Clearance of $^{131}$I-labeled Murine Monoclonal Antibody from Patients' Blood by Intravenous Human Anti-Murine Immunoglobulin Antibody

J. Simon W. Stewart, Gregory B. Sivolapenko, Victoria Hird, Kevin A. A. Davies, Mark Walport, Mary A. Ritter, and Agamenon E. Epenetos

Imperial Cancer Research Fund & Department of Clinical Oncology, Hammersmith Hospital [J. S. W. S., V. H., A. A. E.], and the Departments of Immunology [G. B. S., M. A. R.] and Rheumatology [K. A. A. D., M. W.], The Royal Postgraduate Medical School, Du Cane Road, London W12 ONN, United Kingdom

**ABSTRACT**

Five patients treated with intraperitoneal $^{131}$I-labeled mouse monoclonal antibody for ovarian cancer also received i.v. exogenous polycolonal human anti-murine immunoglobulin antibody. The pharmacokinetics of $^{131}$I-labeled monoclonal antibody in these patients were compared with those of 28 other patients receiving i.p.-radiolabeled monoclonal antibody for the first time without exogenous human anti-murine immunoglobulin, and who had no preexisting endogenous human anti-murine immunoglobulin antibody.

Patients receiving i.v. human anti-murine immunoglobulin antibody demonstrated a rapid clearance of $^{131}$I-labeled monoclonal antibody from their circulation. The (mean) maximum $^{131}$I blood content was 11.4% of the injected activity in patients receiving human anti-murine immunoglobulin antibody compared to 23.3% in patients not given human anti-murine immunoglobulin antibody. Intra venous human anti-murine immunoglobulin antibody decreased the radiation dose to bone marrow (from $^{131}$I-labeled monoclonal antibody in the vascular compartment) 4-fold. Following the injection of human anti-murine immunoglobulin antibody, $^{131}$I-monoclonal/human anti-murine immunoglobulin antibody immune complexes were rapidly transported to the liver. Antibody dehalogenation in the liver was rapid, with 87% of the injected $^{131}$I excreted in 5 days. Despite the efficient hepatic uptake of immune complexes, dehalogenation of monoclonal antibody was so rapid that the radiation dose to liver parenchyma from circulating $^{131}$I was decreased 4-fold rather than increased. All patients developed endogenous human anti-murine immunoglobulin antibody 2 to 3 weeks after treatment.

**INTRODUCTION**

Injecting radiolabeled antibody to eradicate tumor deposits is an old idea (1, 2). The development of numerous MAbs to tumour associated antigens has made this idea more feasible. Although tumor localization is readily evident by immunoscintigraphy (3–5) the tumor-to-normal tissue ratios are often only 3:1 to 5:1 (6). Radiolabeled immunoglobulin has a 3–5-day effective half-life in the circulation (7, 8) with consequent irradiation of normal tissue (7, 9). Administering a lethal radiation dose to tumor cells by injecting radiolabeled MAb, might be expected to exceed normal tissue tolerance, with fatal bone marrow toxicity (6, 10).

We have isolated HAMA directed against the monoclonal antibody HMFG1 from patients' serum by affinity chromatography, and have undertaken a pilot study in patients with ovarian cancer to investigate how i.v. HAMA alters the pharmacokinetics of $^{131}$I-labeled MAb administered i.p. One object of the study was to determine whether the systemic toxicity associated with i.p. $^{131}$I-labeled MAb could be reduced by increasing the blood clearance. We also examined whether i.v. HAMA provided sufficient passive immunization to prevent the production of endogenous HAMA. If this were found to be the case, multiple i.p. radioimmunotherapy treatments might then be possible using existing murine antibodies.

**MATERIALS AND METHODS**

Monoclonal Antibody. The administered monoclonal antibody was HMFG1. This is a mouse IgG, that recognizes a large glycoprotein normally expressed on the membranes of epithelial cells in lactating breast, and abnormally expressed on many neoplasms of epithelial origin (11). Immunohistochemical studies have shown that almost all serous ovarian tumors express the antigen recognized by HMFG1 (12). Histochemical sections of tumor obtained at each patient's original operation demonstrated positive immunoperoxidase staining with HMFG1.

