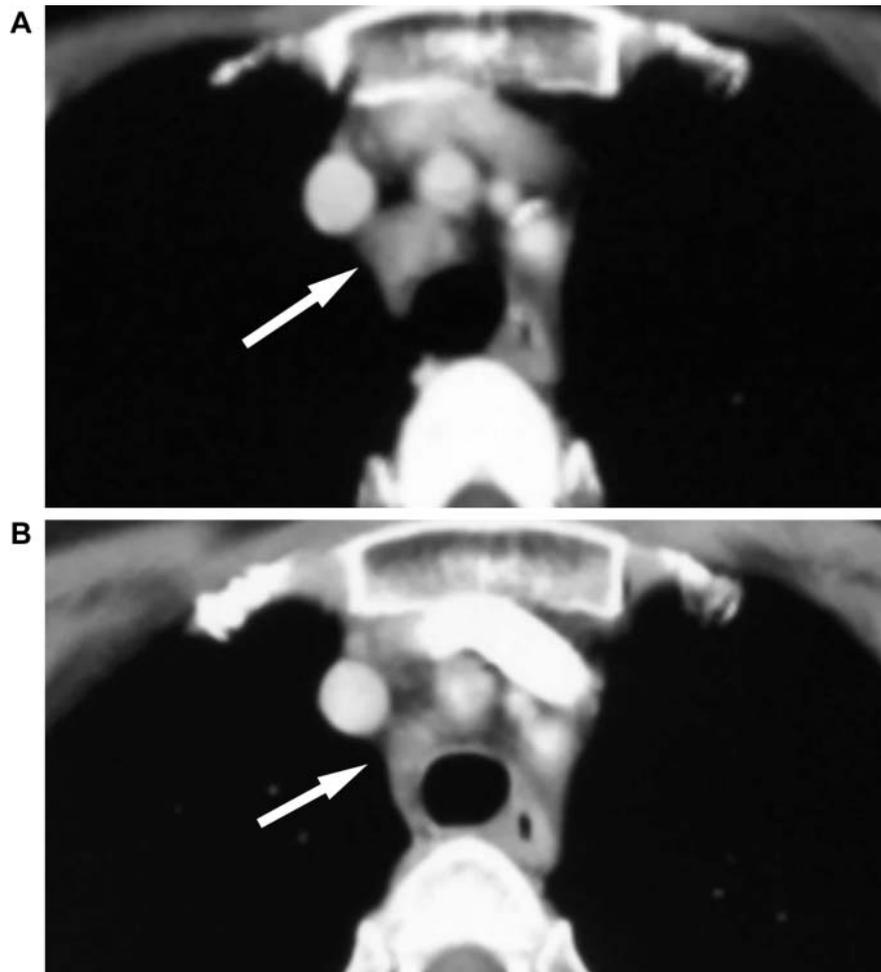


Figure 1. A. Before the administration of CD3-LAK, the swollen paratracheal lymph node was 18 mm in diameter as shown by CT (arrow). B. After the administration of CD3-LAK four times, which was effective enough to cut down the lymph node size by 44% reduction in diameter as shown by CT (arrow).

lymph nodes. The swollen lymph node was diagnosed as a metastatic lesion from ovarian cancer on the basis of biopsy findings. Serum CA125 level continued to increase to 106 U/ml; consequently, CD3-LAK immunotherapy was temporarily withdrawn after its administration 12 times. Lentinan was administered three times at a dose of 2 mg every two weeks. In August 2004, serum CA125 level decreased to 41 U/ml. CT confirmed the marked shrinkage of the lymph node, and the cervical vein compressed by the tumor was released (Figures 3-A and 3-B). The patient was later additionally administered CD3-LAK three times and lentinan seven times, and then followed up for five months. A follow-up CT showed no significant exacerbation or development of new lesions.

