Biological Considerations for Radioimmunotherapy

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Abstract

We have examined three methods that may be useful for improving the therapeutic efficacy of antibody-targeted radionuclides. The principal limitation of radioimmunotherapy is myelotoxicity and thrombocytopenia. These are due mainly to the length of time the radioantibody remains in the blood. The clearance time of a radially labeled immunoglobulin G (IgG) may be decreased by using fragments prepared from the IgG. Using murine monoclonal antibodies against human colonic cancer in an animal model with a transplantable human colonic tumor, we have shown that fractionated doses of 125I-labeled F(ab)2 fragments can provide similar tumoricidal activity as a single injection of IgG, but toxicity to the normal tissues is reduced significantly at this tumoricidal level. Thus, it is expected that improved tumoricidal activity may be achieved by further escalating the dose of F(ab)2, that is administered at each injection. An anti-tumor (second antibody) may also be used to remove an anti-tumor antibody rapidly from the blood. By allowing intact IgG to be used instead of fragments, a higher percentage of the radioabeled anti-tumor antibodies may be concentrated in the tumor to provide higher tumor doses, yet toxicity to the normal tissues may be controlled by the removal of the radioabeled antibody from the blood. We have shown that the injection of a second antibody 48 h after 125I-labeled anti-carcinoembryonic antigen antibody is given can reduce toxicity at least 2-fold without affecting the tumoricidal activity of the radioantibody. A third method for reducing the myelotoxicity of radioantibody treatment involves the use of cytokines to increase the production of white blood cells. For example, interleukin 1 may be given prior to, or sometime after, radioantibody treatment to increase the number of circulating white blood cells and thereby reduce myelotoxicity. Thus, modification of some of the biological factors limiting radioimmunotherapy may provide for improvements in cancer treatment with radioabeled antibodies.

Introduction

Over the past 40 years, studies have shown that antibodies can be developed with some selectivity for human tumors, and when these antibodies are injected parenterally they target preferentially to tumors (1-4). However, only a fraction of the injected antibody binds to the tumor, with the majority of the antibody remaining in the blood and normal tissues for a length of time defined mainly by several properties of the antibody [class or subclass, fragment or whole IgG (5)]. With the recognition that antibodies may be used as vehicles to deliver cytotoxic substances to tumors, the principal concern has been to balance the amount of antibody that targets to the tumor with the amount of antibody that remains in the blood and nontargeted tissues.

Drugs, toxins, and radionuclides have been conjugated to antibodies for targeted tumoricidal activity. The approach of targeting drugs and toxins generally relies on the binding of the antibody conjugate to a tumor cell, followed by the internalization and activation of this conjugate to yield cell death (6, 7). In theory, this approach would require the binding of each tumor cell with the antibody conjugate. Due to the heterogeneous nature of tumors with respect to the binding of most anti-tumor antibodies, destruction of all tumor cells may not be possible. However, a "bystander effect," i.e., the killing of nontargeted cells in the region surrounding the targeted site, may be possible if a high enough concentration of drug or toxin can be brought to the tumor. Nonspecific adsorption of the antibody conjugate or the free drug by the bystander tumor cells would widen the zone of cytotoxicity. The bystander effect can occur with radionuclide-targeted antibodies without the requirement of internalization and activation of the radionuclide as long as the energy of the isotope is high enough to penetrate a distance beyond a cell diameter. For example, α-particles and Auger electrons may need to be internalized for their energies to impart enough irradiation to the nucleus of a cell to cause its death, whereas high energy β-particles can cause cell death in a zone around the targeted cell without internalization of the isotope (8, 9). Although the bystander effect produces a wider zone of cell death in the tumor, a similar effect is produced in normal tissues. For radioisotopes, the bone marrow is the most radiosensitive organ. Thus, the most important consideration in RAIT is the optimization of dose to the tumor versus the bone marrow. Toxicity is caused principally by the exposure of the bone marrow to the radioactivity passing through the blood (10). However, with the addition of radionuclides having bone-seeking properties to the list of radionuclides used for therapy, radioactivity in the bone, as well as in the blood, will need to be considered for dosimetric calculations.