HMFG1, Donors for exogenous HAMA were chosen from patients who had previously received i.p. radiolabeled MAb in other studies and had developed high HAMA titres (13). Written, informed consent was obtained to venesect a 200-ml blood specimen, a sample of which was tested for hepatitis B surface antigen and antibodies to human immunodeficiency virus, by the Department of Virology, Hammersmith Hospital. Serum was separated once clotting had occurred, and stored at $-20^\circ$C. Anti-HMFG1 antibodies were purified from this serum using affinity chromatography with HMFG1, coupling on CNBr-activated Sepharose 4B beads (Pharmacia, Sweden). Dry beads were washed with 1 mm HCl, and incubated with HMFG1 in coupling buffer (0.1 m NaHCO3, 0.5 m NaCl, pH 8.5) for 2 h at room temperature. The mixture was then transferred to the blocking buffer (1 m ethanolamine, pH 8.0), and incubated for a further 2 h at room temperature. Finally the gel was washed with coupling buffer and 1 m NH3 followed by PBS, pH 7.4. The patient's serum was added, and after washing the column with PBS the anti-HMFG1 antibodies were eluted off using 1 m NH3. Fractions were collected, and those containing the antibodies (determined by absorption at 280 nm) were separated and immediately dialysed against PBS. Finally the anti-HMFG1 antibodies were filtered (Millipore, France), and kept at 4°C until used. All samples were tested for sterility and pyrogenicity (Blood Products Laboratory, Elstree, England). Fast protein liquid chromatography analysis, using a Superose 6 column (Pharmacia, Sweden), of the purified HAMA revealed that over 90% of the antibody was IgG. This was also biologically confirmed, when the immunoreactivity of the antibodies was tested by an ELISA, described later.

Radiolabeling. Iodine-131-labeled HMFG1 was supplied by Unipath Ltd., UK. Trichloroacetic acid precipitation was used to confirm that more than 85% $^{131}$I was protein bound. Approximately 2 mg of the administered HAMA was labeled with 0.5 mCi of $^{131}$I using the N-bromosuccinamide method (14), which enabled the kinetics of the exogenously administered HAMA to be assessed.

Patients. A pilot study to examine the potential usefulness of i.v. HAMA in five patients was approved by the Hammersmith Hospital Ethics Committee. All five patients had previously undergone cytoreductive surgery and postoperative chemotherapy for ovarian carcinoma. The kinetics in these patients were compared with those in a group of 28 patients who received i.p. monoclonal antibody labeled with $^{90}$Y or $^{111}$In. We have found that there is no significant difference between the serum pharmacokinetics of intraperitoneally administered $^{131}$I or $^{90}$Y-labeled antibodies for therapy (15). Informed consent was obtained from all patients. A pretreatment laparoscopy was performed to assess residual disease, and insert a peritoneal catheter for i.p. administration of $^{131}$I-labeled MAb.
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TREATMENT PROCEDURE. The treatment protocol in patients receiving i.p. radiolabeled MAb has been described previously (7, 15). 131Iodine radiolabeled antibody was infused with 1.5 liters of 0.9% saline into the peritoneal cavity. Patients remained in a radiation controlled room (reverse barrier isolation) for 5 days after treatment. The five patients received HAMA at various times after the i.p. infusion of MAb (see Table 1). HAMA was infused i.v. over 20 min in 50 ml of 0.9% saline. Blood samples were taken every 12 h to measure total and protein-bound 131I activity, and more frequently following HAMA infusions as shown in Fig. 2. Urine was collected continuously for 5 days following MAb infusion to measure 131I activity excreted. Patients were reviewed weekly after treatment to assess clinical toxicity and to measure hematological and biochemical parameters.

Pharmacokinetics and Dosimetry. The pharmacokinetics of i.p. MAb in patients receiving i.v. HAMA were compared to those in the previous 28 patients who had received i.p. radiolabeled MAb as part of phase I studies of i.p. radioimmunotherapy and did not have a preexisting anti-mouse immunoglobulin response. Nine of these patients received 131I-labeled MAb, and 19 received 90Y-labeled MAb. The kinetics were also compared to those of five patients who had been treated with 131I-labeled HMFG, i.v. for a second time, and had developed endogenous human anti-mouse immunoglobulin antibodies (15).

The 131I activity in blood samples of known weight was determined by counting the activity in a well scintillation counter against standard samples of known 131I activity. The whole blood 131I activity was extrapolated from these measurements by estimating the patients blood volume, according to their body surface area (16).

