Objective Regressions of T- and B-Cell Lymphomas in Patients following Treatment with Anti-Thymocyte Globulin

Richard I. Fisher,1 Bruce A. Silver, Christian P. Vanhaelen, Elaine S. Jaffe, and Jeffrey Cossman

ABSTRACT

We have conducted a clinical trial utilizing anti-thymocyte globulin (ATG) for the treatment of patients with non-Hodgkin's lymphomas. Six patients were treated; 50% reductions in tumor mass of short duration were observed in one patient with a T-cell lymphoma and two patients with B-cell lymphomas. In vitro assays have been performed in an attempt to study the reactivity and potential mechanism of antitumor action of the ATG. The ATG bound to essentially all normal blood mononuclear leukocytes as well as tumor cells from patients with T-, B-, or null cell lymphomas demonstrating its lack of specificity. Furthermore, complement-mediated lysis of normal mononuclear leukocytes, normal T- or B-cells, and tumor cells from two unresponsive patients were all comparable; moreover, since this lysis occurred only at concentrations of ATG that are not attainable in vivo, it is unlikely that complement-mediated cytolototoxicity accounts for the responses observed. Peripheral blood lymphocyte counts and total erythrocyte rosettes did decrease during ATG treatment. Thus, objective tumor responses in both B- and T-cell non-Hodgkin’s lymphomas can be achieved with a very nonspecific antiserum although significant toxicity resulted. Whether the magnitude or duration of response can be increased with monoclonal antibodies remains to be determined. Future success with serotherapy might require use of either a battery of different monoclonal antibodies or a single monoclonal antibody that can deliver radioisotopes, chemotherapy, or toxins to the tumor cells.

INTRODUCTION

Several investigators have documented the occurrence of objective tumor regressions in patients with Sézary syndrome who were treated with ATG2 (1, 7, 8). The ATG used in the studies from this country has been utilized extensively in the prevention of allograft rejections following renal transplantation (5). However, the specificity and mechanism of action of this antiserum have not been well characterized. To date, there are no reports of ATG administration in an attempt to treat patients with other more common forms of non-Hodgkin’s lymphomas. Indeed, the therapeutic usefulness of this form of treatment still remains undefined.

In this report, we present the results of a study of the therapeutic value of ATG for widespread non-Hodgkin’s lymphomas that are refractory to combination chemotherapy. Attempts have been made to classify the specificity and mechanism of action of the ATG towards normal lymphocyte subpopulations as well as the patients’ own tumor cells.

MATERIALS AND METHODS

ATG. ATG (ATGAM) was kindly provided by the Upjohn Co., Kalamazoo, Mich. ATG is the IgG fraction isolated from the plasma of horses that have been immunized with human thymocytes. The ATG has been absorbed with human plasma and RBC stroma.

Preparation of Cell Suspensions. Peripheral blood MNL were isolated from heparinized blood by centrifugation over Ficoll-Hypaque (Lymphoprep; Litton Bionetics, Kensington, Md.) as described previously (3). Single-cell suspensions from lymph nodes involved by lymphomas were prepared immediately following surgery. Cell surface markers were determined immediately, or the cells were cryopreserved over liquid nitrogen. Immunological markers were not altered by the freezing or thawing process (4).

Immunotyping of Neoplastic Cells. Surface membrane immunoglobulin was detected by direct immunofluorescence using individual heavy- and light-chain specific antibodies as well as polyvalent anti-immunoglobulin antibodies as described previously (6). The B-cell lymphomas expressed only one light-chain isotype, or the neoplastic cells were uniformly stained by the polyvalent antibody.

