Prolonged Disease-free Period in Patients with Advanced Epithelial Ovarian Cancer after Adoptive Transfer of Tumor-infiltrating Lymphocytes

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ABSTRACT

Thirteen patients with epithelial ovarian cancer, who did not show any detectable lesion after cisplatin-containing chemotherapy following primary operation, were treated with adoptive transfer of tumor-infiltrating lymphocytes (TIL group). Eleven patients with almost equivalent conditions of disease, who were treated with only chemotherapy following primary operation, served as a control group. The median time of follow-up was 36 (range, 23-48) months in the TIL group and 33 (range, 14-48) months in the control group. The estimated 3-year overall survival rate of disease-free patients in the TIL group and in the control group was 100% and 67.5%, respectively. A significant difference was noticed between the overall survival rate of the TIL group and the control group (P < 0.01). Furthermore, the estimated 3-year disease-free survival rate of the patients in the TIL group and in the control group was 82.1% and 54.5%, respectively. The disease-free survival rate of patients in the TIL group and in the control group was significantly different (P < 0.05). These results suggest that the adoptive transfer of TILs after all chemotherapy has been finished might be one promising method to achieve complete cure of advanced epithelial ovarian cancer.

INTRODUCTION

Chemotherapeutic agents have been used for over 20 years to treat cancers as a supplement to surgery and radiotherapy and can achieve cures of certain diseases, such as leukemia and lymphoma, and prolong lives of patients with ovarian cancer (1-4). However, even now, epithelial ovarian cancer with advanced condition cannot be completely overcome by the conventional treatment, and recurrence of the disease is detected in two thirds of the patients within about 3 years (1-4).

TILs are lymphoid cells generated from solid tumors by culturing single-cell suspensions with rIL-2. Rosenberg et al. reported (5) that objective regression of metastatic melanoma was observed in 11 of 20 patients treated with the adoptive transfer of TILs. In our clinical trials (6), 5 of 7 patients with epithelial ovarian cancer treated with TIL infusion alone exhibited more than a 50% decrease of tumor. This result suggests that epithelial ovarian cancer is similar to metastatic melanoma in sensitivity to TILs. However, since the duration of response obtained by TILs in single use lasts only 3-5 months, TILs can hardly improve the survival rate of patients in this manner.

In an attempt to eliminate minimal residual tumor and to improve the survival rate of patients, we treated 13 patients with epithelial ovarian cancer with the adoptive transfer of cryopreserved TILs after cisplatin-containing chemotherapy following a primary operation.

PATIENTS AND METHODS

Patients. Between April 1989 and March 1992, 43 patients with histologically documented epithelial ovarian cancer of advanced stage (International Federation of Obstetrics and Gynecology Stage II, III, or IV) were enrolled in this study. They were treated in the Department of Obstetrics and Gynecology of either Niigata University Hospital, Niigata Cancer Center, or Niigata City Hospital. Eligibility criteria were as follows: age not less than 18 years; Eastern Cooperative Oncology Group performance status of 3 or lower (able to perform minimal self-care); life expectancy more than 2 months; no chemotherapy or radiotherapy for 4 weeks prior to entry into protocol; adequate bone marrow function (WBC count >4000/mm^3; platelet count >100,000/mm^3), hepatic function (total bilirubin concentration >2.0 mg/dl), and renal function (creatinine concentration <1.5 mg/dl); and no active infection. All patients gave informed consent according to the Japanese Government Good Clinical Practice Guidelines. In 19 patients, residual tumor mass was clinically detected after completion of chemotherapy following a primary operation. These patients were excluded from this study and were treated with second-line chemotherapy. In the other 24 patients in whom no residual tumor was detected by CT scan, ultrasonogram, internal examination, and/or MRI, 11 patients whose TILs were <1 × 10^9 cells after cryopreservation or consent to receiving TILs was not obtained were considered as a control group, and the remaining...
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Clinical protocol for Fig. 1 therapy (TIL group; Fig. 1). With 100 units/ml rIL-2, the TILs were frozen and cryopreserved.