Discussion

The adoptive transfer of tumor-infiltrating lymphocytes to patients with epithelial ovarian cancer was reported to

enhance immunomodulation (5). Other investigators have reported that a group of patients with advanced epithelial ovarian cancer treated post-operatively with tumor-infiltrating lymphocytes showed a significantly longer disease-free period than untreated patients (6). These reports have demonstrated that adoptive immunotherapy potentially contributes to the treatment of ovarian cancer. Recent reports have further shown that CD3-LAK not only prevented post-operative recurrence but also exhibited a very low incidence of adverse reactions. The efficacy of CD3-LAK immunotherapy was thus clinically demonstrated for advanced cancer (7). In the present case, serum tumor marker level decreased with the shrinkage of mediastinal lymph nodes following the administration of CD3-LAK alone without any chemotherapy. CD3-LAK was therefore considered to be effective for the treatment of cancer that metastasized to the lymph nodes. However, metastasis to the right cervical lymph node was detected during CD3-

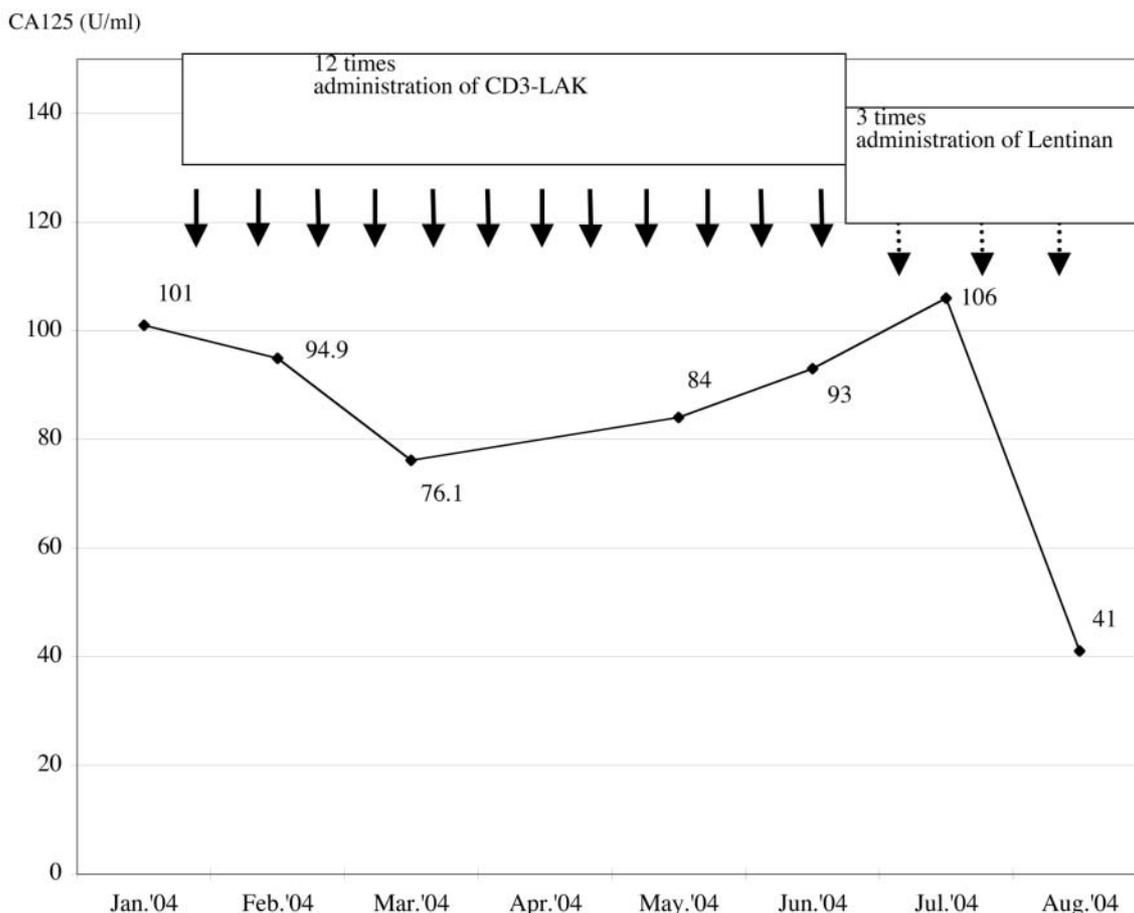


Figure 2. Clinical course. After the administration of CD3-LAK four times, serum CA125 level decreased from 101 to 76.1. Two months later, serum CA125 level increased; but it decreased again after the administration of lentinan three times.

