Immunomodulation in Patients with Epithelial Ovarian Cancer after Adoptive Transfer of Tumor-infiltrating Lymphocytes

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ABSTRACT

The immunomodulation determined by natural killer cell activity, delayed-type hypersensitivity to purified protein derivative and phytohemagglutinin, and phenotypic changes of peripheral blood lymphocytes was characterized in 12 patients with epithelial ovarian cancer who received adoptive transfer of tumor-infiltrating lymphocytes (TILs) after cisplatin-containing chemotherapy (TIL group). As a control, 10 patients with epithelial ovarian cancer who did not receive infusions of TILs were also examined in the same fashion. In the TIL group, peripheral blood lymphocytes showed increased percentages of cells bearing the CD8 antigen, in contrast to stable percentages of CD4 antigen-bearing cells, resulting in a decreased ratio of CD4+ to CD8+ cells. The percentages of CD16 and CD56 antigen-bearing cells also increased in proportion to augmentation of natural killer cell activity against K562 cells. Additionally, with regard to cell-mediated immunity determined by delayed-type hypersensitivity to phytohemagglutinin and purified protein derivative, significantly and slightly enlarged erythema was observed 2 and 8 weeks, respectively, after the injection of TILs (phytohemagglutinin, P < 0.05; purified protein derivative, not statistically significant). The control group showed no major changes in any of the immunological markers. These results suggest the possibility that the adoptive transfer of TILs induces immunonivation of cellular immunity and enhances natural killer activity in patients with epithelial ovarian cancer.

INTRODUCTION

Lymphocytes infiltrating into solid tumors can be isolated surgically from both murine and human tumors and propagated in vitro with high or low concentrations of rIL-2 (1–3). The majority of TILs cultured with rIL-2 are cells (in increased number) with both cytotoxic and helper function, mainly reactive to autologous tumor cells (3–5). Animal experiments have demonstrated that TILs activated by rIL-2 have 50–100 times greater therapeutic potency than lymphokine-activated killer cells (1). In clinical trials, regression of tumors has been observed after the adoptive transfer of cultured TILs to patients with metastatic malignant melanoma, renal cell carcinoma, lung cancer, or epithelial ovarian cancer (6–10).

The potential of TILs in the therapy of human cancer has encouraged studies to optimize the effect of this treatment. One of the questions regarding TIL infusion is its possible effect of immunomodulation in patients. The antitumor effect of TIL infusion has been suggested to direct tumor cytolysis mediated by TILs concentrated in tumor sites (11, 12). However, the function of TILs used alone or in combination with systemic injection of rIL-2 is probably more complicated and may be mediated indirectly and partly by augmented immunity of patients through the secretion of cytokines, because TILs are known to secrete a number of cytokines such as γ interferon, tumor necrosis factors α and β, and rIL-2 (13–16).

In humans, issues of the specificity and identity of effector TILs for autologous tumor cells have long been controversial (3, 17–20), although in vitro experiments indicate that the specific cytolytic function of autologous tumor cells is mainly associated with CD8+ cytotoxic T-lymphocytes (3, 5, 21, 22). TILs used in adoptive immunotherapy studies consist of a variety of lymphocytes, such as CD3+ CD4+, CD3+ CD8+, CD16+, and CD56+ lymphocytes. Additionally, noncytolytic CD4+ TILs have been found in melanoma to regulate the cytolytic function of CD8+ TILs (23), and CD8+ TILs have been reported to have a helper function mediated by secretion of cytokines (13, 14). These findings suggest the possibility that infused TILs produce not only direct cytolysis to the tumor cells but also secondary effects on cytolysis of tumor cells, by augmentation of NK cell activity through cytokines secreted from TILs. The purpose of this study was to evaluate the effect of the infusion of TILs on immunological modifications, both phenotypic and functional, in 12 patients with epithelial ovarian cancer.

MATERIALS AND METHODS

Patients. Twenty-two patients with histologically documented epithelial ovarian cancer of advanced stage (International Federation of Obstetrics and Gynecology Stage II, III, or IV) were considered for this study. They were treated in either the Department of Obstetrics and Gynecology, 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 for 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/mm3; platelet count, >100,000/mm3); 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 Japanese Government Good Clinical Practice Guidance. Twelve patients received TIL treatment (TIL group), and the other 10 patients served as controls without treatment (control group).

Treatment Design. TILs were obtained from cancer tissues resected at a primary operation. When the number of cells reached approximately 5 × 10⁸ 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 were administered to all patients according to the following schedule: 350 mg/m² cyclophosphamide on day 1, 40 mg/m² Adriamycin on day 1, 50 mg/m² cisplatin on day 1, and 350 mg/m² 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. After recovery from toxicity due to the last chemotherapy cycle, the patients were given infusions of thawed TILs at one time. rIL-2 was used only for TIL cultivation and was not administered to the patients.