In order to examine the main biological concern of RAIT, namely hematopoietic toxicity, we have studied the biodistribution and therapeutic potential of radially labeled antibodies directed against colorectal cancer in animals bearing a human colorectal xenograft. We have initially investigated three approaches to reduce myelotoxicity that do not interfere with the tumoricidal benefit of radioantibody treatment. Indeed, by reducing the myelotoxicity of the treatment, greater tumoricidal effects may be achieved by permitting further escalation in the administered radioactivity. In this report, we have summarized some of our findings when using antibody fragments, SA, or myelostimulation by IL-1 to improve RAIT.

Materials and Methods

The model systems (antibodies and animal models) and some of the procedures have been described previously (11-13), and are presented briefly below.

Animal Model. The CEA-producing human colonic tumor xenograft, GW-39 (14), serially transplanted in the cheek pouch of 8-10-week-old female Syrian hamsters (Sasco, Omaha, NE) was used for most of these studies. Tumors taken from animals were first minced with scissors and then passed through a 40 mesh wire screen (E.C. Collector; Thomas Scientific, Swedesboro, NJ). The tumor was rinsed from the screen with sterile 0.15 M NaCl containing 1.0% gentamicin to give a 20% tumor cell suspension (v/w). The tumor cell suspension (0.5 ml) was injected into each cheek pouch, and after allowing for the desired length of time for tumor growth, the animals were given injections of radioabeled antibody.

Antibodies. NP-4, an IgG1 MAb that recognizes a CEA-specific epitope (15), and affinity-purified goat anti-CEA antibodies have been...
used for several of the different studies. NP-4 was purified from ascites by protein A and ion exchange chromatography (S-Sepharose; Pharmacia, Piscataway, NJ). The goat anti-CEA antibody was purified by passage over a CEA immunoadsorbent (16). Their purity was confirmed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis, immuno- 
nelectrophoresis, and size exclusion high-pressure liquid chromatography (Zorbax GF-250; Dupont, Wilmington, DE). The immunoreactivity was determined after radioiodination with $^{131}I$ (New England Nuclear, Boston, MA) to a specific activity of 12–15 mCi/mg by the chloramine-T method (17). The radiolabeled antibody was passed over a CEA immunoadsorbent, and the percentage bound in the adsorbed fraction was normalized to the total recovered activity. The total activity recovered was generally greater than 85%. The immunoreactivity for NP-4 IgG was in excess of 85%, and the goat antibody was 60 to 75%. No aggregation was detected in either preparation by size exclusion high-pressure liquid chromatography, and there was less than 2% unbound radiodine in the goat antibody and less than 4% for NP-4. F(ab')2 fragments of NP-4 were prepared by pepsin treatment followed by purification using gel filtration and ion-exchange chromatography. The purity of the fragments was determined as outlined above for the IgG. An irrelevant IgG, an IgGl anti-AFP MAb (AFP-7-31; Immunomedics, Inc., Newark, NJ), was purified using the same procedures outlined above, and was used as a control in several of the experiments.

Experimental Designs: RAIT with IgG versus F(ab')2. At either 1, 4, or 7 days after tumor transplantation, hamsters were given i.p. injections of a single dose of either 0.5, 1.0, 2.0, or 3.0 mCi of $^{131}I$-labeled NP-4 IgG. A total of 6–8 animals were used for each group. A separate group of untreated animals with age-matched tumors served as a control for tumor growth in the absence of radioantibody treatment. At the antibody protein doses used in these studies, tumor growth is unaffected (data not shown). Another group of animals was given injections of the same amount of $^{131}I$-anti-AFP antibody. Tumor growth was monitored by measuring the 3-dimensional size of the tumor on a weekly basis. The change in tumor size over time was determined by comparing the tumor size measured immediately prior to radioantibody injection (4- and 7-day-old tumors) or 7 days after radioantibody injection (1-day-old tumors) to the size determination made on subsequent weeks. Toxicity was determined by either loss in body weight or total pWBC count monitored weekly. The pWBC was determined by flow cytometry on randomly selected animals each week, as described previously (12, 18). A single 2.0-mCi injection or multiple injections (2 or 3 injections of 2.0 mCi/injection) of F(ab')2, fragments was also studied. The multiple injections of F(ab')2 were spaced on a 3-day interval based on biodistribution studies that indicated that less than 0.1% of the injected dose/g blood remained, and maximum tumor accretion occurred by day 1 and held constant for 3 days.

