Systemic Adoptive T-Cell Immunotherapy in Recurrent and Metastatic Carcinoma of the Head and Neck

A Phase 1 Study

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Objective: To evaluate the feasibility and toxic effects of systemic adoptive T-cell immunotherapy in patients with unresectable squamous cell carcinoma of the head and neck (SCCHN).

Design: Nonrandomized phase 1 clinical trial.

Setting: Academic tertiary care hospital.

Patients: Between April 1, 1996, and September 30, 1998, 17 patients with confirmed recurrent and metastatic SCC of the upper aerodigestive tract were enrolled. Two patients did not receive T cells because of poor vaccine response. Fifteen patients were successfully treated with T-cell immunotherapy.

Intervention: Patients were vaccinated on the thigh with irradiated autologous tumor cells admixed with granulocyte-macrophage colony-stimulating factor (GM-CSF) followed by 3 additional daily injections of GM-CSF at the vaccination site. Eight to 10 days later, tumor cell vaccine-draining inguinal lymph nodes were resected, and lymph node lymphocytes were activated with staphylococcal enterotoxin A and expanded in interleukin 2 in vitro. Resulting cultured cells were infused into patients peripherally on an outpatient basis.

Results: Toxic effects of infusion were limited to grade 2 reactions in 3 of 16 treatments. One patient required overnight hospitalization for fever and emesis. Median cell expansion was 37 times (range, 4-416 times), and median cell dose was $7.5 \times 10^9$ (range, $1.3 \times 10^8$ to $4.2 \times 10^{10}$). Infused cells were predominantly CD3+ (97%), being a mixture of CD4+ and CD8+ cells. Three patients demonstrated stabilization of previously progressive disease. Two patients experienced favorable clinical courses after adoptive T-cell transfer, including 1 patient with no evidence of disease 4 years after surgical resection of a vertebral body metastasis.

Conclusions: Adoptive immunotherapy is a technically feasible and safe treatment with low toxicity and may demonstrate therapeutic activity in patients with unresectable SCCHN.

Arch Otolaryngol Head Neck Surg. 2000;126:1225-1231

Improving survival in patients with advanced-stage squamous cell carcinoma of the head and neck (SCCHN) remains a formidable challenge. Advances in chemoradiation regimens that allow for significant improvements in organ preservation, combined with technical modifications in surgery and reconstruction, have led to improvements in patients' quality of life, but without a commensurate increase in survival. Alternative treatments to improve survival are therefore being investigated. Among various innovative approaches, immunotherapy uses the patient's own immune system to generate a defense mechanism for controlling and eradicating tumor cells.

Two forms of immunotherapy exist for the treatment of cancer: active and passive. Adoptive immunotherapy is an approach of passive immunotherapy that uses tumor-sensitized T lymphocytes. Clinically, it involves the harvest of immunologically sensitized T cells, in vitro activation and expansion of these lymphocytes, and reintroduction of these cells to the host to effect the regression of established tumors. Several clinical studies have demonstrated the ability of adoptively transferred tumor-reactive T cells to mediate the regression of established tumors. The essential determinants of efficacy include the quality, source, specificity, and number of the T lymphocytes. Initial attempts at adoptive immunotherapy for the treatment of
PATIENTS AND METHODS

PATIENTS

Patients with histologically confirmed unresectable or distant metastatic SCC of the upper aerodigestive tract were eligible for inclusion in the study. Further eligibility criteria included the following: an Eastern Cooperative Oncology Group performance status of 0 to 1, white blood cell count of greater than 2.0 × 10^9/L, platelet count of greater than 100 × 10^9/L, serum urea nitrogen level of less than 8.9 mmol/L (<25 mg/dL), creatinine level of less than 159 μmol/L (<1.8 mg/dL), aspartate aminotransferase level less than twice normal, total bilirubin level of less than 25.7 μmol/L (<1.5 mg/dL), and negative results of serologic examination for hepatitis B virus and human immunodeficiency virus. The following warranted exclusion from the study: immunotherapy within the previous 4 weeks, pregnancy, a previous severe reaction to any blood product, active and unexplained febrile illness, active collagen vascular disease or autoimmune disease, a diffusion capacity of carbon monoxide of less than 50% predicted, left ventricular ejection fraction of less than 0.45, central nervous system metastases, or history of another malignant neoplasm.

