Antibody-Radionuclide Conjugates as Part of a Myeloablative Preparative Regimen for Marrow Transplantation

By Frederick R. Appelbaum, Paul Brown, Brenda Sandmaier, Christopher Badger, Friedrich Schuening, Theodore Graham, and Rainer Storb

The behaviors of an anti-Ia antibody (7.2) and an antibody directed at a lymphocyte adhesion molecule (5.5) radiolabeled with $^{131}$I were studied in normal dogs. Antibody 7.2 localized to spleen and, to a lesser extent, to marrow and lymph nodes. Antibody 5.5 rapidly localized to marrow and spleen, achieving tissue/blood ratios >6:1 within three hours of injection that were maintained for at least 48 hours. Prior treatment with cyclophosphamide (CY) markedly altered the distribution of 5.5 but had much less effect on the distribution of 7.2 and almost no effect on the distribution of a control antibody. When animals were treated with increasing doses of $^{131}$I labeled to S.5, lethal myelosuppression occurred when a dose of 6 mCi/kg was reached. At this dose, the otherwise lethal effects of $^{131}$I could be reversed with autologous marrow transplant support.

For many patients with acute leukemia, treatment with high-dose chemoradiotherapy follows by allogeneic marrow transplantation offers the best and sometimes the only chance of cure.1,2 Chemoradiotherapy administered before marrow transplantation serves both to immunosuppress the patient adequately to prevent rejection of the transplanted marrow and to eradicate the malignant disease. A combination of high-dose cyclophosphamide (CY) plus 12 to 16 Gy external-beam total body irradiation (TBI) fractionated over three to seven days has been the most commonly used preparative regimen. Preparative regimens such as these deliver very close to the maximally tolerated dose of chemoradiotherapy. In a retrospective review of 195 patients with acute leukemia undergoing marrow transplantation after treatment with CY-TBI, 15.4% of patients had either life-threatening or fatal nonhematopoietic toxicity believed to be due primarily to the preparative regimen.3 The most common forms of severe toxicity were venoocclusive disease of the liver, interstitial pneumonia, renal failure, and severe stomatitis.

Despite use of these near-maximal doses of chemoradiotherapy, currently used preparative regimens are neither as immunosuppressive nor as tumoricidal as necessary. Although graft rejection is uncommon after transplantation of unmanipulated marrow from an HLA-identical donor, if the donor is incompletely matched or if T cells are removed from the marrow inoculum, the incidence of graft rejection is much higher. With matched unmanipulated marrow, rejection occurs in <2% of donors, whereas graft rejection rates of 9% to 20% occur with marrow grafts mismatched for one or two HLA loci, respectively. With use of T-cell-depleted marrow in matched siblings, rejection rates of 10% to as high as 60% have been reported.4-7 These observations illustrate the need for preparative regimens with greater immunosuppressive effects.

An even more pressing problem is the need for preparative regimens with greater antitumor effects. Tumor recurrence remains the most important cause of treatment failure after marrow transplantation for most hematologic malignancies. For patients with acute lymphocytic leukemia (ALL) or acute nonlymphocytic leukemia (ANL) in relapse, chronic myelogenous leukemia (CML) in blast crisis, or recurrent non-Hodgkin's lymphoma (NHL), relapse rates following marrow transplantation are >50%.1,2 Even if transplantation is performed early in the disease (eg, in first remission for ALL, ANL, and NHL or in chronic phase for CML), relapse rates are 20% to 30%.1,2

One approach to development of preparative regimens with greater antitumor effects without increased toxicity is the use of monoclonal antibodies (MoAbs) as carriers for radionuclides to deliver more radiotherapy to the tumor while avoiding normal nonmalignant cells. We have used a canine model to begin to explore this approach. In a previous study, we reported the behavior of a $^{131}$I-labeled anti-Ia antibody (antibody 7.2) in normal dogs.8 Antibody 7.2 was of interest because most myeloid and lymphoid malignancies express class II antigens. As compared with levels achieved with an irrelevant control antibody, blood levels of $^{131}$I-labeled 7.2 decreased rapidly in the first three hours, during which time the antibody specifically localized to lymph nodes, spleen, and marrow. On the basis of the concentration curves generated over time, we estimated that a dose of $^{131}$I-labeled 7.2 sufficient to deliver 10 Gy to blood would deliver 16.3 Gy to marrow and 32.3 Gy to spleen while delivering no more than 10 Gy to any normal organ.