Culture and Infusion of TILs. TILs were isolated from cancer tissue by the methods described elsewhere (3). Viable cells were then counted and placed in anti-CD3-coated plates at the density of 2 × 10⁶ cells/ml, with
complete culture medium free from exogenous IL-2, in an humidified atmosphere containing 5% CO₂ at 37°C. The number of initially viable cells from each tumor sample was 2-6 × 10⁶ cells. The complete culture medium used was described elsewhere (3). After 1 week of CD3 activation, the cells were removed to plain 6-well plates (Coster), at a density of 2 × 10⁵ cells/ml in complete medium with rIL-2. After 2-3 weeks of cultivation, the number of TILs reached approximately 5 × 10⁶ cells; the TILs were then frozen in 30% human AB serum with 7.5% dimethylsulfoxide, using a programming freezer (Planer Products Ltd.), and were cryopreserved in liquid nitrogen for several months. For administration, they were thawed rapidly at 37°C (with a recovery rate of 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 × 10⁹. The TILs in 100 ml of sterile saline supplemented with 20 ml of 25% albumin were administered i.v. to patients for 15-30 min at one time. Twelve patients whose number of cells reached 1 × 10⁹ by the injection were selected for further investigation.

Evaluation of Immunomodulation. As shown in Fig. 1, immunomodulation of the TIL group was evaluated. Cell-mediated immunity was measured by the delayed-type hypersensitivity reaction in skin, using the s.c. injection of PHA and PPD before and 2, 8, and 16 weeks after the TIL injection. NK activity in freshly isolated peripheral blood was evaluated before and 2, 8, and 16 weeks after the injection. Likewise, phenotypic analysis of freshly isolated peripheral lymphocytes was performed using flow cytometry before and 1, 2, 4, 8, and 16 weeks after the injection. Immunomodulation of the TIL group was compared to that of the control group.

Flow Cytometry. TILs and peripheral lymphocytes (1 × 10⁹) were washed in phenol red-free HBSS, containing 1% fetal calf serum and 0.2% sodium azide, at 4°C, stained with an appropriate fluorescein isothiocyanate-labeled monoclonal antibody, incubated at 4°C for 45 min, washed twice, and resuspended in 0.5 ml of medium for FACS analysis. The monoclonal antibodies used were anti-CD3, -CD4, -CD8, -CD16, -CD25, -CD56, and -HLA-DR (Becton Dickinson Japan, Tokyo, Japan).

Skin Tests. PHA (10 μg of PHA diluted in 0.1 ml of distilled water) was applied intradermally to the medial forearm; the response was measured at 24 h and evaluated by measuring the mean of the long and short diameters of erythema. PPD (0.05 μg of PPD diluted in 0.1 ml of distilled water) was applied in the same way and the response was measured at 48 h.

In Vitro Cytotoxicity. In vitro cytotoxicity of TILs was assessed by using fresh frozen targets of autologous allogeneic tumor cells and K562 cells. NK activity of peripheral lymphocytes was assessed by using the NK cell-sensitive fresh frozen targets of autologous allogeneic tumor cells and K562 cells. NK activity of peripheral lymphocytes was assessed by using the NK cell-sensitive fresh frozen targets of autologous allogeneic tumor cells and K562 cells. NK activity of peripheral lymphocytes was assessed by using the NK cell-sensitive fresh frozen targets of autologous allogeneic tumor cells and K562 cells.

Lymphokine Secretion and Detection. Supernatants of cultured TILs just before administration and patients' sera were tested. TILs (5.0 × 10⁶ cells) initially stimulated with anti-CD3 antibody for 1 week and cultured for an additional 4 weeks (2 weeks before freeze and 2 weeks after thaw) in complete medium plus 100 IU/ml rIL-2, as described in "Culture and Infusion of TILs," were plated at 1.0 × 10⁶ cells/ml in 5-ml volume in 6-well plates (Coster). They were incubated at 37°C for 48 h and then the supernatant was aspirated, centrifuged at 1400 rpm to remove any cells, decanted, and frozen at -80°C. Sera of the patients in the TIL group were also frozen at -80°C 1 h before and 1, 2, and 5 h and 1, 3, 7, 14, 28, and 42 days after the injection of TILs. The supernatants and sera were thawed and tested in duplicate in IL-1β, IL-2, TNF-α, and IFN-γ enzyme-linked immunosorbent assays (British Bio-technology, Ltd).