T-LYMPHOCYTE ACTIVATION AND EXPANSION

Eight to 10 days after vaccination, draining inguinal LNs were surgically removed. Lymph nodes were minced and teased apart with 20-gauge needles and pressed with the blunt end of a 10-mL plastic syringe in the presence of serum-free medium (X-VIVO 15; Biowhittaker Inc, Walkersville, Md). Finally, the mixture was filtered through nylon mesh (Nytex; Tetko Inc, Briarcliff Manor, NY) to obtain a single-cell suspension. Lymphocytes were activated in serum-free medium supplemented with 10% human AB serum at a cell concentration of 2 × 10^6/mL, 2 mL/well in 24-well plates with staphylococcal enterotoxin A (SEA) (Sigma-Aldrich Corp) at 50 ng/mL. Two days later, activated cells were centrifuged and resuspended at 1.5 × 10^6/mL to 2.5 × 10^6/mL in serum-free medium supplemented with IL-2 (60 IU/mL) (Chiron Therapeutics, Emeryville, Calif). Growth was monitored daily until cell concentration reached approximately 1 × 10^6/mL, when cultures were harvested using a cell harvester (CS 3000; Baxter, Deerfield, Ill) and resuspended in 250 to 300 mL of 0.9% sodium chloride containing 5% dextrose, 3% human albumin (Baxter), and IL-2 (60 IU/mL) for intravenous infusion. In a few cases, T cells were restimulated after initial SEA stimulation and IL-2 expansion with immobilized anti–CD3 mAb (OKT3; Ortho Biotech, Raritan, NJ). In this case, cells were suspended at 80 × 10^6 to 100 × 10^6 per 75-cm² flask for 14 hours at 37°C, followed by a second round of IL-2 expansion. Patient 5 received 2 treatments of the adoptive immunotherapy approximately 5 months apart.

FLOW CYTOMETRY

Cell suspensions obtained from LNs before and after ex vivo expansion were stained directly with conjugated human cancer involved the use of peripheral blood lymphocytes as the effector cells. Stimulation of the peripheral blood lymphocytes with high concentrations of interleukin 2 (IL-2) resulted in the generation of lymphokine-activated killer (LAK) cells, which demonstrated the ability to cause regression of a wide variety of small tumor deposits in animal models. In human studies, however, therapy with LAK cells and conjunctural systemic IL-2 resulted in a poor response rate as well as multiple organ toxic effects due to the IL-2. In contrast to the nonspecific LAK cells, lymphocytes that infiltrated into the solid tumors were hypothesized to have the immunologic specificity to that neoplasm. Indeed, tumor-infiltrating lymphocytes (TILs) were found to have major histocompatibility complex class I restricted specificity and were significantly more potent than LAK cells at treating micrometastases. However, because of the intrinsic heterogeneity and growth characteristics of TILs, it has been difficult to establish the feasibility of TILs for the clinical treatment of cancer patients.

Recent studies have focused on the tumor-reactive properties of sensitized lymph node (LN) cells. Lymphocytes from LNs draining a growing tumor are triggered to mount an initial immune response resulting in tumor-sensitized pre-effector cells that are not yet functional. These pre-effector cells, when activated in vitro with pan–T-cell reagents such as anti–CD3 monoclonal antibodies (mAbs) and expanded in medium contain-
ADAPTIVE CELL TRANSFER

Patients received oral cyclophosphamide (10 mL/kg) 1 to 2 days before cell infusion to promote homing and function of the transferred cells. In addition, patients received oral acetaminophen (650 mg) and diphenhydramine hydrochloride (25-30 mg) 30 minutes before cell transfer. Cultured lymphocytes were infused intravenously for 1 hour in the outpatient clinic. Intravenous meperidine hydrochloride (25-50 mg) was administered within 1 hour after cell infusion to alleviate nausea, vomiting, or myalgia. Patients were monitored for acute toxic effects for at least 3 hours before discharge.

TOXIC EFFECTS AND RESPONSE CRITERIA

Toxic effects were monitored according to National Cancer Institute Common Toxicity Criteria. Survival was determined as the duration between the time of cell infusion, or vaccination if no treatment was administered, and the time of last follow-up or death. For patients without detectable disease at the time of cell transfer, the occurrence of new lesions was monitored. For patients with evaluable disease, complete response was defined as disappearance of all clinical and radiographic evidence of tumor. Partial response was defined as at least a 50% decrease in the sum of the cross-sectional areas of tumors. Stable disease was defined as any change too small to quantify as partial response or progressive disease during the survival period. Progressive disease was defined as the appearance of a new lesion or an increase in cross-sectional area of a measured lesion by more than 25%.