T-Cells were identified by their ability to form rosettes with sheep erythrocytes which had been treated with amonethylisothiouronium (9). The percentage of the cell suspension forming rosettes was initially determined. The cell suspension was then cytacentrifuged, placed on slides, and stained with a modified Wright’s stain. Lymphomas were considered to be composed of T-cells when the morphologically abnormal lymphoid cells on the cytacentrifuge preparations demonstrated erythrocyte rosette formation. The cell suspensions also contained variable numbers of surface immunoglobulin-positive normal-appearing lymphocytes that expressed both κ and λ light chains. All cases were also studied for intranuclear terminal deoxynucleotidyl transferase by indirect immunofluorescence using an anti-terminal deoxynucleotidyl transferase antibody (provided by Dr. Frederick Bollum, Uniformed Services University for the Health Sciences, Bethesda, Md.) (2). Terminal deoxynucleotidyl transferase activity was identified only in lymphomas of the lymphoblastic type.

Separation of T- and B-Cells. T- and B-cells were separated from peripheral blood MNL by modification of the method of Dean et al. (6). In brief, unfractionated peripheral blood MNL were incubated with neuraminidase-treated sheep RBC at 4°C. The erythrocyte-rosetting T-cell fraction was separated from the non-T-cell fraction by centrifugation over Ficoll-Hypaque. Both T- and non-T-cell fractions were then subjected to a second erythrocyte rosette procedure with separation over Ficoll-Hypaque. Sheep RBC were lysed by brief exposure to a hypotonic lysing buffer. Lymphocytes that twice formed rosettes with sheep RBC comprise our T-cell population; cells that were erythrocyte rosette negative in both separations, i.e., non-T-cells, are referred to as our B-cell population even though they contain B-cells, monocytes, and null cells. In our laboratory, the T-cell fractions obtained in this manner contain 94.3 ± 0.74% (S.E.) erythrocyte rosetting cells and 1.0 ± 0.4% B-cells as determined by immunofluorescence with a
with non-Hodgkin's lymphomas was conducted. All patients had been well. The plates were mixed for 10 sec on a Microshaker (Cooke informed consent prior to treatment. Whenever possible, patients treated previously with and were refractory to combination chemother 
apy. All patients had measurable disease. Whenever possible, patients had lymph node biopsies prior to ATG treatment in order to obtain tumor cells for immunological cell surface markers and for in vitro 
with FACS II (Becton Dickinson Electronics Laboratory, Sunnyvale, Calif.). 
Compartment-dependent Antibody Cytotoxicity. Complement-de 
dependent cytotoxicity of the ATG against normal peripheral blood MNL, T-cells, B-cells, and patients' tumor cells was assayed by modification of the method of Sachs (13). Briefly, 2 x 10^7 lymphocytes or tumor cells were suspended in Roswell Park Memorial Institute Tissue Culture Medium 1640 with 10% heat inactivated AB serum and 0.3 ml of radioactive sodium chromate (Amersham Corp., Arlington Heights, Ill.) (specific activity, 1 mCi/ml) for 1 hr at 37° and then washed twice. During this time, ATG at the desired maximal concentration was added to the appropriate wells of a 96-well U-bottom microtiter plate (Cooke Laboratory Products, Alexandria, Va.); serial 1:2 dilutions filled the remainder of the experimental wells. No antibody was added to wells that would be used to determine background or maximum chromium release. Fifty thousand 51Cr-labeled target cells were added to every well. The plates were mixed for 10 sec on a Microshaker (Cooke Laboratories) and incubated for 15 min at 37°. Each well was diluted with medium, the plates were centrifuged, and the supernatants were briskly poured off. A 1:2 dilution of guinea pig complement was added to each well except those to be used for determination of maximum lysis or medium background. Maximum release of chromium was determined by adding 5% Triton X-100 to the appropriate wells. The plates were shaken to resuspend the target cells and incubated for 30 min at 37°. Each well was again diluted with medium, the plates were centrifuged, and the supernatants were collected with a Titertek supernatant collection system (Flow Laboratories, Inc., Rockville, Md.). The cells it was 70.5%. Thus, the ATG appears not only to bind to 
lesions was considered a partial responder, while any patient with a response of lesser magnitude was considered a nonresponder. Each patient received 14 doses of ATG unless rapidly progressive lymphoma 
developed. Patients who did not develop progressive disease were retreated with ATG for 7 consecutive days at monthly intervals.