Statistical Analysis. Differences in the percentages of cell phenotypes, lytic units of specific cytotoxicity, and mean diameters of erythema by skin test were determined by the Wilcoxon rank sum test.

RESULTS

Culture of TILs. From 17 patients with advanced stage epithelial ovarian cancer (International Federation of Obstetrics and Gynecology Stage II, III, or IV) who entered for the adoptive transfer of TILs, 5 preparations failed in continuous culture because of technical problems and, consequently, 12 preparations of TILs were used in this study. Lymphocytes isolated from ovarian cancer tissues were stimulated by solid-phase activation with anti-CD3 antibody for 7 days. When the number of TILs reached approximately 5 × 10⁹ cells, lymphocytes were collected, washed, and cryopreserved in liquid nitrogen for several months. When the patients had recovered from the toxicity of anticancer drugs and their bone marrow function was found to be normal, the TILs were thawed, washed, and cultured for another 2 weeks with 100 units/ml rIL-2.

In all 12 cases, 70-90% of TILs were confirmed to be viable by dye exclusion test when recovered from cryopreservation. Three-h C-FDA cytotoxic assays revealed no major change in killing activity against autologous tumor cells after the cryopreservation (data not shown). In the additional 2-week culture, TILs maintained the same proliferative property and reached 1.4-6.4 × 10⁹ cells.

To characterize the cell surface phenotype of TILs, flow cytometry was performed on cultured TILs just before injection into patients (Table 1). In 12 preparations of TILs, CD3⁺ T-lymphocytes were the dominant cell type and these lymphocytes were activated T-lymphocytes, as judged by the expression of the HLA-DR antigen. Seven preparations were TILs with CD3⁺CD8⁺ cells in excess of 50% (CD8⁺ dominant group), and the rest of the preparations were TILs with CD3⁺CD4⁺ cells in excess of 50% (CD4⁺ dominant group). To examine the cytotoxic properties of TILs, 12 preparations growing in cultures supplemented with rIL-2 were tested simultaneously in a 3-h C-FDA assay (Table 1).

With regard to preferential killing in this study, the cytotoxicity was higher against autologous tumor cells, compared with at least two allogeneic ovarian tumor cell types. Preferential killing of autologous tumor cells was observed in all seven preparations in the CD8⁺ dominant group and in two of five preparations in the CD4⁺ dominant group. In the preparation from patient 10, cytotoxicity against allogeneic fresh tumor cells from patient 7 was markedly higher than that against autologous tumor cells. In the preparation from patient 9, cytotoxicity was low against autologous tumor cells as well as against two allogeneic tumor cell types. The cytotoxic activity of all preparations of both CD8⁺ and CD8⁺ dominant groups against K562 cells was low (10.5-31.5 LUₜ₀/10⁷ cells).

Patients. In 12 cases from the TIL group (Table 2), five serous cystadenocarcinomas, four mucinous cystadenocarcinomas, two endometrioid adenocarcinomas, and one undifferentiated adenocarcinoma were included. Patients' ages ranged from 27 to 79 years, with a median of 54 years. In the control group (Table 3), three cases were
Serous cystadenocarcinoma, three endometrioid adenocarcinoma, two mucinous cystadenocarcinoma, and two clear cell adenocarcinoma.

Tumor reduction surgery revealed that macroscopic residual tumor mass remained in nine patients among 22 patients in the TIL and control groups. However, by completion of three to five courses of cisplatin or 5-fluorouracil/cyclophosphamide/Adriamycin/cisplatin, largest diameter of residual tumor was detected in only one patient (TIL group) and eight patients completed five cycles and seven patients had three or four courses. However, by completion of chemotherapy, the toxicity was severe in all patients. Fifteen patients completed five cycles and seven patients had three or four courses because of toxicity of grade 3 or 4. All patients experienced nausea and vomiting, which were generally mild to moderate in degree. All patients developed alopecia. However, within 1 month after the completion of chemotherapy the patients recovered from toxicity such as anemia, thrombocytopenia, granulocytopenia, body weight loss, and elevation of liver enzymes, and the performance status of all 22 patients was grade 0 or 1. When the cultured autologous TILs were infused into 12 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.

Because TILs were administered to patients in stage II, III, or IV, in principle, five of 10 in the control group and one of 12 in the TIL group were in stage I. However, all patients but one in the TIL group had no detectable lesion, and performance status was grade 0 or 1 in all patients. Therefore, the 10 patients were considered appropriate to serve as controls for evaluation of immunomodulation.