Urine 131I activity was measured by extrapolating the counts from 2-ml samples of activity and expressed corrected for radioactive decay, rather than as actual isotope activity. In this way we could directly compare the pharmacokinetics of 131I- and 90Y-labeled antibody, although their physical half-lives are 193 and 64 h, respectively. Actual blood isotope activity was used to calculate radiodensity. The radiation dose to the hemopoietic bone marrow and liver in the first 5 days after treatment were estimated from the MIRD formula (17). The radiation dose to bone marrow (D marrow) was calculated as follows:

\[ D_{\text{marrow}} = 0.2 \cdot A \cdot S_{\text{marrow}} + A \cdot S_{\text{whole body}} \]

Hemopoietic bone marrow may contain one-fifth the 131I-labeled MAb activity of blood, as hemopoietic marrow accounts for 2.2% of body weight, and is functionally part of the circulation (18). S is the S factor from the MIRD formulation and A is the integrated blood isotope activity in microcurie-hours for the 100 h after treatment. The radiation dose received by the liver in the first 100 h \( D_{\text{liver}} \) may be calculated as follows:

\[ D_{\text{liver}} = 0.06 \cdot A \cdot S_{\text{liver}} + A \cdot S_{\text{whole body}} \]

The liver contains 6% of the blood volume at any one time (18), and its extracellular space is not functionally part of the circulation. Both bone marrow and liver are primarily irradiated by radiolabeled antibody within the organ’s circulation (mostly if particles (90%)), but also receive a contribution from the rest of the body (y-rays (10%)). The radiation dose to the marrow and liver can only be calculated in this way if the blood pool is the important radiation source. This is the case for iodine isotopes, as free iodine released from the MAb during catabolism is rapidly excreted in the urine. The radiation dose to organs cannot be calculated accurately from the 90Y blood activity, as free yttrium released from the MAb accumulates in the liver and bone (19-21).

In three patients the administered HAMA was labeled with 131I. The 125I and 131I activities in blood were measured by counting blood samples in a gamma counter using dual 125I and 131I channels. Blood isotope activity was expressed as total activity. The fraction of 125I or 131I bound to protein was measured by gel filtration, passing 50-µl serum samples through a 20-ml Sephadex G-50 column.

In three patients the radiation activity over the liver, heart, and left subclavian vein was monitored by a specially shielded scintillation counter. Measurements were taken from these areas every 20 min after injection of HAMA, until the measured counts had fallen to pre-HAMA levels. Measurements were then taken every 6 h.

Measurement of the Human Anti-mouse Immunoglobulin Antibodies. A blood sample was taken from each patient before, and 14 or 21 days after treatment with radiolabeled MAb. After clotting, the serum was separated and screened for anti-mouse immunoglobulin antibodies using a previously described ELISA method (13). Briefly, microtiter plates (Sterilin, UK) were coated with 5 µg/ml HMFG, or its F(ab')2 fragment in bicarbonate buffer pH 9.6 for 3 h at 37°C. The plates were then washed three times with washing buffer (PBS, pH 7.4, 0.02% Tween 20-Sigma, UK), and serum applied at 1:10 serial dilutions. After 2-h incubation at 37°C, the plates were again washed, and a species specific anti-human immunoglobulin reagent, peroxidase linked (Amer- sham, International, UK) was applied. The conjugate was incubated for 1 h at 37°C, washed and the substrate 2,2'-azino-di-(3-ethylbenzthio- line sulfonate) (Behring, West Germany) applied. When the color had developed, the absorption was measured at 405 nm using a Titertek multiscan (Flow Laboratories, UK).

In every microtiter plate, and in parallel with the unknown patient’s sample, purified HAMA of known concentration collected from various patients was added to different concentrations, and a standard curve was plotted. Using this curve as a reference, it was possible to determine the total amount of anti-HMFG, antibodies in each patient.

Purified HAMA was further tested in order to determine whether it cross-reacted with the Fc part of human IgG. Polyclonal human immunoglobulin G (Sigma, UK) was therefore coated in the microtiter plate, and an ELISA was performed in the same manner as described above, the only difference being that the secondary antibody used, was a peroxidase-conjugated anti-human immunoglobulin M (DAKO, Denmark).

