Monoclonal Antibody Therapeutic Trials in Seven Patients With T-Cell Lymphoma

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We have studied the clinical effects of a murine monoclonal anti-human T-cell antibody in seven patients with T-cell lymphoma. Four to 17 treatments with anti-Leu-1 were given to each patient over periods of 14–75 days. Doses of antibody ranged from 250 μg to 100 mg. Antibody treatments usually caused a rapid fall in circulating T cells, with return to baseline levels within 24–48 hr. The optimum dose appeared to vary for each patient. Clearance of circulating tumor cells correlated with the amount of antibody bound to cells. Other than dyspnea in one patient, no serious toxicity was noted. Five patients had definite tumor responses, but these were of short duration (1.5–4 mo). Four patients developed anti-mouse immunoglobulin (Ig) antibodies, and in three patients, this was responsible for tumor escape from therapy. Although 95% of the host anti-mouse Ig response was directed against mouse Ig constant region determinants, a small but significant component was found to be antiidiotype.

Preliminary reports have appeared describing the in vivo effects of murine hybridoma monoclonal antibodies in patients with neoplastic disease1–7 and in patients with renal allograft rejection.8 The antibodies used in these studies have been reactive with normal lymphocyte differentiation antigens1–8 or with embryonic antigens.7 Such antigens are also expressed by tumor cells. An example is the anti-Leu-1 monoclonal antibody, which we have administered to patients with T-cell leukemia and lymphoma. This antibody is directed against a human T lymphocyte cell surface antigen that is expressed in high levels by the malignant cells of patients with cutaneous T-cell lymphoma. In our initial studies, anti-Leu-1 demonstrated antitumor activity, but certain limitations on these effects were noted, such as antigenic modulation, free antigen blockade, and effector cell shortage.2–4

In this article, we extend our observations on the in vivo effects of the anti-Leu-1 antibody in seven patients with T-cell lymphoma. Definite clinical responses were observed in five patients, although these responses were of short duration. Four of the patients produced an antibody response against mouse immunoglobulin. In three patients, this was responsible for tumor escape from therapy.

Materials and Methods

Antibody Preparation and Administration

Hybridoma L17F12 has been previously described.5 It secretes a mouse IgG2a antibody that is specific for mature human T cells. The monoclonal antibody was prepared from ascites fluid, as previously described.2 Anti-Leu-1 antibody was diluted into 250 cc of physiologic saline containing 5% human albumin and delivered by continuous intravenous infusion over 4–6 hr.

Clinical Characteristics of Patients Treated With Anti-Leu-1

Seven patients with T-cell lymphoma received anti-Leu-1 antibody (Table I). Patient J.L. has been previously reported.4 Six patients had mycosis fungoides or cutaneous T-cell lymphoma (CTCL). One patient (J.S.) had diffuse large cell lymphoma. In each patient, frozen section immunoperoxidase staining of malignant tissue confirmed the presence of Leu-1 antigen on malignant cells.

Each of these patients had advanced disease that was refractory to conventional chemotherapy and radiotherapy. Three patients had ulcerating cutaneous tumors and four patients had erythroderma. All seven patients had biopsy-proven lymph node involvement with lymphoma, but none had visceral involvement. Patients J.G. and M.B. had elevated WBC counts with greater than 10,000 Sézary cells/cu mm.

Prior therapy included chemotherapy in five patients and radiotherapy to sites of bulky lymph node involvement in two patients. One patient (M.B.) received only cutaneous treatments with electron beam radiotherapy, topical steroids, and nitrogen mustard. One patient (M.C.) received alternating hemibody radiotherapy (1,200 rad) 3 mo before beginning anti-Leu-1 therapy.

During and after treatment with antibody, patients received frequent physical examinations, measurement of blood counts, blood chemistries, and radiographic studies. Urinary creatinine clearances were measured during most antibody infusions. Patients were considered to have a partial response if there was a greater than 50% reduction in the volume of enlarged lymph nodes and if cutaneous tumor or plaques were reduced by 50% or greater. A minimal response was defined as less than 50% reduction in these parameters.