STATISTICAL ANALYSIS

We used t test (Sigmastat; Jandel Scientific, San Rafael, Calif) to determine differences between groups for which the normality test was passed. The Mann-Whitney rank sum test was used for nonparametric analysis. Linear regression analysis was used to determine correlation between data groups.
munotherapy (Table 1). Patient 5 was vaccinated and treated twice with an interval of 5 months. Mean age at the time of transfusion was 58 years (range, 29-78 years). The cohort of treated patients consisted of 10 men and 5 women. Primary sites included the oral cavity (n=5), oropharynx (n=5), supraglottis (n=2), larynx (n=1), nasopharynx (n=1), and the oral cavity and oropharynx (n=1). Initial treatment included external beam radiotherapy for all patients in conjunction with primary surgical resection and systemic chemotherapy.

TUMOR HARVEST

From 10 consecutive patients, we obtained tumor specimens ranging from 0.5 to 6.7 g wet weight. An average yield of $10^6$ viable tumor cells was obtained per gram of tissue, with a range of $5.7 \times 10^6$ to $38.8 \times 10^6$ g. Considering the heterogeneity in quality and necrosis of surgical materials, the numbers of tumor cells obtained were quite consistent.

VACCINATION WITH TUMOR CELLS ADMIXED WITH GM-CSF

Irradiated tumor vaccine was prepared from thawed, cryopreserved tumor cells. Each vaccination site was injected with $1.5 \times 10^6$ to $54.0 \times 10^6$ irradiated (25 Gy) tumor cells. The decision to vaccinate unilaterally or bilaterally was based on the number of tumor cells available. Six patients underwent vaccination unilaterally; 8 had vaccines placed bilaterally. Patient 5 was vaccinated unilaterally for her first treatment and bilaterally for her second treatment. The vaccine sites typically developed 5 to 10 mm of induration, with a maximum of 40 to 80 mm of erythema on the fourth day. This induration and erythema likely resulted from the injection of large numbers of tumor cells with GM-CSF and cannot be interpreted as a typical delayed-type hypersensitivity (DTH) skin reaction. In fact, the standard DTH skin test was performed with intradermal injections of $1 \times 10^6$ irradiated tumor cells before vaccination in patients 1 through 10. At 48 hours after this vaccination, no evidence of DTH was observed in any patient tested. Despite variations in the tumor cell dose, no adverse reactions, such as ulceration, pain, or evidence of tumor growth, resulted at the vaccination site.

LN HARVEST AND CELL CULTURE

Palpably enlarged tumor cell vaccine-draining inguinal LNs were harvested surgically 9 to 11 days after vaccination and processed mechanically under sterile conditions, giving a single-cell suspension. The median number of LN lymphocytes harvested was $10^6$ (range, $25 \times 10^6$ to $600 \times 10^6$). There was no correlation between the numbers of tumor cells used for vaccination and numbers of LN cells harvested ($P = .69$). Cell growth patterns are depicted in the Figure. Median proliferation of LN cells in vitro after initial SEA/IL-2 activation was 37 times (range, 4-416 times) over a mean culture duration of 13 days (range, 8-31 days). Flow cytometric analysis of LN cells before and after in vitro activation and expansion revealed that, although fresh LN cells contained a mean of 54% T cells, 97% to 100% of cultured cells were T lymphocytes. This result demonstrates the selective promotion of T-cell growth provided by the culture system. Before culture, a mean of 75% (range, 67%-79%) of T cells showed positive re-

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*LN indicates lymph node; PD, progressive disease; SD, stable disease; NED, no evidence of disease; and NA, not applicable.
†Cells underwent 2 cycles of activation and expansion during culture.
‡Patient underwent 2 cycles of vaccinations, LN resections, and adoptive immunotherapy.
§See “Patient 10” subsection of “Results” section.
†Indicates survival from time of vaccination.
results of staining for CD4, compared with only 52% (range, 19%-92%) of T cells after culture. This trend was reversed for CD8+ cells, the proportion of which went from a mean of 14% (range, 9%-23%) before culture to 43% (range, 14%-80%) after culture.