RESULTS

Binding of ATG to Normal MNL. The ability of the ATG to bind to normal peripheral blood MNL was assayed using indirect immunofluorescence and FACS II. Preliminary experiments demonstrated that a 1:10 dilution of ATG and a 1:16 dilution of the fluorescein-conjugated goat anti-horse immunoglobulin gave optimal staining. As shown in Chart 1, ATG bound to 96% of normal MNL. Background staining was less than 2%. Subsequent studies revealed that the percentage of cells bound with ATG did not differ among the various batch preparations of ATG that were used in this trial.

Complement-dependent Antibody Cytotoxicity of Normal 

Clinical Studies. The characteristics of the 6 patients who treated with ATG were summarized in Table 2. All patients had diffuse forms of non-Hodgkin’s lymphomas, had visceral spread of their disease, and had been treated extensively with several combination chemotherapy regimens. All patients were severely debilitated at the initiation of ATG therapy. Three of

Clinical Treatment Protocol. A study of ATG treatment for patients with non-Hodgkin’s lymphomas was conducted. All patients had been treated previously with and were refractory to combination chemotherapy. All patients had measurable disease. Whenever possible, patients had lymph node biopsies prior to ATG treatment in order to obtain tumor cells for immunological cell surface markers and for in vitro studies of the mechanism of action of ATG. All patients gave written informed consent prior to treatment. Each patient was initially tested for preexisting sensitization to ATG by an i.d. injection of 0.1 ml of a 1:1000 dilution of ATG. If a patient did not develop any evidence of hypersensitivity with the test dose, treatment with ATG was begun. ATG was administered via a central i.v. catheter in 500 ml 0.9% NaCl solution over 4 to 6 hr. A planned treatment course consisted of 15 mg ATG per kg daily for 14 days. Premedication with 25 mg hydrocortisone and 100 mg hydrocorti 
sone was permitted before each subsequent dose in order to ameliorate the constitutional toxicity of the ATG. Patient response to therapy was evaluated at the end of the 2-week course. Any patient in whom there was a 50% decrease in the product of the diameters of measurable
The patients had T-cell lymphomas, 2 had B-cell lymphomas, and the neoplastic cells from one patient had no detectable cell surface markers, i.e., a null cell lymphoma.

The clinical course of Patient 1 has been described previously in detail (8). In brief, Patient 1 developed a 75% reduction in the size of all lymph nodes with clearing of skin erythema following 1 week of ATG treatment. He had profound thrombocytopenia (platelet count, 1000/cu mm) from previous chemotherapy when ATG therapy was started and he died on Day 8 of an i.c. hemorrhage. Patient 2 had rapidly progressive lymphoma at the initiation of ATG therapy and received only 3 daily doses of ATG in a 30-day period because of septic episodes. He died from progressive tumor on Day 30. Patient 3 had greater than a 50% reduction in the size of her neck nodes that persisted for 6 weeks. This patient was retreated with ATG without clinical improvement. He died 1 year later of disseminated lymphoma. The lymphoma of Patient 5 grew progressively during ATG treatment requiring cessation of treatment on Day 13 and she died 1 month later. Patient 6 developed an increasing number of blast cells in the peripheral blood and the bone marrow on Day 10 and died 1 month later with progressive lymphoma. Thus, of the 6 patients treated with ATG, one patient with T-cell lymphoma and 2 with B-cell lymphomas had objective tumor regressions of short duration. Two patient with T-cell lymphomas and one patient with a null cell lymphoma did not respond to ATG therapy.