After 1 week of CD3 activation, the cells were removed to plain 6-well plates (Costar) at a density of 2 × 10^5 cells/ml in complete medium with rIL-2. After 2–3 weeks of cultivation, the number of TILs reached approximately 5 × 10^6 cells; the TILs were then frozen in 30% human AB serum with 7.5% DMSO, using a programmed freezer (Plancer Product Ltd.), and were cryopreserved in liquid nitrogen for several months. After administration, they were thawed rapidly at 37°C (with a recovery rate 70–95%), washed three times with HBSS, and cultured as described above for another 2 weeks. After 5 weeks of cultivation (3 weeks before freezing and 2 weeks after thawing), the number of cells exceeded 1 × 10^6. Just before administration of TILs, the phenotype of TILs was determined by flow cytometry and in vitro cytotoxicity of TILs was assessed by a 3-h C-FDA assay. The TILs in 100 ml sterile saline supplemented with 20 ml 25% albumin were administered i.v. to patients for 15–30 min simultaneously.

Flow Cytometry. TILs (1 × 10^6) were washed in phenol red-free HBSS containing 1% FCS and 0.2% sodium azide at 4°C, stained with an appropriate FITC-labeled mAb, incubated at 4°C for 45 min, washed twice, and resuspended in 0.5 ml medium for fluorescence-activating cell sorting analysis. The mAbs used were anti-CD3, anti-CD4, anti-CD8, anti-CD16, anti-CD25, anti-CD56, and anti-HLA-DR (Becton Dickinson Japan, Tokyo, Japan).

In Vitro Cytotoxicity. In vitro cytotoxicity of TILs was assessed by using fresh, frozen targets of autologous or allogeneic tumor cells and K562 cells. Cryopreserved tumor cells obtained by enzymatic digestion were thawed and cultured in RPMI 1640 containing 10% human AB serum for 24 h. Single-cell suspension was prepared from monolayers of viable tumor cells by brief incubation with trypsin at 37°C and washed in the medium and labeled with C-FDA (50 μg/ml diluted with RPMI 1640 medium; Sigma Chemical Co., St. Louis, MO) for 60 min at 37°C and washed three times with HBSS. The cells (5 × 10^5) were then incubated with various numbers of effector cells at 37°C for 3 h. After incubation, C-FDA in the supernatant was masked with 5 mM calf hemoglobin (Wako Pharmaceuticals, Ltd., Tokyo, Japan), and C-FDA in the surviving cells was counted with an automated fluorescence microscope photometer (Reitz Compact MT). Results were converted to percentage of cytotoxicity as follows: percentage cytotoxicity = (maximum C-FDA count − test C-FDA count)/(maximum C-FDA count − spontaneous C-FDA count). Target cells incubated in medium alone or with 2% Triton X-100 were used to determine the spontaneous and maximum C-FDA counts, respectively. All percentages were determined using triplicate measurements with three-step titrations of effector cells. The SDs of the replicates were <10%. Conversion to lytic units was performed as performed every 4 weeks. No additional therapy was performed until a recurrent lesion was detected.

Culture and Infusion of TILs. TILs were isolated from cancer tissue according to the methods described elsewhere (7). Viable cells were then counted and placed in anti-CD3-coated plates at the density of 2 × 10^6 cells/ml, with complete culture medium free from exogenous IL-2, in a humidified atmosphere containing 5% CO_2 at 37°C. The number of initially isolated viable cells from each tumor sample was 2–6 × 10^7 cells. The complete culture medium used was described elsewhere (7).

Flow Cytometry. TILs (1 × 10^6) were washed in phenol red-free HBSS containing 1% FCS and 0.2% sodium azide at 4°C, stained with an appropriate FITC-labeled mAb, incubated at 4°C for 45 min, washed twice, and resuspended in 0.5 ml medium for fluorescence-activating cell sorting analysis. The mAbs used were anti-CD3, anti-CD4, anti-CD8, anti-CD16, anti-CD25, anti-CD56, and anti-HLA-DR (Becton Dickinson Japan, Tokyo, Japan).

Fig. 1. Clinical protocol for ovarian cancer in stages II, III, and IV.

13 patients received TIL treatment after completion of chemotherapy (TIL group; Fig. 1).