Measurement of Anti-Leu-1 Antibody Bound to Circulating Cells

Mononuclear cells were prepared from heparinized blood samples by centrifugation over a cushion of Ficoll-Hypaque. Direct and indirect immunofluorescence staining of cell samples was performed with anti-Leu-1, as well as with other T-cell-specific monoclonal antibodies, as previously described, and analyzed using the fluorescence activated cell sorter (FACS III, Becton-Dickinson, Sunnyvale, CA).4,5 The FACS was calibrated with glutaraldehyde-fixed chicken erythrocytes and set at identical photomultiplier tube voltage and gain for every analysis. The amount of murine Ig present on cells...
after treatment was evaluated by staining with fluoresceinated goat anti-mouse antibody (Tago, Burlingame, CA). The degree of cell saturation by anti-Leu-1 after treatment was determined by comparing the staining obtained by fluoresceinated anti-mouse antibody with and without a prior in vitro exposure to excess anti-Leu-1.

Measurement of Serum Levels of Anti-Leu-1 Antibody

Patient sera were obtained at various times after receiving antibody and stored at -20°C. A solid-phase radioimmunoaassay for murine Ig was used to detect unbound circulating anti-Leu-1. The wells of polyvinyl chloride microtiter plates were coated with 10 μg/ml of purified goat anti-mouse Ig (Tago) in phosphate-buffered saline (PBS). After washing, 50 μl of serum was added to wells and incubated for at least 1 hr at 4°C. The wells were washed again, and 125I-labeled goat anti-mouse IgG was added. After incubation at 4°C, the amount of radiolabeled antibody bound to wells was determined using a gamma counter. Quantitation of the assay was performed by measurements of serum with known amounts of murine IgG added.

Assay for Host Anti-Mouse Ig Antibody

The wells of polyvinyl chloride microtiter plates were coated with 10 μg/ml of anti-Leu-1 in PBS. After washing, serial dilutions of sera (50 μl) were added to the wells, incubated 1 hr, and plates washed again. 125I-labeled anti-Leu-1 was then added to the wells. After incubation and washing, the amount of radiolabeled anti-Leu-1 bound to wells was determined by using a gamma counter. The antigen-binding capacity of the sera was calculated by determining the minimum amount of unlabeled mouse IgG that could block the subsequent binding of radiolabeled IgG. Because of its greater sensitivity, a double antibody radioimmuno precipititation assay was performed in some experiments, as previously described.2

Specificity of Human Anti-Mouse Ig Antibodies

The specificity of the anti-mouse IgG antibodies produced by treated patients was examined by immunosorption of serum with mouse immunoglobulins of various isotypes. Purified mouse immunoglobulins from the murine myelomas P1.17 (IgG2a kappa), MOPC-104 (IgM lambda), and murine hybridoma 12E7 (IgG1 kappa) and L17F12 were covalently coupled to Sepharose 4B and used to absorb patient sera. Absorbed sera were then assayed for residual reactivity against anti-Leu-1 as described above.

An assay for host antibodies reactive with the idiotypic determinants of the anti-Leu-1 antibody was performed by measuring the ability of serum to block the binding of anti-Leu-1 antibody to its target antigen. Patient serum was mixed with a dilution of fluoresceinated anti-Leu-1 that could barely saturate 106 cells. Thereafter, the indicated target cells were added, incubated at 4°C for 30 min, washed, and analyzed on the FACS. The blocking activity, which could be absorbed by anti-Leu-1 but not by an unrelated IgG2a myeloma protein, was taken as being due to antidiotypic.

RESULTS

Effect of Antibody Dose on Cell Clearance

The number of treatments, total dose, and duration of therapy with anti-Leu-1 are shown for each patient in Table 1. Individual doses of antibody ranged from 250 μg to 100 mg (see Figs. 1, 2, 3, and 5). Usually, therapy was performed 2-3 times per week. In most cases, administration of antibody caused a rapid fall in circulating T cells, with return to baseline levels within 24-48 hr. Figure 1 demonstrates the typical pattern of changes in circulating cells seen in patient M.B., who was treated over a period of 7 wk. Mouse Ig was detectable in the serum immediately after treatment with doses of 1 mg or more (Fig. 1). The levels of mouse Ig persisted for several days after doses of more than 10 mg. Antibody was not found on circulating cells, and no antigenic modulation was observed during these periods of time. This suggested that the residual circulating antibody was nonfunctional. It is possible that circulating free Leu-1 antigen was blocking antibody binding to target cells, as we have previously reported.2 Because M.B. had relatively stable numbers of circulating malignant cells, correlations could be made among the dose of anti-Leu-1, the amount of antibody bound to cells, and the clearance of cells. Increasing the dose of anti-Leu-1, from 1 mg to 50 mg, caused progressively greater reductions in circulating...
malignant cells (Table 2). Higher doses resulted in greater amounts of murine Ig detectable on cells in vivo, even though the cells that were analyzed were the residual population remaining after other cells had been removed. No plateau in antibody effect was reached over this range of doses.