Although these experiments showed some localization to the marrow and spleen, the degree of localization was modest. Antibody 7.2 reacts only with 14% to 20% of normal canine lymphocytes. In considering use of antibody-radionuclide conjugates as part of a myeloablative preparative regimen for treatment of leukemia or other marrow-based diseases, we believed that targeting normal as well as malignant marrow cells might be important. Therefore, in these...
experiments, we studied the behavior of an antibody which recognizes most normal canine marrow cells. Antibody S.5 recognizes a 90-Kd surface glycoprotein on canine cells analogous to the human Hermes-1 lymphocyte adhesion molecule (B. Sandmaier, unpublished observations). The antigen is expressed in large numbers on most canine marrow cells, lymphocytes, monocytes, and granulocytes. We examined the in vivo distribution over time of antibody S.5 labeled with trace amounts of I\(^{131}\) in normal dogs and in dogs made granulocytopenic with high-dose CY. In addition, we investigated the myelosuppressive effects of increasing doses of I\(^{131}\) linked to antibody S.5 and tested the ability of autologous marrow transplantation to reverse the otherwise lethal effects of high-dose I\(^{131}\) conjugated to antibody S.5.

**MATERIALS AND METHODS**

All research was conducted according to the principles of the Institute of Laboratory Animal Resources of the National Academy of Sciences/National Research Council and published in the Guide for Care and Use of Laboratory Animals.

**Dogs.** Beagles, aged 7 to 15 months weighing 7 to 12 kg and raised at the Fred Hutchinson Cancer Research Center or purchased from commercial kennels were dewormed, vaccinated against distemper, leptospirosis, hepatitis, and parvovirus and were observed for at least 2 months before study.

**MoAbs.** MoAb 6.4 is an IgG2b directed at the Thy 1.1 antigen in mice that does not cross-react with canine cells and was used as a negative control in these studies. MoAb 7.2 (IgG2b), provided by Drs P. Martin and J. Hansen, is directed against a framework determinant of HLA-DR in humans that cross-reacts with an Ia-like class II molecule (p29/34) on canine cells. Antibody S.5 is an IgG1 raised against canine marrow cells surviving radiation which reacts with >50% of normal marrow cells, peripheral blood lymphocytes (PBLs), monocytes, and granulocytes and which binds to a 90-Kd surface glycoprotein, which by radioimmune precipitation and two-dimensional polyacrylamide gel electrophoresis (PAGE) appears analogous to the human Hermes-1 lymphocyte adhesion molecule (B. Sandmaier, unpublished observations). Antibodies were purified from ascites by adsorption and pH stepwise elution from a Staphylococcus protein A-Sepharose column (Sigma Chemical, St Louis). Antibody concentration was determined by a Coomasie blue binding assay standardized with bovine \(\gamma\)-globulin (BioRad Laboratories, Richmond, CA).

**Iodination and characterization.** Iodination was performed in 20-mL glass scintillation vials coated with 100 \(\mu\)L loci of sodium I\(^{125}\) or I\(^{131}\) (NEN, Boston, MA). Antibody was diluted in phosphate-buffered saline (PBS) to a 1 mL vol in the iodogen-coated vial, and radiodine (I\(^{125}\) or I\(^{131}\) labeled Na; ICN Biomedicals, Irvine, CA) was added. The vial was incubated at room temperature with intermittent agitation for ten minutes. Unbound iodine was removed by passage over a Sephadex PD-10, G-25 column (Pharmacia Fine Chemicals, Piscataway, NJ).

Avidity was determined from Scatchard plots of the binding of labeled antibody to viable CT45s human leukemia cells (7.2) or normal canine marrow cells (S.5). Known quantities of antibody were diluted in tissue culture media [RPMI 1640, 2% bovine serum albumin (BSA), and 0.02% sodium azide] and incubated with 2 \(\times\) 10\(^3\) CT 45s or 2 \(\times\) 10\(^3\) AKR/J SL2 murine cells in microtiter plates in a total volume of 0.2 mL for one hour at 37°C. The cells were washed three times, and bound radioactivity was counted. Avidity and immunoreactivity were determined after each individual labeling to insure the quality of the immunoconjugate.