Toxicity from ATG. Because these patients had such advanced disease at the time of treatment, it is difficult to know precisely whether a given toxicity is the direct result of ATG or rather a complication of the underlying illness. However, all but one patient developed fever and chills during the course of the infusion that required premedication with diphenhydramine and hydrocortisone as described previously. Three patients developed skin rashes with an urticarial appearance. None of the skin rashes were associated with any signs of a systemic anaphylactic reaction, nor did the rash prevent completion of treatment. The major dose limiting toxicity was thrombocytopenia. All patients developed platelet counts of <100,000/cu mm which persisted for the duration of the therapy as shown in Table 3. When the platelet count fell below 50,000/cu mm, ATG therapy was postponed until the platelet count increased. In cases where the thrombocytopenia was due to bone marrow infiltration by the underlying disease, therapy was continued cautiously. No patient developed clinically significant renal impairment. One patient had transient hematuria and another proteinuria, but neither one developed azotemia. Patient 1 did develop a blood urea nitrogen of 50 mg/100 ml and a creatinine of 1.6 mg/100 ml following a hypotensive episode caused by gastrointestinal hemorrhage and bacterial sepsis. At autopsy, there was no evidence of glomerulonephritis. Finally,

### Table 1

<table>
<thead>
<tr>
<th>ATG dilution</th>
<th>% of lysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:10</td>
<td>67.5 ± 5.6</td>
</tr>
<tr>
<td>1:20</td>
<td>68.2 ± 4.6</td>
</tr>
<tr>
<td>1:40</td>
<td>42.8 ± 2.4</td>
</tr>
<tr>
<td>1:80</td>
<td>32.8 ± 2.6</td>
</tr>
<tr>
<td>1:160</td>
<td>22.4 ± 1.2</td>
</tr>
<tr>
<td>1:320</td>
<td>23.0 ± 3.0</td>
</tr>
<tr>
<td>No ATG (complement control)</td>
<td>12.8 ± 0.8</td>
</tr>
</tbody>
</table>

* Mean ± S.E. for the percentage of maximum chromium release observed in normal peripheral blood MNL by ATG.

### Table 2

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Histological diagnosis</th>
<th>Stage</th>
<th>Tumor sites</th>
<th>Immuno-logical phenotype</th>
<th>Prior therapy</th>
<th>ATG dose</th>
<th>Response duration</th>
<th>Survival after ATG</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63</td>
<td>M</td>
<td>Sezary syndrome, DUL*</td>
<td>IVA</td>
<td>Nodes, skin</td>
<td>T-Cell</td>
<td>Topical steroids, electron beam, BACOP, POMP, VP-16</td>
<td>5,775 mg in 7 days</td>
<td>PR (75% regression) for 8 days</td>
<td>Dead on Day 8</td>
<td>i.c. hemorrhage</td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td>M</td>
<td>DHL</td>
<td>IVB</td>
<td>Nodes, pancreas</td>
<td>T-Cell</td>
<td>ProMACE, MOPP, RT</td>
<td>2,790 mg in 3 days</td>
<td>PD</td>
<td>Dead on Day 30</td>
<td>Progressive lymphoma</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>F</td>
<td>DHL</td>
<td>IVA</td>
<td>Nodes, liver</td>
<td>B-Cell</td>
<td>ProMACE, MOPP</td>
<td>14,000 mg in 14 days</td>
<td>PR (50% regression) for 2 wk</td>
<td>Dead in 1 yr</td>
<td>Progressive lymphoma</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>M</td>
<td>DIL</td>
<td>IVA</td>
<td>Nodes, marrow, blood</td>
<td>B-Cell</td>
<td>CVP, bleomycin + Adriamycin</td>
<td>18,100 mg in 14 days</td>
<td>PR (50% regression) for 6 wk</td>
<td>Dead in 1 mo</td>
<td>Progressive lymphoma</td>
</tr>
<tr>
<td>5</td>
<td>38</td>
<td>F</td>
<td>DHL</td>
<td>IVB</td>
<td>Nodes, soft tissue, pleura, breast</td>
<td>Null cell</td>
<td>ProMACE, MOPP, RT</td>
<td>9,750 mg in 13 days</td>
<td>PD</td>
<td>Dead in 1 mo</td>
<td>Progressive lymphoma</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>M</td>
<td>Lymphoblastic lymphoma</td>
<td>IVA</td>
<td>Nodes, marrow, blood</td>
<td>T-Cell</td>
<td>ProMACE, MOPP, vincristine + daunomycin + L-asparaginase</td>
<td>8,550 mg in 10 days</td>
<td>PD</td>
<td>Dead in 1 mo</td>
<td>Progressive lymphoma</td>
</tr>
</tbody>
</table>