Statistics. The Mann-Whitney test for nonparametric distributions (22) was used to test the significance between radiation doses to organs in patients treated with or without HAMA.

RESULTS

Pharmacokinetics. The pharmacokinetics of radiolabeled MAb in blood following i.p. administration is illustrated in Fig. 1. In the 28 patients receiving MAb for the first time (HAMA

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Table 1 Amount of HAMA and time of injection after i.p. infusion of 131I-labeled HMFG,

<table>
<thead>
<tr>
<th>Patient</th>
<th>i.v. HAMA administration</th>
<th>i.p. 131I HMFG (mCi/mg)</th>
<th>Time after i.p. MAb injection (h)</th>
<th>mg HAMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>117/10</td>
<td>17</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Patient 2</td>
<td>130/15</td>
<td>0</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Patient 3</td>
<td>115/10</td>
<td>17</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Patient 4</td>
<td>113/10</td>
<td>18</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Patient 5</td>
<td>113/10</td>
<td>18</td>
<td>41</td>
<td></td>
</tr>
</tbody>
</table>

* HAMA preparations that were labeled with 131I.
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Fig. 2. Blood 131I activity following the i.p. injection of 131I-labeled MAb expressed as the percentage of the injected activity. The percentage of I-131 not bound to MAb is also illustrated.

Fig. 3. HAMA concentration in serum expressed as a percentage of each injection. HAMA was given at 17 and 39 h in patient 3 (○), 0 and 39 h in patient 4 (▲), and 18 and 41 h in patient 5 (△).

Fig. 4. Radiation activity over liver following infusion of 131I-labeled MAB. Arrows, time of i.v. injections of HAMA.

Fig. 5. Renal 131I excretion, expressed as the percentage of the injected 131I activity, in HAMA negative patients (□) N = 8, patients with endogenous HAMA (●) N = 5, and patients given i.v. HAMA (△) N = 5. Bars, ±2 standard errors of the mean.

negative), 23% of the injected isotope activity was in the circulation at 40 h. More than 80% of 131I and 95% of 90Y activity was protein bound, as determined by Sephadex G-50 gel filtration. In our hands using the cyclic anhydride chelate of DPTA for 90Y-labeled MAb, there was no significant difference in the blood pharmacokinetics of patients receiving 131I- and 90Y-labeled antibodies. The percentage of injected isotope activity in the blood was in fact slightly higher for 131I than 90Y (data not shown). The blood pharmacokinetics were altered in the five patients who received i.v. HAMA (Fig. 1).

In patients 1, 3, and 5 who received i.p. labeled HMFG1 prior to HAMA, the initial pharmacokinetics were as expected. The percentage of injected 131I in the circulation of these three patients ranged from 7 to 11% prior to i.v. HAMA. However, 15 min after the injection of HAMA there was a rapid decrease in circulating 131I with only 2.7, 3, and 2.5% of the injected 131I activity in the circulation. One h after the injection of HAMA less than 36% of circulating 131I was protein bound. After clearance of 131I-labeled HMFG1 from the circulation, the blood 131I activity gradually increased and the fraction of protein bound 131I activity increased (Fig. 2).

Patients 2 and 4 received i.v. HAMA immediately before their i.p. treatment, and had altered pharmacokinetics from the beginning of their treatment. A second i.v. injection of HAMA in four patients produced a further clearance of HMFG1, (see Table 1) from the circulation, with predominantly free 131I remaining in the blood (Fig. 2).

When less than 20% of the injected HAMA remains in the circulation (about 7 mg), 131I-labeled HMFG1 rapidly accumulates in the blood. In three patients (patients 3, 4, and 5), the HAMA was labeled with 125I so that the clearance of HAMA from the circulation could be studied. Human anti-murine immunoglobulin is rapidly cleared from the blood (Fig. 3). Hepatic 131I activity was monitored in three patients (Fig. 4). There was a rapid increase in counts over the liver within 15 min after the injection of HAMA. However this increased 131I activity in the liver lasted only 10 h, following which counts in the liver decreased with a half-life of 18–22 h. Free iodine released from catabolized antibody was excreted in the urine. Fig. 5 compares the 131I excretion in the five patients who received a second treatment and had endogenous HAMA with those given exogenous HAMA in this study, and those treated for the first time. After the administration of exogenous HAMA there is a rapid excretion of 131I so that by 5 days (120 h) almost as much 131I has been excreted as in patients with endogenous HAMA.