Treatment Design. TILs were obtained from cancer tissues resected at a primary operation. When the number of cells reached approximately 5 × 10^6 after 2–3 weeks of cultivation with 100 units/ml rIL-2, the TILs were frozen and cryopreserved in liquid nitrogen for several months. After the primary operation, 5-fluorouracil-cyclophosphamide-Adriamycin-cisplatin or cyclophosphamide-Adriamycin-cisplatin was administered to all patients. 5-Fluorouracil-cyclophosphamide-Adriamycin-cisplatin was administered according to the following schedule: 350 mg/m^2 cyclophosphamide on day 1, 40 mg/m^2 Adriamycin on day 1, 50 mg/m^2 cisplatin on day 1, and 350 mg/m^2 5-fluorouracil as a continuous infusion on days 1–5. The cyclophosphamide-Adriamycin-cisplatin regimen excluded 5-fluorouracil administration. All patients underwent chemotherapy for three to five cycles. Internal examination, check for tumor marker in serum, and examination by ultrasonogram, CT scan, and/or MRI were performed to evaluate the effect of operation and chemotherapy. Only patients who matched the eligibility described above and did not show any detectable lesion after completion of chemotherapy following the primary operation were considered for this study. After recovery from toxicity due to the last chemotherapy cycle, the patients were given infusions of thawed TILs simultaneously. rIL-2 was used only for TIL cultivation and was not administered to the patients. After discharge, patients visited the hospital regularly for early detection of recurrence, and internal examination, check for tumor marker in serum, and examination by ultrasonogram or CT scan were performed every 4 weeks. No additional therapy was performed until a recurrent lesion was detected.

Culture and Infusion of TILs. TILs were isolated from cancer tissue according to the methods described elsewhere (7). Viable cells were then counted and placed in anti-CD3-coated plates at the density of 2 × 10^6 cells/ml, with complete culture medium free from exogenous IL-2, in a humidified atmosphere containing 5% CO_2 at 37°C. The number of initially isolated viable cells from each tumor sample was 2–6 × 10^7 cells. The complete culture medium used was described elsewhere (7).
described previously (8). One lytic unit was defined as the number of effector cells mediating 50% lysis of 5 × 10^7 target cells.

Statistical Analysis. Survival data were obtained from the day of administration of TILs until the death of patients or last contact when the patient is still alive. Survival curves and differences between survival curves were calculated using the Kaplan-Meier method.

RESULTS

Culture and Infusion of TILs. We propagated TILs with rIL-2 from freshly resected tumors of 13 patients with advanced stage ovarian cancer. In all 13 preparations, 70–95% of TILs were confirmed to be viable by the dye exclusion test when recovered from cryopreservation. After recovery from cryopreservation, no major change was observed in cell surface markers, growth rate, and cytotoxic activity. Phenotypes of the cultured TILs in the 13 patients are presented in Table 1. All rIL-2 expanded TIL cultures consisted of mainly CD3^+ T lymphocytes, and these lymphocytes were activated T lymphocytes, as judged by the expression of the HLA-DR antigen. In 9 of 13 preparations, the cells were mainly CD3^+ CD8^+ cells (CD8^+ dominant group), and in the remaining 4 preparations, TILs with CD3^+ CD4^+ cells were in excess of 50% (CD4^+ dominant group). All 13 propagated TIL preparations were tested at least once during the culture period for cytotoxic activity against a variety of target cells, including fresh autologous tumor, fresh allogeneic tumor of the same histological type, and the natural killer-sensitive K562 cultured leukemia cell line. With regard to preferential killing in this study, the cytotoxic activity was higher against autologous tumor cells compared with at least two allogeneic ovarian tumor cell types. Preferential killing of ovarian tumor cells was observed in seven of eight preparations in the CD8^+ dominant group and one of three preparations in the CD4^+ dominant group. In the preparation from patient 7, autologous tumor cells were observed in seven of eight preparations in the CD8^+ dominant group and one of three preparations in the CD4^+ dominant group. In the preparation from patient 7, cytotoxicity was low against autologous tumor cells as well as against two allogeneic tumor cell and K562 cell types. The preparations from patients 11 and 13 showed high cytotoxic activity against some allogeneic tumor cell types. The cytotoxic activity of all preparations tested against K562 cells varied (10.5–28.3 lytic units/10^7 cells); however, generally it was low compared with that against both autologous and allogeneic fresh tumor cells.

Table 1  Phenotypic flow cytometry analysis and characteristics of killing of fresh cells of cultured TILs propagated from epithelial ovarian cancer tissues