* DUL, diffuse undifferentiated lymphoma; DHL, diffuse histiocytic lymphoma; DIL, diffuse intermediate lymphoma; BACOP, bleomycin, Adriamycin, cyclophosphamide, vincristine, prednisone; POMP, prednisone, vincristine, 6-mercaptopurine, methotrexate; ProMACE, prednisone, vincristine, methotrexate, Adriamycin, cyclophosphamide, VP-16; MOPP, mechloethamine, vincristine, prednisone, procarbazine; RT, radiotherapy; CVP, cyclophosphamide, vincristine, prednisone; PR, partial response; PD, progressive disease.
This paper presents the results of a study of ATG for the treatment of non-Hodgkin’s lymphomas. The 6 patients all had widely disseminated disease that was refractory to treatment with multiple chemotherapeutic agents and was progressing rapidly prior to ATG treatment. Indeed, 4 of the 6 patients died within 1 month following ATG treatment and the other 2 patients died from widespread lymphoma at 5 and 12 months, respectively. One of the 3 T-cell lymphoma patients and both of the B-cell lymphoma patients had objective responses to ATG therapy. The responses were of short duration ranging from 1 to 6 weeks. Although each of the patients had also received modest doses of corticosteroids in an attempt to ameliorate the constitutional effects of the ATG, the objective responses can be attributed to the ATG treatment since all patients had previously proven refractory to significantly higher doses of steroids.

In addition to our previously described response of a T-cell lymphoma (Patient 1) (8), 2 other investigators have reported objective responses of T-cell lymphomas following ATG treatment (1, 7). In each case, the patients had disease classified pathologically as being part of the Sézary-mycosis fungoides spectrum. To date, there are no reports of ATG therapeutic trials in the more common forms of non-Hodgkin’s lymphomas, i.e., B-cell tumors.

The ATG used in this study has been used extensively in the prevention of allograft rejection following renal transplantation (5). However, the specificity and mechanism of action of the antisera have not been well defined. We observed that the ATG bound to 96% of lymph node cells from Patients 2 and 6, respectively. Both patients had T-cell lymphomas that failed to respond to ATG treatment. ATG also bound to 99% of lymph node cells from the null cell lymphoma that was also unresponsive to ATG (Chart 2). Finally, 99% of cells from Patient 4, a B-cell tumor that regressed with ATG treatment, also bound the ATG.

The remaining cells from the lymph nodes of the 2 T-cell lymphoma patients who failed to respond to ATG were also studied in the complement-dependent antibody cytotoxicity assay to determine whether the ATG could lyse the cells. Maximum lysis was again obtained at a 1:10 to 1:20 dilution of ATG. At these dilutions, 80% of the cells were killed in each case.

**DISCUSSION**

This paper presents the results of a study of ATG for the treatment of non-Hodgkin’s lymphomas. The 6 patients all had widely disseminated disease that was refractory to treatment with multiple chemotherapeutic agents and was progressing dramatically.

In 4 patients, a limited number of cells were obtained from pretreatment lymph node biopsies that were pathologically proven to contain malignant cells. The ability of the ATG to bind to these cells was analyzed by indirect immunofluorescence. In each case, the patients’ cells were tested with the same batch preparation of ATG that had been used clinically. ATG bound to 91 and 98% of the lymph node cells from Patients 2 and 6, respectively. Both patients had T-cell lymphomas that failed to respond to ATG treatment. ATG also bound to 99% of lymph node cells from the null cell lymphoma that was also unresponsive to ATG (Chart 2). Finally, 99% of cells from Patient 4, a B-cell tumor that regressed with ATG treatment, also bound the ATG.