After discharge, patients visited the hospital regularly for early detection of recurrence, and internal examination, checks for tumor markers in serum, and examination by ultrasonogram or CT scan were performed every 4 weeks. During this experiment, neither signs of recurrence nor newly developed metastases were detected in any patient. In patient 4, a tumor mass with a hypercalcificated portion was measured by CT scan 3 days before administration of TILs. The size of the residual cancer did not show any increase on CT scan.
during 33 months of observation. Patient 11 was treated with TILs by her request, even though she had an early stage of ovarian cancer (International Federation of Obstetrics and Gynecology Stage Ia).  

Delayed-Type Hypersensitivity Response. The delayed-type hypersensitivity response of ovarian cancer patients was scored by measuring the diameter of erythema 24 h and 48 h after intradermal injection of PHA and PPD antigens, respectively (Fig. 2). In all 12 patients in the TIL group, the response to PHA antigen was significantly increased either 2 weeks (23.6 ± 5.6 mm) or 8 weeks (23.3 ± 4.4 mm) after the injection of TILs, compared to pretreatment scores (16.7 ± 4.6 mm), and this effect of hyperresponse to PHA antigen disappeared after 16 weeks (17.3 ± 3.4 mm). In both CD4+ and CD8+ dominant groups, increased response to PHA antigen was observed 2 and 8 weeks after injection (data not shown). Additionally, a similar effect was observed in the response to PPD antigen in the TIL group, but the difference between responses before and after TIL treatment was small and not statistically significant. Administration of TILs may have enhanced the response to the mitogen (PHA) that produces nonspecific proliferation of lymphocytes more strongly than the secondary response to the sensitized antigen (PPD). In the control group, activated responses to either PHA or PPD antigens were not observed.

Phenotypic Changes in Peripheral Blood Lymphocytes. Lymphocyte subsets expressing CD3, CD4, CD8, CD16, and CD56 antigens in the peripheral blood of patients in the TIL and control groups were analyzed for 16 weeks using flow cytometry (Fig. 3). In the TIL group, significant changes were observed in the percentages of CD8+ cells (P < 0.05) at 4 and 8 weeks after the TIL infusion and CD16+ cells (P < 0.05) at 4 and 8 weeks, but not CD3+ and CD4+ lymphocytes. On the other hand, no changes were seen for all subpopulations of peripheral blood lymphocytes in the control group.

Cytotoxic Activity of Peripheral Blood Lymphocytes against K562 Cells. To determine whether NK activity can be enhanced by transfused TILs, the cytotoxic activity of freshly isolated peripheral blood lymphocytes was determined by C-FDA assay, using K562 cells as target cells (Fig. 4). The cytotoxicity of peripheral blood lymphocytes was assayed before and 2, 8, and 16 weeks after TIL treatment, and increased cytolytic activity with K562 cells was observed in the TIL group. A significant difference was noted between mean cytolytic unit values (LU/k107 cells) measured before and after the infusion of TILs (before therapy, 30.2 ± 9.2 LU/k107 cells; 2 weeks later, 44.7 ± 19.5 LU/k107 cells, P < 0.05; 8 weeks later, 42.1 ± 14.0 LU/k107 cells, P < 0.05). In both the CD4+ and CD8+ dominant groups, enhanced NK activity of peripheral lymphocytes was observed. In seven patients of the TIL group the highest cytolytic activity was seen 2 weeks after the treatment and activity subsequently decreased at 8 and 16 weeks; in four patients the highest activity was observed 8 or 16 weeks after treatment. The control group showed no remarkable change.

![Table 3 Characteristics of the patients treated without adoptive transfer of cultured TILs after chemotherapy](image_url)
Cytokine Levels in Supernatants of Cultured TILs and in Patients’ Sera. The supernatants from serial experiments were assayed for IL-1β, IFN-γ, TNF-α, and TNF-β (Table 4), and cytokine secretion was confirmed, except for TNF-β (IL-1β, 13–18 pg/ml; IFN-γ, 0.6–34 IU/ml; TNF-α, 3.2–56 pg/ml). TNF-β was not detected in any of three supernatants. Cultured TILs in both CD4+ and CD8+ dominant groups secreted about the same levels of each cytokine.

Sera of seven patients in the TIL group were assayed for IL-2, IFN-γ, TNF-α, and TNF-β. IL-1β, IFN-γ, TNF-α, and TNF-β were not detected either before or after infusion of TILs. An elevated level of IL-2 (maximum, 127 pg/ml) was noticed transiently in the sera of patients 1 and 2 from 1 to 14 days after TIL treatment (Fig. 5).

DISCUSSION

Several difficulties still remain to be resolved in adoptive transfer of TILs, concerning the identification of effective subpopulations that mediate lysis of tumor cells and their correlation with clinical effects.