**Antibody localization.** The double-isotope labeling method of Pressman was used along with external body scanning. All dogs were given Lugol's solution, diluted 1:20, at 2 mL/day starting 5 days before study. On the first day of study a mixture of 1 mg I\(^{131}\)-labeled relevant antibody/kg (either 7.2 or S.5) and 1 mg I\(^{125}\)-labeled irrelevant antibody/kg (6.4) was infused in 15 seconds with the dog anesthetized and placed under a \(\gamma\)-camera. Images were obtained at 2-min frames during the first hour after infusion and then at 5-min frames for the next two hours. Static scans were performed at 48 hours. Representative areas over the liver, spleen, lung, and marrow were identified, and activity curves representing counts per pixel for these areas were generated.

Blood samples were obtained at one, five, 30, and 60 minutes after infusion and then at two, three, 24, and 48 hours. At 48 hours, representative animals were killed with pentobarbitol, and samples of various tissues were removed, rinsed of excess blood, blotted dry, and weighed. For marrow, Jamshidi needle biopsy specimens rather than aspirates were used. Content of I\(^{131}\) and I\(^{125}\) in tissue and blood samples were measured in a multiple-channel \(\gamma\)-counter (Auto-Gamma spectrometer, Model 5330, Packard Instruments, Donners Grove, IL). Data were corrected for decay of I\(^{131}\) and I\(^{125}\) and for crosstown from I\(^{131}\) and I\(^{125}\). Results were expressed as percentage of injected dose per gram of tissue.

Biodistribution curves for organs of interest (lungs, liver, marrow, and spleen) were determined by establishing a correlation between counts per pixel obtained by scanning and the radionuclide concentration per gram of tissue measured directly in a well counter.

Some animals received cyclophosphamide 50 mg/kg over 15 minutes five days before biodistribution studies. These animals were otherwise treated identically to those studied without CY pretreatment.

**Marrow ablation and transplant studies.** Dogs to be treated with escalating doses of I\(^{131}\) conjugated to S.5 were started on Lugol's solution diluted 1:20 at 2 mL/day. Five days later, dogs received 1 mg/kg antibody S.5 conjugated with increasing doses of I\(^{131}\). From the time of injection of the antibody-radionuclide conjugate until recovery of peripheral blood counts, dogs received supportive care consisting of oral nonabsorbable antibiotics (polymyxin and neomycin), intravenous (IV) antibiotics (ampicillin and amikacin), and irradiated RBC and platelet transfusions as previously described. For the autologous marrow transplant studies, animals were placed under general anesthesia and had marrow aspirated from both humeri and femora, after which the marrow was processed and stored in 10% dimethyl sulfoxide (DMSO) in the vapor phase of liquid nitrogen as previously described. Animals were allowed to recover for at least 2 weeks before being treated with the antibody-radionuclide conjugate. Marrow was thawed and infused eight days after infusion of the conjugate. Supportive care of transplanted animals was otherwise identical to that received by nontransplanted animals.

**RESULTS**

**Cell binding.** Scatchard analyses of 7.2 binding to CT 45s and S.5 to normal dog marrow cells are shown in Fig 1A and B. Based on the molecular weight (mol wt) of the antibodies and the number of cells in the incubation, for 7.2 the association constant was 1.3 \(\times\) 10\(^4\) (mol\(^{-1}\)) and the number of molecules bound per cell was 2.2 \(\times\) 10\(^3\); for S.5, the association constant was 2.1 \(\times\) 10\(^4\) (mol\(^{-1}\)) and the number of molecules bound was 2.0 \(\times\) 10\(^3\).

**Biodistribution in normal animals.** Mean blood levels of the radionuclide associated with the irrelevant control (n = 7), 7.2 (n = 4), and S.5 (n = 3) are shown in Fig 2. The levels of radionuclide over the first 12 hours presumably
Fig 1. Scatchard plot of binding (nanograms bound/well) of antibody 7.2 (A) or S.5 (B) to target cells.

reflect the amount of circulating antibody, since during that time >90% of the activity was cell-free and precipitable with trichloroacetic acid (TCA). The early decrease in the concentration of 7.2 and S.5 presumably represents antigen-specific binding since this decrease did not occur with the irrelevant antibody 6.4. The slope of the curves of 7.2 and S.5 after the early decrease remained steeper than that of the control antibody, suggesting that binding of antibody to antigen continued after the early phase.

The animals receiving the labeled antibody were imaged at hours 0 to 3 and hour 48 after infusion and then autopsied. Table 1 shows localization of antibodies 7.2 and S.5 as compared with control antibody 6.4 in various organs; 7.2 localized most dramatically to the spleen and less so to marrow and lymph nodes whereas S.5 localized predominantly to marrow and spleen, but amounts of S.5 greater than that in blood were noted in liver, lung, and lymph nodes.