TOXIC EFFECTS

Toxic effects were minimal after T-cell transfer. One patient experienced chills the night of infusion that resolved spontaneously (patient 8); in another, fever and chills developed that responded to oral acetaminophen (patient 14); and a third patient had fever and emesis that persisted for 30 hours, necessitating overnight hospitalization (patient 9). All of these adverse effects represent grade 1 to 2 toxic effects. Toxic effects in patients did not correlate with the number of T cells administered ($P = .98$). No grade 3 to 4 reactions were observed.

CLINICAL OUTCOME

There was no relationship between survival duration and the number of lymphocytes infused ($P = .94$). Ten patients experienced progressive disease after cell infusion, with a median survival of 6 months and a mean of 7.7 months (range, 2-19 months) from the time of infusion (Table 2). Three patients demonstrated stabilization of previously progressive disease, with a median survival of 15 months and a mean of 22 months (range, 14-36 months). Two patients experienced better-than-expected clinical courses. Patient 6 is alive with no evidence of disease (NED) 48 months postinfusion, while patient 10 is alive with NED at the primary site and lungs 35 months after treatment. Although the purpose of this phase 1 study is not to seek clinical responses, and although the responses we observed may be anecdotal, they are intriguing.

Patient 6

Patient 6 is a 42-year-old man treated in June 1995 at an outside hospital for a T2 N0 M0 SCC of the left base of the tongue with 72-Gy external beam radiation. After a biopsy-proven recurrence discovered September 1995, the patient underwent a distant metastatic workup with negative results in preparation for salvage surgery. In October 1995, a total glossectomy, total laryngectomy, left mandibulectomy, oropharyngeal resection, and left modified radical neck dissection preserving the spinal accessory nerve. Pulmonary metastases were noted on chest x-ray film May 1997, which were addressed with multiple wedge resections. In August 1997, the patient was vaccinated with 11.7 x 10^6 irradiated tumor cells and GM-CSF. Enlarged inguinal LNs were harvested 6 days later. He received 2.8 x 10^10 activated and expanded lymphocytes in September 1997, with no adverse effects. His status remained NED until November 1998, when routine evaluation revealed a left midcervical mass and a 1.3-cm paratracheal mass without central necrosis. Biopsy of the midcervical mass revealed recurrent SCC, necessitating a radical neck dissection with deltopectoral flap reconstruction performed in January 1999. A follow-up computed tomographic scan of the chest obtained in November 1999 demonstrated growth of the right paratracheal mass to 2.1 cm without central necrosis. Biopsy was refused. The patient remains asymptomatic and otherwise has NED in the primary site and lungs 35 months after cell infusion.

Patient 10

Patient 10 is a 58-year-old man who received a diagnosis April 1993 of T2 N2c M0 SCC of the right tongue base. Initial treatment included 2 courses of chemotherapy (cisplatin and fluorouracil) and 70-Gy external beam radiation, followed by a planned right modified radical neck dissection preserving the spinal accessory nerve. Pulmonary metastases were noted on chest x-ray film May 1997, which were addressed with multiple wedge resections. In August 1997, the patient was vaccinated with 11.7 x 10^6 irradiated tumor cells and GM-CSF. Enlarged inguinal LNs were harvested 6 days later. He received 2.8 x 10^10 activated and expanded lymphocytes in September 1997, with no adverse effects. His status remained NED until November 1998, when routine evaluation revealed a left midcervical mass and a 1.3-cm paratracheal mass without central necrosis. Biopsy of the midcervical mass revealed recurrent SCC, necessitating a radical neck dissection with deltopectoral flap reconstruction performed in January 1999. A follow-up computed tomographic scan of the chest obtained in November 1999 demonstrated growth of the right paratracheal mass to 2.1 cm without central necrosis. Biopsy was refused. The patient remains asymptomatic and otherwise has NED in the primary site and lungs 35 months after cell infusion.

COMMENT

Patients with advanced HNSCC reportedly exhibit depressed cell-mediated immune function. Previous attempts at immunotherapy have therefore focused on the up-regulation of general immune function using...
nonspecific immune stimulants such as bacillus Calmette-Guérin (BCG) vaccine, Corynebacterium parvum, IL-2, and interferons alpha and gamma (IFN-alpha and IFN-gamma).