In contrast to patient M.B., most other patients did not show a clear dose-response effect. Lack of a dose-response relationship in these patients resulted, in part, from modulation or loss of Leu-1 antigen during antibody infusion. This is illustrated in Fig. 2 for patient J.G. in whom the first dose of antibody, 1 mg, caused a greater reduction in circulating T cell than subsequent doses with 10 mg or 25 mg. Antigenic modulation was seen in this patient with doses of 10 mg or more, but no modulation was seen following the 1-mg dose. It appeared that antigenic modulation was at least partly responsible for the reduced effectiveness observed with 10-mg and 25-mg doses. The degree of antigenic modulation was variable from patient to patient. For instance, circulating cells sampled imme-

\[ \text{Table 2. Dose Response Effect In Vivo} \]

<table>
<thead>
<tr>
<th>Antibody Dose (mg)</th>
<th>Pretreatment PBM Cells/cu mm</th>
<th>Reduction in PBM Cells/cu mm (%)</th>
<th>Amount of Antibody on Cells</th>
<th>Percent Antibody Saturation $^\ddagger$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16,849</td>
<td>0 (0)</td>
<td>1.5</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>15,687</td>
<td>1,407 (9)</td>
<td>12.0</td>
<td>5</td>
</tr>
<tr>
<td>25</td>
<td>18,509</td>
<td>4,763 (25)</td>
<td>35.0</td>
<td>12</td>
</tr>
<tr>
<td>50</td>
<td>17,787</td>
<td>8,685 (49)</td>
<td>56.0</td>
<td>24</td>
</tr>
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$^\ddagger$Percent antibody saturation determined by comparing mean fluorescence channels of posttreatment cells stained with fluoresceinated goat anti-mouse Ig and analyzed on the FACS. The mean fluorescence channels above that of pretreatment cells similarly stained are shown and indicate the amount of mouse Ig on cells.

Clinical Results

Treatment with anti-Leu-1 produced tumor regres-

\[ \text{Fig. 1. Changes in peripheral blood lymphocyte counts and serum levels of mouse Ig are indicated in relation to anti-Leu-1 treatments.} \]

\[ \text{Fig. 2. The percent reduction in circulating Leu-4 antigen-positive cells is shown for some antibody treatments in patient J.G. Leu-4 is an independent marker for T cells and indicates cell removal rather than antigenic modulation. The serum levels of mouse Ig immediately after each treatment are also shown. Antibody therapy became less effective as human anti-mouse Ig was produced.} \]
der. Some lesions appeared to have completely regressed, but biopsies revealed scanty infiltration with abnormal lymphocytes. Immunoperoxidase staining showed that these cells were Leu-1 antigen positive. In the erythrodermic patients (J.G., M.B., D.H.), responses were often preceded by increased scaling, which was then replaced by clinically normal skin. These patients also noted a marked decrease in pruritus. The responses were usually apparent by the second or third week of treatment and were maximal by 4–5 wk.

One patient (D.H.) had a partial response that might be attributable to cyclophosphamide (350 mg/sq m x 5 days), which she received along with her first dose of antibody. However, this patient's tumor regression was not noted until the fourth week of treatment, long after an antitumor response to cyclophosphamide might be expected. Patient M.B. had a minimal response in skin and lymph nodes, but refused additional therapy after 34 days on study. The patient with diffuse large cell lymphoma (J.S.) showed no clinical response to anti-Leu-1 therapy except for transient reductions in circulating T cells. Patient M.C. was not evaluable for tumor response. The duration of all tumor responses was short (1.5–4 mo).