Fig. 3. Phenotypic changes of peripheral blood lymphocytes from patients of the TIL group (●) and the control group (○). Sequential analyses of CD3+, CD4+, CD8+, CD16+, and CD56+ subpopulations after TIL infusion are illustrated.
assay. The minimum detectable level of cytokines was as follows: IL-1, 12 pg/ml; IFN-γ, 48-h supernatants were collected and tested in duplicate by enzyme-linked immunosorbent activity of peripheral blood lymphocytes from one individual.

Patients of the TIL group (●) and the control group (○). Each line represents the lytic activity of peripheral blood lymphocytes from one individual.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>IL-1 (pg/ml)</th>
<th>IFN-γ (IU/ml)</th>
<th>TNF-α (pg/ml)</th>
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<tr>
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<td>3</td>
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<td>7</td>
<td>18</td>
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* ND, not done.

The secretion of IL-1, IFN-γ, TNF-α, and TNF-β by cultured TILs

TILs at 1 × 10⁸ cells/ml were cultured in complete medium plus 100 IU/ml IL-2. Then 48-h supernatants were collected and tested in duplicate by enzyme-linked immunosorbent assay. The minimum detectable level of cytokines was as follows: IL-1, 12 pg/ml; IFN-γ, 0.03 IU/ml; TNF-α, 7.5 pg/ml; TNF-β, 20 pg/ml.

These results support the idea that cytokines such as α, β, and γ interferon are potent stimulators of lymphocyte migration into the skin and are also major mediators of lymphocyte recruitment in delayed-type hypersensitivity reactions (31, 32).

Enhanced cell-mediated immunity, activated NK activity, and increased percentages of the CD8⁺CD16⁺CD56⁺ subpopulation were observed in both the CD4⁺ dominant group and the CD8⁺ dominant group. Explanations for the lack of correlation between the phenotype of the transfused TILs and immunoactivation of patients might be that infused TILs are still mixtures of a variety of cells and that many unresolved issues remain regarding the function of CD4⁺ and CD8⁺ cells and of class I and class II MHC-restricted cells. Additionally, no correlation was observed between the NK cell-like cytotoxicity of infused TILs and that of peripheral blood lymphocytes.

Significant increases in CD3⁺ and CD56⁺ lymphocytes were previously documented only in patients treated with both high doses of IL-2 and TILs, and not in patients treated with TILs alone (30), in contrast to our present study. However, it is difficult to compare our results with others because of differences in the histology of the tumors, methods of TIL administration, variations in TIL activation and growth such as CD3 antibody activation (33), and the usage of cryopreservation (34).

In the present study immunomodulation, especially the activation of cellular immunity, was clearly observed in TIL-treated patients. Moreover, the enhanced NK activity was seen in peripheral blood lymphocytes of TIL-treated patients, although infused TILs did not show high NK activity. The mechanism of immunoactivation is obscure; whether cytokines secreted from infused TILs activate immune response cells or whether a heterofore unsuspected immune reaction is triggered by infused TILs is presently unknown. Nevertheless, an increasing number of cytokines and immunomodulators have been found to activate the cellular immunity of patients and to enhance the cytokytic activity of cultured TILs. The prospect of immunomodulators manipulated in some way to up-regulate immune status in combination with adoptive transfer of TILs offers an attractive model for further investigation.

In an attempt to kill all of the tumor cells, we treated patients with adoptive transfer of cryopreserved TILs after cisplatin-containing chemotherapy. The status of the 12 patients with adoptive transfer of TILs was observed for 22–33 months. At present, in all of the 11 patients who did not show any detectable lesion before adoptive transfer of TILs, no lesion has yet been detected by CT scan, although in one case

![Fig. 4.](image)

Cytolytic activity against K562 cells of peripheral blood lymphocytes from patients of the TIL group (●) and the control group (○). Each line represents the lytic activity of peripheral blood lymphocytes from one individual.

![Fig. 5.](image)

IL-2 levels in sera of patients treated with adoptive transfer of cultured TILs after chemotherapy. Patients' serum samples were tested in duplicate by enzyme-linked immunosorbent assay.
the serum level of CA125, a tumor marker, has slightly increased. One patient with a lesion detected by CT scan before TIL treatment is alive, time of 26.5 months (range, 22–33 months), the 2-year survival rate is 0, and size of the lesion is unchanged, with progressive common epithelial ovarian cancer is 47–63% (34–36). There has been reported that the 2-year survival rate for patients with metastatic melanoma. J. Clin. Oncol., 10: 170–174, 1992.


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