Radiation Dose to Bone Marrow and Liver. The radiation dose to bone marrow in patients receiving HAMA was calculated by applying the MIRD formulation to the integrated blood milli-curie hours (see “Materials and Methods”). The mean radiation dose to marrow per milli-curies of administred 131I-labeled MAb was 0.21 cGy (range, 0.14–0.25 cGy) in the five patients receiving exogenous HAMA, compared with 0.97 cGy (range, 0.63–
1.09 cGy) in patients receiving a first treatment. The dose to liver from each mCi of ¹³¹I-labeled MAb in the circulation was 0.11 cGy (range, 0.07–0.15 cGy). This was significantly lower (P = 0.001) than the mean radiation dose to the liver in nine patients receiving ¹³¹I-labeled MAb with no HAMA, 0.44 cGy (range, 0.30–0.57 cGy).

Immune Response to HMFG. All patients developed their own antibodies against HMFG, as measured by the ELISA system described earlier. We measured the patient’s antibodies formed against the MAb and the exogenously administered labeled HAMA that was still in circulation 14 days postadministration. Using the data from the ¹³¹I-labeled HAMA administered to three of five patients, 5–15% of the injected HAMA was still circulating, i.e., 2–6 mgs. We estimated the total amount of circulating human anti-mouse immunoglobulin antibody and found it to be 3125, 1200, 133, 125, and 66 mg, respectively, for each patient (based on a serum volume of 2.5 liters), which is well above not only the estimated amount of administered HAMA still circulating, but also the total amount of HAMA administered.

Toxicity. There was no serious toxicity related to the administration of nine injections of HAMA. Patients 1 and 4 complained of hot flushes immediately after the injection. This was associated with a sinus tachycardia of 110–120. Patients 4 and 5 developed a single episode of rigor 20 min after one of the HAMA injections. These side-effects subsided spontaneously within a few minutes without medical intervention. In addition, patients 1 and 2 complained of lethargy for 10 days after the injection of HAMA. All but one patient demonstrated a degree of myelosuppression in their leukocyte or platelet count following treatment. Myelosuppression was mild with no patient developing more than a 60% fall in either platelets or neutrophils (Fig. 6). The blood count nadir in most cases was observed at 5–6 weeks after treatment.

DISCUSSION

The injection of i.v. anti-mouse immunoglobulin antibody increased the clearance of circulating murine monoclonal antibody. This has been reported by other workers (23–25) using rabbit or goat anti-murine antibody. The advantage of using human anti-mouse immunoglobulin antibody is that this could be less immunogenic. By conjugating the HMFG, to Sepharose 4B beads, we were able to isolate human anti-HMFG, of high specificity and affinity, with little cross-reaction against human immunoglobulins.

Following the injection of HAMA there was immediate clearance of HMFG, from the blood to the liver and presumably spleen. This was followed by rapid monoclonal antibody dehalogenation so that the circulating ¹³¹I was not protein bound and excreted in the urine. Without HAMA the effective half-life of ¹³¹I-labeled antibody in the circulation was 2–5 days (7, 8).

By increasing the clearance of ¹³¹I from the circulation, the radiation dose to normal organs is decreased. It is possible however that the reticuloendothelial system which is responsible for clearing immune complexes receives a higher radiation dose than it might otherwise. However, the ¹³¹I clearance is so rapid, that this potentially increased radiation dose is offset by the decreased radiation dose the reticuloendothelial system receives from ¹³¹I in the vascular compartment. Although there is an immediate 30% increase in the counts measured by a scintillation counter over the liver following HAMA, the counts returned to normal within 4 to 10 h (Fig. 4). This means that the radiation dose to the liver due to circulating ¹³¹I, is decreased 4-fold. One could expect the radiation dose the bone marrow receives from circulating ¹³¹I to be decreased by a similar margin.