The final concentrations of isotope in marrow, lung, liver, and spleen as determined by actual measurement of autopsy specimens in a well counter were correlated with the activity of these organs as measured by external imaging, and the activity curves shown in Fig 3A and B were constructed. These curves demonstrate rapid uptake of isotope in marrow and spleen.

Biodistribution after CY pretreatment. Transplant preparative regimens often combine high-dose CY with TBI because of CY’s antitumor and immunosuppressive effects.

**Table 1. Localization of $^{131}$I-7.2 and $^{131}$I-S.5 in Normal Dogs**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Antibody 7.2 (n = 4)</th>
<th>Antibody S.5 (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$^{131}$I-7.2</td>
<td>$^{131}$I-6.4</td>
</tr>
<tr>
<td>Blood</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.06 ± 0.10</td>
<td>0.04 ± 0.08</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.14 ± 0.07</td>
<td>0.08 ± 0.10</td>
</tr>
<tr>
<td>Small bowel</td>
<td>0.59 ± 0.15</td>
<td>0.22 ± 0.25</td>
</tr>
<tr>
<td>Colon</td>
<td>0.64 ± 0.20</td>
<td>0.24 ± 0.16</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.41 ± 0.19</td>
<td>0.28 ± 0.04</td>
</tr>
<tr>
<td>Lung</td>
<td>0.46 ± 0.17</td>
<td>0.28 ± 0.09</td>
</tr>
<tr>
<td>Liver</td>
<td>0.84 ± 0.24</td>
<td>0.26 ± 0.07</td>
</tr>
<tr>
<td>Lymph node</td>
<td>1.87 ± 0.54</td>
<td>0.12 ± 0.00</td>
</tr>
<tr>
<td>Spleen</td>
<td>4.08 ± 0.70</td>
<td>0.27 ± 0.04</td>
</tr>
<tr>
<td>Marrow</td>
<td>1.96 ± 0.06</td>
<td>0.30 ± 0.06</td>
</tr>
</tbody>
</table>

Tissue/blood ratios are expressed as percentage of injected dose per gram of tissue as compared with activity of the same isotope in blood at 48 hours; thus, tissue/blood ratio of 4.08 for $^{131}$I-7.2 in spleen means that at 48 hours there was 4.08 times more $^{131}$I per gram of spleen than per gram of blood. Specific localization is the ratio between tissue/blood values of $^{131}$I-relevant and $^{131}$I-irrelevant antibodies. All values are mean ± SD.
MYELOABLATION WITH ANTIBODY-RADIONUCLIDES

Table 2. Localization of $^{131}$I-7.2 and $^{131}$I-S.5 in Dogs Pretreated With CY

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Antibody 7.2 (n = 2)</th>
<th>Antibody 5.5 (n = 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$^{131}$I-7.2</td>
<td>$^{131}$I-5.5</td>
</tr>
<tr>
<td>Blood</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.37</td>
<td>0.13</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.50</td>
<td>0.20</td>
</tr>
<tr>
<td>Small bowel</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Colon</td>
<td>0.65 ± 10</td>
<td>0.32 ± 0.02</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.77 ± 0.02</td>
<td>0.39 ± 0.06</td>
</tr>
<tr>
<td>Lung</td>
<td>0.59 ± 0.10</td>
<td>0.37 ± 0.01</td>
</tr>
<tr>
<td>Liver</td>
<td>0.70 ± 0.16</td>
<td>0.31 ± 0.02</td>
</tr>
<tr>
<td>Lymph node</td>
<td>2.2 ± 0.63</td>
<td>0.16 ± 0.04</td>
</tr>
<tr>
<td>Spleen</td>
<td>1.9 ± 0.6</td>
<td>0.35 ± 0.01</td>
</tr>
<tr>
<td>Marrow</td>
<td>0.82 ± 0.08</td>
<td>0.34 ± 0.06</td>
</tr>
</tbody>
</table>

Values as in Table 1.

*Only one sample was available for muscle with 7.2 and for pancreas with both antibodies; no sample was available for small bowel with 7.2.