LAK immunotherapy. Lentinan, a biological response modifier, was therefore administered to treat this metastasized cancer. Lentinan, which contains β -1,3-glucan purified from *lentinus edodes* as a major ingredient, has been reported to have an antitumor effect (8-11). It has been reported that lentinan has the immunologic action of enhancing tumor immunity by stimulating receptors on antigen-presenting cells so as to change the Th1/Th2 balance such that the Th1 level is greater than the Th2 level (12-14). In this case, the lentinan and CD3-LAK acted on cervical lymph node metastatic cancer cells by evading the immunosurveillance system.

In conclusion, the present case shows that adoptive immunotherapy and lentinan are beneficial for a patient with lymph node metastatic cancer.

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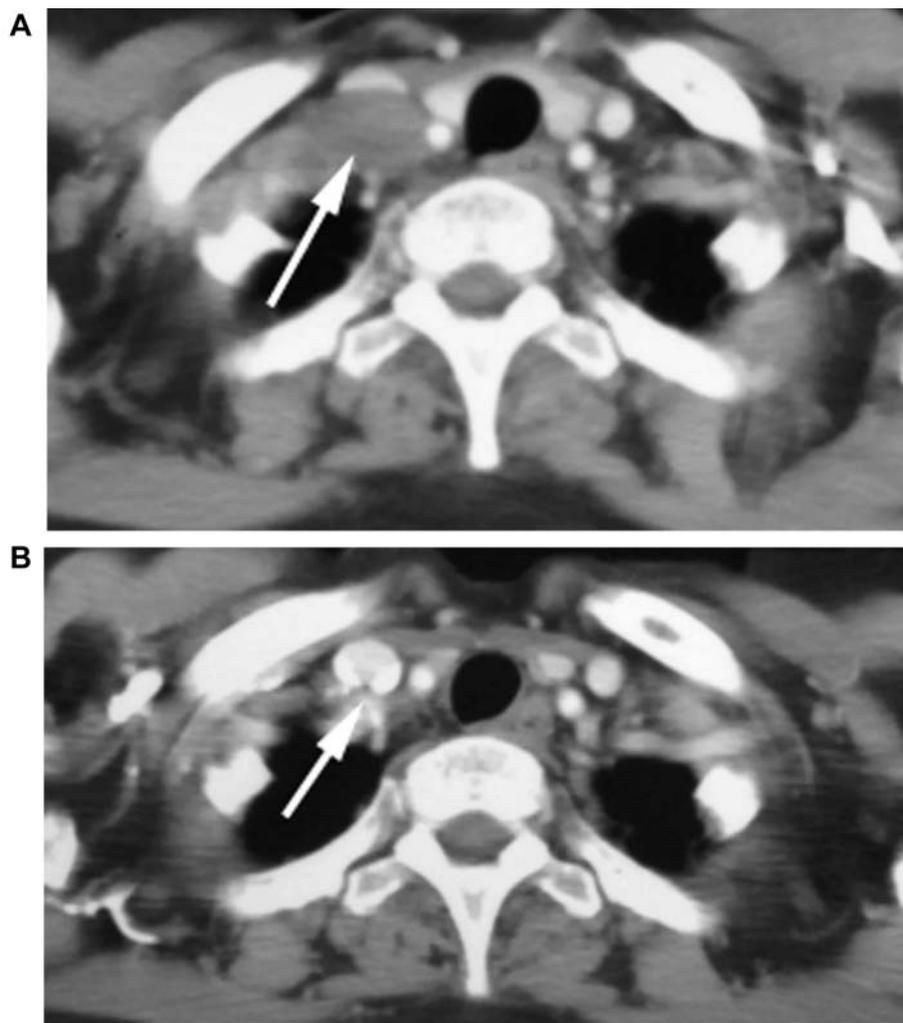


Figure 3. A. As serum CA125 level increased, the right cervical lymph node appeared swollen on a CT image (arrow). B. After the administration of lentinan three times, the right swollen cervical lymph node was not detected on a CT image (arrow).

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