Our patients, however, still demonstrated myelosuppression (Fig. 6) despite calculated radiation doses of only 18–46 cGy over 200 h. It is possible that we have underestimated the extra radiation dose the reticuloendothelial system receives in clearing the immune complexes. Patients receiving ¹³¹I for thyroid cancer only develop mild marrow suppression after 97–450 mCi ¹³¹I delivering 200 cGy to the blood (26). In these patients there would seem to be a discrepancy between the calculated radiation dose to the marrow from circulating ¹³¹I and the observed myelosuppression. This has not, however, been the case in our previous experience (8). Although the increased ¹³¹I activity in the liver lasted only a few hours (Fig. 4), other parts of the reticuloendothelial system may have received greater radiation doses due to more prolonged retention (25).

Monoclonal antibody is absorbed from the peritoneal cavity so that about 20% of the given amount is in the circulation 40 h after i.p. infusion (about 2–3 mg). Although we used a HAMA to MAb ratio of 3:1 to clear the radiolabeled MAb from the circulation, the ratio of HAMA to MAb in the circulation immediately after the injection of HAMA is higher (up to 10:1). Others have used similar (23) or higher ratios (25) when using anti-antibody from animals. Serum HAMA was rapidly depleted after 20 h, and radiolabeled MAb (re)accumulated in the blood. This was accompanied by a sharp fall in the fraction of total free ¹³¹I (Fig. 2). The fraction of circulating ¹³¹I which is protein bound may be measured by either gel filtration or trichloroacetic acid precipitation, and this would have provided a convenient way of assessing whether more HAMA was required. We were unable to determine in just five patients, the optimal time to administer HAMA.

Three of the five patients experienced either a rigor and/or a warm sensation accompanied by flushing and tachycardia immediately after the HAMA infusion. We assume that this is related to the rapid formation of immune complexes and complement activation. Although no serious complications were observed in these patients, HAMA should probably be given by slow infusion so that the immune complexes are formed gradually. This may be particularly important if greater amounts of MAb and HAMA were injected, with the formation of more immune complexes. The easiest way to give HAMA is to begin i.v. infusion immediately prior to giving i.p. radiolabeled MAb. As MAb is slowly cleared from the peritoneal cavity into the circulation, immune complexes would be formed gradually. The crossing of immunoglobulin from the circulation to the peritoneal cavity is slow (27), and it is unlikely that HAMA injected i.v. will interfere with MAb tumor targeting in the peritoneal cavity.
cavity. Animal studies using a similar model have shown that
the i.v. administration of anti-bodies does not remove i.p.
jected antibody from i.p. tumor deposits (28). If further
HAMA was required to clear MAbs from the circulation (deter-
mined by a rise in the protein bound:free formed ratio) then a
constant, rather than a 20-min infusion of HAMA should be
given.

A reduction in the radiation dose to normal tissue should
allow greater isotope activities to be given with increased ther-
apeutic effect. Reduced radiation doses to tissue only occur if
the radiolabel is excreted. Several groups (19, 24, 29) including
ourselves, are currently working with metal radiolabel chelates
such as \(^{90}\text{Y}\) rather than \(^{125}\text{I}\). Using the present generation of
chelating agents only 10–20% of the radiometal is excreted
when the MAb is catabolized (19, 24, 29). The administration of
HAMA to patients receiving these isotopes could increase
radiation toxicity, especially if bone-seeking isotopes such as
\(^{90}\text{Y}\) (19, 23, 24, 27) are used. HAMA could only be used with
metal chelates if the metal radiolabel remain linked to the
chelate after MAb catabolism, so that the complexed metal
would be excreted in the urine.

Although the administration of i.v. HAMA was successful in
decreasing the potential radiation toxicity in patients, there was
no suppression of the patient’s own immune response to mouse
antibody. All patients developed high titer of endogenous
HAMA 2 to 3 weeks after treatment. It is possible that if more
HAMA was given prior to the administration of MAb then
passive immunization would have been more effective. How-
ever, if i.v. HAMA is going to decrease toxicity the mouse
antibody must be injected into the peritoneal cavity, and only
form complexes with HAMA in the circulation. Injecting MAb
into the peritoneal cavity, and presenting it directly to the
lymphatics, may make passive immunization extremely difficult
to achieve.

In conclusion this study demonstrated that administration of
exogenous HAMA is a procedure which could potentially de-
crease the systemic toxicity seen following the administration of
i.p. radiolabeled antibodies. Should this be the case, up to 4-
fold higher isotope activities should be given in the future in
order to increase the dose of radiation to the i.p. tumor.

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