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The ATG used in this study has been used extensively in the prevention of allograft rejection following renal transplantation (5). However, the specificity and mechanism of action of the antisera have not been well defined. We observed that the ATG bound to 96% of normal MNL when studied by indirect immunofluorescence on FACS II. ATG lysed 66% of MNL from normal individuals when studied in a complement-mediated antibody cytotoxicity assay. When normal MNL were separated into T- and B-cell-enriched populations, 82 and 70% of the cells were lysed, respectively. Thus, we have not found any evidence to suggest that this ATG selectively binds or kills subpopulations of normal lymphocytes, specifically T-lymphocytes. In each situation, maximum lysis was obtained at a 1:10 or 1:20 dilution of ATG and lysis diminished rapidly with subsequent dilutions. Since these concentrations of ATG are not attained in vivo, it is unlikely that ATG acts via complement-mediated cytotoxicity. Edelson et al. (7) reached a similar conclusion when they reported the complement-mediated lysis of purified T-cells by ATG. They also demonstrated that ATG lysed 80% of normal T-cells when rabbit serum was used as a
source of complement, but substantially less lysis was observed when human complement was used. Thus, comparable lysis can be achieved regardless of whether guinea pig or rabbit complement is used.

We were able to study cells from the pathologically involved lymph nodes from 4 patients. ATG bound to greater than 90% of cells from the 2 T-cell lymphoma patients who did not respond clinically to treatment, 99% of cells from the unresponsive null cell lymphoma, and 99% of cells from a responsive B-cell lymphoma. In addition, 80% of cells from the 2 nonresponder T-cell lymphomas were lysed by ATG. Thus, ATG is capable of binding to malignant T-cells, B-cells, and lymphocytes lacking surface markers. However, we have not been able to identify those patients who would respond clinically to ATG by studying either the in vitro binding or cytotoxicity of tumor cells by ATG. Other mechanisms such as antibody-dependent cellular cytotoxicity might define the patients who would respond to the ATG. Unfortunately, sufficient tumor cells were not available from any of the responding patients to study this potential mechanism of action.

Toxicity from the ATG infusions was significant. Fever, chills, and skin rashes were seen in most patients but did not require interruption of treatment. Thrombocytopenia was dose limiting, especially in these heavily pretreated patients who frequently had low platelet counts and poor bone marrow reserve when therapy was initiated. This problem could be managed clinically by interrupting treatment for several days, thus permitting the platelet count to rise. In this study, no significant renal impairment was obtained in spite of the infusions of this heterologous protein.

It seems unlikely that patients with non-Hodgkin’s lymphomas, who have as widespread disease or extensive pretreatment as the patients in this study, will obtain significant long-term benefit from treatment with this type of ATG. However, the ATG clearly has biological activity in B-cell, as well as T-cell, non-Hodgkin’s lymphomas. Recently, several groups have reported the clinical results of serotherapy with monoclonal antibodies in various types of lymphoma or leukemia (10-12). All of these patients had circulating tumor cells in their peripheral blood. Reductions in circulating tumor cells have been observed, but they have lasted for several hr only. Objective tumor regressions in other tissues have not yet been described. Improvements in the magnitude of antitumor response or its duration should occur when issues such as optimal dose, optimal schedule, potential removal of circulating free antigen, etc. are resolved. Alternatively, single monoclonal antibodies might be utilized to deliver radioisotopes, chemotherapy, or toxins to the tumor cell. However, even the limited success we have achieved with this very nonspecific ATG is somewhat surprising and suggests that utilization of a limited battery of monoclonal antibodies directed against a given tumor should be investigated.

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REFERENCES

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