Accordingly, the influence of CY pretreatment on the distribution of radionuclide-antibody conjugates was studied. Table 2 shows the organ distribution of $^{131}$I-7.2 and $^{131}$I-S.5 in animals that received 50 mg/kg CY 5 days before injection of antibody-radionuclide conjugate. CY pretreatment did not dramatically alter the biodistribution of the control antibody 6.4 and had only a minor effect on the distribution of antibody 7.2. However, the biodistribution of antibody S.5 was markedly altered, with far more antibodylocalizing to the liver and lung after CY pretreatment.

**Myelosuppression after administration of $^{131}$I-S.5.** Five animals received 1 mg/kg antibody S.5 conjugated to $^{131}$I at doses of 1.9, 2.5, 4.2, 6.0, and 8.3 mCi/kg, respectively. As shown in Table 3, animals receiving 1.9, 2.5, and 4.2 mCi/kg all developed profound pancytopenia but eventually recovered hematopoiesis. The time to recovery was roughly proportional to the dose of $^{131}$I received. Both animals that received 6 and 8.3 mCi/kg/$^{131}$I died of marrow aplasia at ~1 month posttreatment. The half-life ($t_1/2$) of $^{131}$I in the marrow of these animals is shown in Table 4 and is compared with that of animals receiving trace doses of S.5. In all animals, the $t_1/2$ was roughly similar. Also shown in Table 4 are the marrow/blood ratios in these animals. Trace doses do not ablate the marrow, and in these cases high tissue/blood ratios were observed. In animals whose marrow was destroyed, the tissue/blood ratios were lower during the time while marrows were aplastic and only increased with recovery of hematopoiesis.

**Effect of autologous marrow transplantation on myelosuppression with $^{131}$I-S.5.** Two animals had autologous
Our results are encouraging in that cells of I-S.5, the amount of isotope in the marrow as compared with any other organ (except the spleen) was at least threefold greater and this ratio was reached within a few hours of antibody infusion and maintained during the period of observation. These findings suggest that use of an antibody-radionuclide conjugate to boost the radiation dose to marrow-based diseases during a marrow transplant preparative regimen should be possible.

How much immunosuppression antibody-radionuclide conjugates would provide is unknown. The conjugate does localize to the spleen and, to a lesser extent, to lymph nodes, but whether high doses of 131I linked to S.5 or similar antibodies would be immunosuppressive enough to allow engraftment of allogeneic marrow has not yet been tested. At least until the immunosuppressive effects of these sorts of conjugates are determined, they would probably be used in autologous transplantation or, if used in allogeneic transplantation, would probably be combined with other immunosuppressive agents. For this reason, we studied the effects of a dose of CY administered before the antibody-radionuclide conjugate. Pretreatment with a large dose of CY markedly altered distribution of 131I-S.5. Presumably, the effect of CY was to increase the expression of the antigen recognized by S.5 on cells in spleen, liver, and lung. This was probably a specific effect in that pretreatment did not alter the distribution of the irrelevant antibody or of antibody 7.2. The exact population of cells affected and whether this was a direct or indirect effect of CY is not known. Nevertheless, treatment with chemotherapy clearly can alter biodistribution of an antibody-radionuclide conjugate; thus, if use of a combination of chemotherapy and antibody conjugates is to be considered, either the effect of the chemotherapy must be studied or the antibody-conjugate must be administered before the chemotherapy.

Since 131I-S.5 localized well to the marrow, we used this conjugate to begin studies of marrow ablation and reconstitution. An initial dose of 2 mCi 131I/kg conjugated to 1 mg/kg S-5 was administered. The choice of this dose of radionuclide was somewhat arbitrary. As shown in Table 3, the course of myelosuppression after this dose was approximately that which occurred with a dose of 200 to 300 cGy external-beam TBI. A dose of 4 mCi/kg led to severe myelosuppression and a dose of ≥6 mCi/kg was lethal in two of the two animals studied. These findings are consistent with the view that each microcurie of 131I/kg linked to S.5 yields a myelosuppressive effect equivalent to ∼100 cGy external-beam TBI since a dose of 2 mCi/kg yields myelosuppression equal to ∼200 cGy TBI and a dose of 6 mCi/kg is lethal, and since the LD50 of external-beam TBI in dogs is between 400 and 600 cGy.