<table>
<thead>
<tr>
<th>Patient</th>
<th>CD3</th>
<th>CD4</th>
<th>CD8</th>
<th>HLA-DR</th>
<th>CD16</th>
<th>CD25</th>
<th>CD56</th>
<th>% of Positive cells</th>
<th>No. of cells injected (×10^3)</th>
<th>Killing activity (LUs/10^7 cells)</th>
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<tr>
<td>TIL cultures with CD3^+ CD4^+ cells in excess of 50% (CD4^+ dominant group)</td>
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<td></td>
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<td>3</td>
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<td>88.1</td>
<td>10.7</td>
<td>99.1</td>
<td>2.3</td>
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<td>99.4</td>
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<td>44.3</td>
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<td>2.8</td>
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<td>16.7</td>
<td>99.2</td>
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<td>9.0</td>
<td>3.5</td>
<td>16.2</td>
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</tr>
<tr>
<td>11</td>
<td>98.3</td>
<td>80.5</td>
<td>14.7</td>
<td>98.0</td>
<td>0.8</td>
<td>65.4</td>
<td>8.0</td>
<td>1.5</td>
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<td>68.3</td>
<td>92.9</td>
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<td>2</td>
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<td>68.2</td>
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<td>28.7</td>
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<td>98.0</td>
<td>7.0</td>
<td>33.9</td>
<td>9.1</td>
<td>2.0</td>
<td>104.9</td>
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<tr>
<td>12</td>
<td>99.2</td>
<td>20.4</td>
<td>82.1</td>
<td>99.9</td>
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<td>65.2</td>
<td>20.0</td>
<td>1.0</td>
<td>98.9</td>
<td>21.3</td>
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<tr>
<td>13</td>
<td>99.9</td>
<td>37.6</td>
<td>60.8</td>
<td>84.8</td>
<td>0.1</td>
<td>26.7</td>
<td>11.4</td>
<td>2.6</td>
<td>69.3</td>
<td>18.6</td>
</tr>
</tbody>
</table>

* ND, not done.
* Fresh tumor cells from patient 2.
* Fresh tumor cells from patient 5.
* Fresh tumor cells from patient 7.
* Fresh tumor cells from patient 10.
* Fresh tumor cells from patient 4.
* Fresh tumor cells from patient 8.
* Fresh tumor cells from patient 6.
* Fresh tumor cells from patient 9.
* Tumor cells from patient 11.
Adoptive Immunotherapy Using Cryopreserved IL

The ages of the patients ranged from 42 to 68 (median, 49) years. Primary tumor reduction surgery revealed that residual tumor mass remained in 9 of 13 patients in the TIL group and in 6 of 11 patients in the control group (“Residuum,” Table 4). However, by completion of cisplatin-containing chemotherapy, macroscopic residual tumor mass had entirely disappeared in these 15 patients and they were diagnosed to be free of disease by examinations such as internal examination, ultrasonography, CT scan, and/or MRI. When the cultured autologous TILs were infused into 13 patients of the TIL group, no remarkable complications such as nausea, vomiting, hepatitis, oliguria, hypotension, or respiratory distress due to increased capillary permeability and loss of intravascular fluid were observed in any patient.

**Survival Analysis.** Survival data were available for all 24 patients. The observation period ranged from 23 to 44 (average, 33.6) months in the TIL group and from 14 to 48 (average, 34.6) months in the control group. The estimated 3-year overall survival rate of disease-free patients in the TIL group and in the control group was 100% and 67.5%, respectively (Fig. 2). The difference between the overall survival rate of patients in the TIL group and that of patients in the control group was statistically significant \( P < 0.05 \). Recurrent lesions were detected in the vaginal stump of two patients from the TIL group after 22 and 32 weeks from TIL administration. Before completion of cisplatin-containing chemotherapy, nine patients in the TIL group and six patients in the control group had macroscopic residual tumor after the primary operation (“Residuum,” Table 4). For these patients, the estimated 3-year disease-free survival rate in the TIL group and in the control group was 76.2% and 33.3%, respectively (Fig. 3). The difference between the disease-free survival rate of patients in the TIL group and that of patients in the control group was statistically significant \( P < 0.05 \).

**DISCUSSION**

Although chemotherapy with the cisplatin-containing regimen is reported to be relatively effective in the treatment of epithelial ovarian cancer, the median survival rate for patients at an advanced stage is only about 2 years (4). TILs have been isolated from solid tumors by culturing single-cell suspensions with rIL-2 and shown to express specific lysis of autologous tumors (7). The administration of TILs mediates tumor regression in patients with a variety of human tumors (9); however, in...
our clinical trials, the duration of responses is limited (6). The critical point of adoptive transfer of TILs in combination with chemotherapy is to establish adequate conditions, especially with regard to timing for infusion of lymphocytes and the injection of anticancer drugs.