The mechanism of the antitumor response to monoclonal antibody is not clear. It was difficult to demonstrate mouse Ig bound to tumor cells in the skin by frozen section immunoperoxidase staining. However, it is likely that anti-Leu-1 reached cutaneous sites of lymphoma, since skin biopsies taken at times when there were persistent levels of circulating mouse Ig demonstrated antigenic modulation of tumor cells (J.L., J.G., C.I.). These biopsies stained with anti-Leu-4, an independent T-cell marker, but not with anti-Leu-1. Corresponding biopsies taken at times when there was no serum mouse Ig showed staining with both anti-Leu-1 and anti-Leu-4.

There was no clinical or histologic evidence for an inflammatory reaction at regressing cutaneous lesions, with the exception of patient C.I. After four antibody treatments and coincident with the onset of an antibody response against mouse Ig, this patient developed pain and edema at tumor sites with each subsequent infusion of antibody. Biopsy of a cutaneous plaque during this reaction showed intercellular edema around collections of tumor cells in the dermis and epidermis. No human Ig or complement could be demonstrated in this tissue.

**Toxicity**

Monoclonal antibody treatments given by slow IV infusion were well tolerated. As shown in Table 1, 45 treatments in 3 patients (J.L., J.G., D.H.) were associated with no toxicity. Patient J.S. developed hives, without hypotension or bronchospasm, during his third and fourth treatments, but this was not seen with subsequent doses of antibody. The hives developed about halfway through the infusions, which were then continued at a slower rate. These symptoms resolved within several hours of the end of the infusion. The symptoms were not responsive to, nor prevented by, the antihistamine diphenhydramine. Acute respiratory distress, lasting about 1 hr, developed after doses of 20 mg and 25 mg in patient M.B. This was not associated with hypotension, and no changes were seen on chest roentgenogram. This elderly patient had underlying congestive heart failure and chronic obstructive pulmonary disease.

Patient M.C. developed disseminated herpes simplex infection and bowel perforation while on the study. She died 21 days after beginning monoclonal antibody therapy (MAT). This patient had received alternating hemiodyalysis 3 mo prior to antibody therapy. She also received cyclophosphamide (375 mg/sq m x 5 days) with her first dose of anti-Leu-1. It is unlikely that anti-Leu-1 was related to this infection, since the antibody had not resulted in prolonged effects on circulating T cells.

No hematologic, renal, or hepatic toxicity was noted in any patient.

**Development of Anti-Mouse Ig Antibody**

Four patients (C.I., J.G., D.H., J.S.) developed a humoral immune response against murine Ig. The kinetics and magnitude of these responses are shown in Fig. 3. Three patients made no anti-mouse Ig (J.L., M.B., M.C.). Two of these patients, M.B. and M.C., were immunoincompetent, since they did not mount antibody responses when immunized with other antigens, such as tetanus toxoid and key-hole limpet hemocyanin. The immune competence of patient J.L. was not tested.

As would be expected, the presence of anti-mouse Ig antibodies inhibited the in vivo effect of anti-Leu-1. For instance, in patient J.G., the initial four doses of anti-Leu-1 caused reductions in circulating T cells (Fig. 2). At that point, antibody against mouse Ig became detectable. Subsequent doses caused progressively less effect, despite increases in the amount of anti-Leu-1 given. The serum level of mouse Ig immediately after each treatment is also shown in Fig. 2. No free antibody could be detected after anti-mouse antibodies were made, even with higher doses of anti-Leu-1. Similar results were found in each of the four patients who made anti-mouse Ig.

Tumor escape from therapy was related to the development of anti-mouse Ig in patients C.I., J.G., and D.H., since their clinical response ended when high levels of anti-mouse Ig were reached. The develop-
opment of anti-mouse Ig was not associated with any allergic reactions.

Characterization of Anti-Mouse Ig Antibody Response

We determined the specificity of the antibodies made against the mouse anti-Leu-1 molecule by these patients. Immune sera from patients C.I. and J.G. were absorbed with immunoabsorbents containing either the anti-Leu-1 antibody or other mouse IgGs. The amount of reactivity with each of these immunoabsorbents is shown in Table 3. Each of the unrelated mouse proteins removed most, but not all, of the reactivity against anti-Leu-1. This suggested that the host antibodies were directed primarily against antigenic determinants common to all mouse Ig molecules. However, the possibility that the residual antibodies were directed against idiotype determinants of the anti-Leu-1 molecule was examined by using a blocking assay. This assay demonstrated that sera absorbed with the unrelated protein P1.17 were still capable of blocking the binding of anti-Leu-1 to its target antigen, whereas all blocking activity could be absorbed by the anti-Leu-1 molecule itself (Fig. 4). Therefore, some of the anti-mouse Ig antibodies were directed against variable-region antigenic determinants on the anti-Leu-1 molecule. The proportion of anti-mouse Ig that was antiidiotype was less than 4% in patient C.I. and less than 6% in patient J.G. (Table 3).