Bacillus Calmette-Guérin is an attenuated strain of tuberculous bacillus initially used to vaccinate against tuberculosis. Several trials of BCG vaccine in conjunction with chemotherapy in the management of advanced HNSCC have been attempted since 1972, with mixed results. However, as severe toxic effects were experienced by 5% of patients receiving BCG, the benefit of this treatment remains controversial. The use of C parvum, a powerful macrophage stimulant, with methotrexate chemotherapy did not improve survival or response when compared with methotrexate alone. In contrast, IL-2 works by enhancing the cytotoxic function of lymphocytes, promoting the production of LAK cells. Lymphokine-activated killer cells have demonstrated in vitro antitumor properties. Incorporation of IL-2 in HNSCC immunotherapy protocols, alone and in combination with IFN-alpha, has met with some success. Unfortunately, the regimens of high-dose IL-2 result in grade 3 or 4 adverse effects to nearly every organ system, including vascular leak syndrome. Interferon gamma, which promotes cellular immunity, has shown some promise in limited trials.

Previous attempts to treat patients with adoptive immunotherapy using LAK cells or TILs have always included systemic IL-2 to improve function and survival of the transferred cells in vitro. However, in preclinical studies, we have found that the benefits of systemic IL-2 administration appear to be site specific; although IL-2 improved host response against pulmonary metastases, it decreased efficacy of adoptive immunotherapy for intracranial tumors. More important, our preclinical animal studies clearly demonstrated that the transfer of activated LN cells alone could mediate potent antitumor effects. Thus, IL-2 was not administered to patients treated in a recent clinical trial of adoptive immunotherapy for glioblastoma multiforme and renal cell carcinoma. With the omission of systemic IL-2, no grade 3 or 4 reactions were observed.

The main goal of the phase 1 clinical trial is to establish the feasibility of procedures and to define the adverse effects of the treatment. Toxic effects associated with vaccination, LN harvest, and lymphocyte infusion were minimal, with 3 grade 1 reactions during 16 infusions (patient 5 received 2 treatments). All treatment was performed on an outpatient basis. However, one patient was admitted overnight for fever and chills. The lack of toxic effects likely was related to the omission of concurrent systemic IL-2 infusion. This also indicates that the transfusion of autologous activated T lymphocytes is well tolerated.

It is likely that the lack of response to therapy in most patients is indicative of the overwhelming disease at the time of immunization and cell infusion. However, 2 patients survived longer than anticipated after adoptive immunotherapy. It is difficult to quantify the response in a conventional manner, as these patients underwent resection of metastases (lung and spinal cord), so radiologic regression of tumor could not be observed. Historically, we would have expected patient death within 5 to 6 months.

Ideally, in vitro functional and immunologic characteristics of T cells generated for the adoptive immunotherapy would provide a secondary end point to correlate and predict clinical outcomes. However, there have been no documented examples illustrating the validity of particular in vitro assays that are consistently associated with clinical responses. Recent studies in the active immunotherapy of metastatic melanoma with several defined, HLA class I restricted cytotoxic T-cell peptides have analyzed immunologic responses of vaccinated patients. By assaying the IFN-gamma production of patients’ CD8 T cells stimulated in vitro with corresponding peptides or by enumerating peptide-specific T-cell precursor frequency using HLA/peptide tetramers, it was clear that vaccination resulted in increased melanoma antigen-specific responses. However, such responses did not correlate with clinically evident regression of tumors. In fact, clinical responses appeared to have an inverse correlation with the quantifiable T-cell-specific immune response. These conclusions were made based on a significant clinical response rate, which is not the case in the present study. In addition, the number of tumor cells used for vaccination had no bearing on the size of the lymphocyte harvest, and the number of T cells infused during treatment did not affect patient survival. These observations are likely caused by the wide variability in patient factors secondary to the nature of a phase 1 study. More importantly, we demonstrated the feasibility and lack of toxicity of adoptive immunotherapy in the treatment of SCCHN. In response to these results, we have initiated a phase 2 study to evaluate the therapeutic efficacy of adoptive immunotherapy in the treatment of patients with advanced neck disease. These patients will have undergone complete resection of the cancer but will be at high risk for locoregional or systemic relapse. We hope that the adjuvant use of systemic adoptive immunotherapy will result in a decreased rate of relapse after complete resection, and thus improve patient survival.

Accepted for publication April 11, 2000.

Presented at the 1999 Annual Meeting of the American Head and Neck Society, Palm Desert, Calif, April 24, 1999.

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REFERENCES