Recently, we reported (10) that the adoptive transfer of TILs induces immunoactivation of cellular immunity in patients, as demonstrated by delayed-type hypersensitivity to phytohemagglutinin, natural killer cytolytic activity against K562 cells, and percentages of cells bearing the CD8 antigen in peripheral blood. These findings suggest the possibility that observed tumor regression was mediated in part by the activated cellular immunity. Cisplatin-containing chemotherapy, if it is administered after adoptive transfer of TILs, interferes with the immunoactivation of cellular immunity in patients induced by TILs. Additionally, drug-resistant tumor cells often possess increased

Fig. 2 Overall survival rate of patients with ovarian cancer stage II, III, and IV who were diagnosed as having no evidence of disease after completion of chemotherapy.
immunogenicity and sensitivity to immunotherapy (11–13). We also examined the influence of cryopreservation of TILs to investigate whether TILs can be used with suitable timing in the clinical setting, since TILs could not grow and might lose cytotoxicity when the period of cultivation exceeds 3 months. No major change was noted in growth rate and in cell surface markers; slightly decreased but still valuable cytotoxic activity against autologous fresh tumor cells was recognized after recovery from cryopreservation (7). These findings, along with the results of the clinical trial of TILs (6), led us to initiate the treatment of patients with adoptive transfer of cryopreserved TILs after the completion of chemotherapy.

As shown in Table 1, TILs demonstrated preference killing of autologous tumor cells in seven of eight cultures in the CD8+ dominant group and in one of three cultures in the CD4+ dominant group. However, we considered the cytotoxicity against tumor cells to be a measure of the mixed cell activities, since (a) histocompatible cells were not targeted in our assay, we could not clarify the cell type responsible for the cytotoxicity. (b) Cultured TILs consisted of mainly CD3+CD4+ cells or CD3+CD8+ cells or mixtures of both, while substantial numbers of CD56+ or CD16+ TILs were also present in some cases. (c) Ten of 11 preparations, with the exception of preparation 7, had some cytotoxic activity against allogeneic tumor cells as well as autologous tumor cells, and several TILs could kill K562 cells in addition to autologous and allogeneic tumor cells.

A significant difference was noted between the overall survival rate of disease-free patients in the TIL group and that of patients in the control group. One of our interests was to evaluate whether adoptive transfer of TILs prolongs the disease-free survival time of patients. In this study the difference between the disease-free survival rate of patients in the TIL group and that of patients in the control group was statistically significant. It has been well documented that the degree of completion of a primary operation influences prognosis of patients with epithelial ovarian cancer of advanced stages, although the patients receive several courses of chemotherapy (14–16). In our clinical study of patients with stage III epithelial ovarian cancer, 5-year survival rate in cases with no macroscopic residual tumor was 84%, in patients with tumors <2 cm, 41%, and in patients with tumors >2 cm, 22%. In this study, no sign of recurrence was detected in four patients in the TIL group and five patients in the control group who had no residual tumor at the time of primary operation. Furthermore, when the analysis was carried out on patients with macroscopic residual tumor in primary operation, a significantly increased disease-free survival rate was observed in the TIL group, indicating that TILs can eliminate a small number of residual tumor cells which are refractory to anticancer drugs.

In a large part of the clinical trials, TILs were administered to the patients with measurable tumor mass, and tumor regression was assumed to reflect direct tumor lysis mediated by infused TILs (4, 5). However, few reports have dealt with the prognostic analysis on TIL-treated patients. This article is the first report of the survival rate of patients with epithelial ovarian cancer treated with our new protocol combined with TILs and chemotherapy.

In this study, no significant differences were observed among patients in the TIL group despite different conditions of transferred TILs, such as the ratio of CD4+:CD8+ cells, number of cells injected, and degree of killing activity against autologous tumor cells. Therefore, we could not predict the effect of TILs by their characteristics. We also estimated whether immunomodulation in patients induced by TILs influences the recurrence. One of two patients with recurrent disease that was in the TIL group showed very little change in delayed-type hypersensitivity to phytohemagglutinin and natural killer activity after transfer of TILs compared with patients with nonrecurrent disease, while in the other patient, immunoactivation was clearly induced (data not shown). An explanation for the lack of correlation between the clinical outcome and the phenotype of transfused TILs might be that infused TILs are still a mixture of a variety of cells and that many unsolved issues remain regarding the function of CD4+ and CD8+ cells and of class I and

4 K. Tanaka, unpublished data.
class II MHC-restricted cells. Since the number of patients was quite small to evaluate the correlation between immunomodulation and disease-free survival rate, further study is needed to investigate the parameter to predict effectiveness of TILs.

This study suggests that adoptive transfer of cryopreserved TILs after all chemotherapy has been finished is one feasible method to obtain favorable clinical outcomes.

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