Table 3. Characteristics of Human Anti-Mouse Ig Response

<table>
<thead>
<tr>
<th>Immunoabsorbent (Idiotype)</th>
<th>Mean Percent Reactivity Removed by Immunoabsorbent ± Standard Error*</th>
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<tbody>
<tr>
<td>NHS§</td>
<td>0.0 ± 9.6</td>
</tr>
<tr>
<td>Anti-Leu-1 (IgG2a)</td>
<td>100.0 ± 0.2</td>
</tr>
<tr>
<td>P1.17 (IgG2a k)</td>
<td>96.1 ± 2.1</td>
</tr>
<tr>
<td>12E7 (IgG1 k)</td>
<td>57.7 ± 1.5</td>
</tr>
<tr>
<td>MOPC 104E (IgM λ)</td>
<td>76.5 ± 1.3</td>
</tr>
</tbody>
</table>

*Triplicate samples of immunoabsorbed sera were tested for residual anti-mouse activity against anti-Leu-1 and compared to unabsorbed sera.
†Immune serum from patient C.I. collected 52 days after beginning therapy.
‡Immune serum from patient J.G. collected 69 days after beginning therapy.
§Normal human serum.
MONOCLONAL ANTIBODY TRIAL

Fig. 4. Sera from patient J.G. (I) and C.I. (II) were assayed for ability to block fluoresceinated anti-Leu-1 binding to T cells. FACS histograms obtained in the presence of pretreatment serum (C), in the presence of immune serum absorbed with the unrelated mouse IgG2a P1.17 (B), and in the presence of unabsorbed immune serum (A). Absorption of immune serum with the homologous anti-Leu-1 protein removed all blocking activity (not shown in figure).

**Attempt to Prevent Host Anti-Mouse Ig Response**

We tried to prevent the development of anti-mouse Ig in patients D.H. and M.C. by giving cyclophosphamide 12–24 hr after an initial dose of anti-Leu-1. This method of drug-induced immunologic tolerance has been reported to prevent humoral immune responses to cellular and protein antigens in mice and humans. D.H. made a definite anti-mouse Ig response, beginning at day 20, despite this maneuver. M.C. was not evaluable for the development of anti-mouse Ig because of her death.

D.H. and M.C. were found to have impaired cell clearance with antibody treatment 10–18 days after receiving cyclophosphamide (Fig. 5). This correlated with the drug-induced myelosuppression observed in these patients, as determined by peripheral blood white cell count nadir. In D.H., this impairment was reversible with return of blood counts to normal levels and could explain her delay in response to antibody therapy.

**DISCUSSION**

In this study, we have investigated the pharmacokinetics, toxicity, immunogenicity, and clinical effects of anti-Leu-1 in seven patients with T-cell lymphoma. These patients were selected for study because their tumor cells expressed the Leu-1 antigen, and they had failed the usual treatment for their disease. Anti-Leu-1 was given intermittently, 2–3 times per week, in an attempt to avoid problems of antigenic modulation, free antigen release, and effector cell exhaustion. A wide range of doses was studied in these subjects. We were not able to establish a single optimum dose because of the many variables that existed. These variables included: tumor burden, amount of tumor cell surface antigen, host effector cell competence, changing pharmacokinetics of the antibody, and antigenic modulation in each patient. It is likely that the optimum dose will differ for each patient depending on these variables. This was demonstrated by patients J.G. and M.B., in whom increasing doses had different effects. In M.B., higher doses were more effective, as cell clearance depended on the amount of antibody bound to cells. Thus, the optimum dose was dependent on achieving maximal deposition of antibody on target cells while avoiding antigenic modulation. It appeared from our studies that most antigenic modulation occurred when target cells were 50% or more saturated with antibody. The optimum dose also seemed to vary with individual patients’ abilities to clear antibody-coated cells. Treatment regimens that minimize antigenic modulation while preserving effector cell clearance must be developed. Of course, this strategy relates to effects on circulating tumor cells and may need to be modified when considering penetration of antibody into other tissues and the effects in sites other than the blood.