We wished to test whether the otherwise lethal effects of a dose of 131I linked to S.5 could be reversed with marrow transplantation. In this experiment, the timing of marrow reinfusion was important. Unlike with external-beam TBI, the radiation dose delivered to marrow with an antibody-radionuclide conjugate is not suddenly turned off but instead disappears with a t½ determined both by the physical t½ of the radionuclide and by the rate of disappearance of the antibody-radionuclide conjugate from the marrow space as a result of biologic factors. When we administered trace doses of 131I-S.5, the effective t½ of the radionuclide in marrow was ∼30 hours. This presumably reflects both the t½ of 131I and metabolism of the radionuclide conjugate, with release and clearance of the free 131I. We anticipated that the t½ might be shortened when myeloablative doses of 131I-S.5 were administered due to destruction of marrow cells. However, the t½ in the animals receiving myeloablative doses of 131I-S.5 was not shorter than with trace doses, suggesting that the t½ as predicted by trace doses of the antibody-radionuclide is a reasonable estimate of what happens with higher doses.

In the marrow transplant experiments, marrow was rein-
fused on day 8. This represents approximately five half-lives of the isotope in marrow. Based on the initial amount of isotope in marrow and blood and the observed t/2 in both organs, we estimated that marrow infused on day 8 would receive no more than 35 cGy from residual radiation in the animal. In a previous study, we measured the sensitivity of newly transplanted marrow to further external-beam irradiation. In that experiment, animals received a lethal dose of TBI followed by autologous marrow grafts; 24 hours after transplantation, the animals were exposed to a second dose of TBI. The study showed that doses of radiation up to 150 cGy postgrafting were well tolerated. To reestablish hematopoeisis, therefore, we infused marrow on day 8 and, indeed, with doses of marrow very similar to those used in humans, both animals engrafted.

That the reinfused marrow would be exposed to a small amount of residual radiation (35 cGy in these experiments) is of some concern because of the potential of mutagenesis and possible carcinogenesis. If this approach of antibody-radioisotope therapy as part of a transplant-preparative regimen can substantially reduce relapse rates posttransplant while providing improved immunosuppression and fewer toxicities, a small but definable risk of subsequent carcinogenesis may be acceptable. It may also be possible to reduce the exposure of the reinfused marrow to radiation and therefore reduce this risk by using a shorter acting radionuclide or by delaying the marrow infusion by as much as a week and making up the difference with hematopoietic growth factors such as GM-CSF, which accelerate hematopoietic recovery posttransplant.

Biodistribution and associated dosimetry of an antibody to marrow might be improved in several ways. The antigen recognized by S.5 does not exist on all marrow cells. Thus, a more widely expressed antigen might make a better target. S.5 does react with circulating cells. Binding of labeled antibody to these cells probably results in clearance of these antibody-coated cells in the lung, liver, and spleen and thus results in a decreased amount of antibody available for localization to the marrow. Administration of a dose of unlabeled antibody before a dose of labeled antibody might clear these cells from circulation, permitting better localization of a subsequent dose of antibody labeled with a radionuclide. The antibody–radioisotope complex we used had a relatively short marrow t/2, presumably due to internalization, digestion, and release of free iodine. Most of this free iodine was cleared fairly rapidly from circulation and excreted in the urine, since blood levels of free iodine made up no more than 10% of the total blood radionuclide level. If this process of dehalogenation could be reduced or prevented, the specificity of antibody-radioisotope therapy might be increased even further by eliminating the nonspecific effects of the circulating free iodine. To this end, other methods of linking 131I to an antibody might be explored as well as the use of other isotopes. However, even without any alterations, our approach shows encouraging results, demonstrating that marrow can be targeted specifically with antibody-radioisotope conjugates.

Targeted therapy using antibody-radioisotope conjugates has been of interest for many years. Preclinical work exploring the use of such conjugates recently culminated in initiation of therapeutic trials in humans. As examples, 131I-labeled antiferritin antibodies to treat patients for hematoma and Hodgkin's disease. More recently, Rosen et al studied use of an 131I-labeled T101 murine MoAb in patients with cutaneous T-cell lymphoma. 131I-labeled antibodies to treat patients with B-cell lymphoma with an 131I-labeled anti-B-cell antibody, an approach we also have been exploring. These trials, in general, have yielded encouraging results, suggesting that it is possible, with antibody-radioisotope conjugates, to deliver radiotherapy with some degree of specificity to sites of tumors and thereby spare normal organs. The results presented here suggest that marrow cells are particularly easy to target. This observation supports the view that use of antibody-radioisotope conjugates may provide a way to improve the current results obtained with marrow transplantation as treatment for patients with leukemia or other hematologic malignancies.

REFERENCES

patients with monoclonal antibody directed against marrow cells surviving radiation. Transplantation 44:607, 1987


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