It is probable that antibody-coated cells were removed by the reticuloendothelial system, as we have previously shown. Herlyn and Koprowski, and others, have shown that macrophages are the most likely effector cell mediating antibody-coated target cell destruction. As has been reported by Shin et al., we found that cytotoxic chemotherapy compromised clearance of antibody-coated cells. The time course of the compromise suggested the involvement of a cell population that had a turnover similar to granulocytes and monocytes (Fig. 5). Some tissue sites lack sufficient numbers of effector cells to destroy tumor cells effectively. In CTCL, lymphocyte migration patterns may also be related to the mechanism of action of antibody. It is possible that tumor regression
occurred because cells removed from the body by the reticuloendothelial system are replaced by cells from other compartments, such as lymph nodes and skin. The rapid redistribution of cells from skin or lymph nodes to blood would then result in tumor shrinkage in these sites. Still other possible mechanisms of action exist, such as immunoregulation or induction of a host antitumor response.

In this extended experience, the in vivo effect of anti-Leu-1 was found to be similar to that previously described. However, unlike our previous report, where a sustained reduction in circulating T cells was achieved in patient J.L., the remainder of patients in this study had rapid return of cell counts to baseline levels. It is probable that these differences are related to variation in the kinetics of tumor growth.

Repeated infusions of anti-Leu-1 were usually well tolerated. One patient (J.S.) developed hives after two treatments. It was unlikely that this represented an allergic reaction, since subsequent infusions were tolerated with no side effects. The most serious toxicity associated with antibody infusion was that of respiratory distress noted in patient M.B. This was thought to be related to agglutination of antibody-coated cells in the pulmonary circulation, as we have noted in a subhuman primate. This patient's Sézary cell count and underlying cardiopulmonary disease predisposed her to this complication. Patient M.C. developed fatal disseminated herpes simplex, but this complication could be explained by the dose of cyclophosphamide she had received shortly before and the hemibody radiation 3 mo before antibody treatment. Anti-Leu-1 caused no obvious immunosuppression. In fact, some patients were able to mount a humoral immune response against the murine monoclonal antibody itself.

Four of seven patients in this study produced anti-mouse Ig antibodies. This immune response was not associated with allergy, immune complex disease, or any other toxicity. However, once significant amounts of antibody were produced, the beneficial effects of anti-Leu-1 were lost (Fig. 2). Furthermore, it was no longer possible to detect free circulating anti-Leu-1, even after large doses of the antibody. We were able to show that host antibodies could block binding of anti-Leu-1 to target cells in vitro. Thus, host antibodies neutralized the in vivo effect both by increasing the removal of anti-Leu-1 from serum and by blocking interaction with antigen in these four patients.

Most of the anti-mouse Ig antibody response was directed against mouse Ig constant region determinants (Table 2). Immunoabsorption with the isotype-matched (syngeneic) P1.17 myeloma protein removed 94%-96% of reactivity against the anti-Leu-1 antibody. This absorbed sera was still able to block binding of anti-Leu-1 to its target antigen (Fig. 4). Since P1.17 and anti-Leu-1 are identical, except for the variable region, we conclude that antiidiotypic antibodies to anti-Leu-1 were produced by the patients. We have reached similar conclusions in normal subhuman primates given anti-Leu-1. This has important implications for future studies of monoclonal antibody therapy (MAT). In particular, the use of antibody fragments, or of human monoclonal antibodies, might also be limited by the development of host antiidiotypes.

These studies offer promise for the application of monoclonal antibodies in lymphomas and leukemias. With only mild or negligible levels of toxicity, definite antitumor effects can be achieved. The monoclonal antibodies bind to tumor cells in vivo and lead to their destruction. In the future, these beneficial effects should be improved upon by optimizing dose and schedule. Means will have to be found to prevent immune responses against mouse Ig either by induction of immunologic tolerance or immunosuppression. When cytotoxic agents are attached to the antibody molecule, more effective killing of tumor cells may occur, as well as an abrogation of the immune response.

All of the patients in our study had progressive large tumor burdens and extensive prior therapy that compromised effector cell function. MAT should be most effective when used in the setting of minimal tumor burden and a competent host effector cell system. Thus, use of MAT as an adjuvant to other forms of therapy when the patient is in clinical remission has the greatest potential.

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