Dosimetry. Radiation dose estimates were calculated as described previously (11, 18). The doses were calculated from biodistribution studies using $^{131}I$-NP-4 IgG or F(ab')2, injected into hamsters bearing 4-day-old GW-39 tumors.

SA Studies. Since there is cross-reactivity between an anti-mouse IgG antibody and hamster IgG, the NP-4 MAb could not be used as the primary radiolabeled antibody. Instead, goat anti-CEA antibody was used in combination with an affinity-purified donkey anti-goat IgG as the SA (19). A single injection of 2.0 mCi of $^{131}I$-labeled goat anti-CEA antibody was given i.c. in hamsters bearing 4-day-old GW-39 tumors (0.2–0.3 cm$^3$). After 48 h, the SA was injected i.c. into one-half of the animals at a SA:primary antibody ratio of 50:1 (20). Toxicity and tumor growth were compared in the 2 groups as described above. A more detailed description of this procedure has been reported earlier (13).

IL-1 Treatments. Recombinant human IL-1 (courtesy of Dr. Peter Lomedico, Hoffmann-La Roche Inc., Nutley, NJ) (specific activity, 2.5 $\times 10^6$ units/mg) was administered as a single injection i.p. 24 h prior to, or 7 days after, the start of RAIT. Age-matched female Syrian hamsters (8–10 weeks old) were assigned to 4 groups: untreated; IL-1 alone (1 $\times 10^9$ units); $^{131}I$-labeled antibody alone (1.0 mCi goat anti-CEA); and IL-1 combined with radioantibody treatment. Total pWBC were quantitated using an Ortho Spectrum flow cytometer on day 0 (immediately prior to any treatment), and at weekly intervals thereafter.

Results

Determination of MTD for Single Injections of $^{131}I$-NP-4 IgG. We have shown previously (11) that the growth of a 1-day-old tumor could be inhibited completely by a single 1.0-mCi injection of $^{131}I$-NP-4 IgG, but as tumor size progressed, it became increasingly difficult to inhibit tumor growth. We have extended this study to show the optimal tumoricidal effect at the highest dose of $^{131}I$-NP-4 that could be tolerated by 100% of the hamsters. Fig. 1 shows the toxicity for single injections of $^{131}I$-NP-4 IgG from 0.5 to 3.0 mCi. Loss of body weight may be considered as a measure of general toxicity, representing the cumulative effects to several organs. We have determined empirically that an excess of 20% loss in body weight will lead to the death of some animals. By this criterion, a single injection of 2.0–3.0 mCi of $^{131}I$-NP-4 is considered the MTD, i.e., the dose at which 100% of the animals survive. Although in 2 separate studies 15 of 16 animals survived challenge with 3.0 mCi of $^{131}I$-NP-4 IgG, it took 8 to 10 weeks for these animals to recover to their initial body weight. Myelotoxicity indicated that even with 1.0 mCi of $^{131}I$-NP-4, pWBC decreased by 50% within 1 week after radioantibody injection, with recovery taking an additional 4–5 weeks. With 3.0 mCi, there was a 80–85% decline in pWBC that remained reduced for 9 weeks.

The tumoricidal effect of these doses on 1-, 4-, or 7-day-old GW-39 tumors is shown in Fig. 2. Injection of 1.0 mCi of $^{131}I$-NP-4 was able to cure a majority of 1-day-old tumors (11). However, it took 2.0 mCi of $^{131}I$-NP-4 IgG to prevent the growth of a 4-day-old tumor (0.2–0.3 cm$^3$) for 3 months, and it took 3.0 mCi of $^{131}I$-NP-4 to prevent the growth of a 7-day-old tumor (0.3–0.45 cm$^3$). Despite the prevention of growth in these latter cases, 10–20% of the cells in masses removed after 3 months appeared to be viable (Fig. 3). Since this is the MTD for the single administration of $^{131}I$-NP-4 IgG, additional injec-
assumed that a dose of 1305 rads to the blood given as a single injection in the sequence of 3 injections could be increased as a single 2.0-mCi injection of 125I-NP-4 IgG (Fig. 4).

However, faster clearance of the radiolabeled MAb from the blood is the SA, or anti-antibody method (19, 20). The difference between this method and antibody fragments is that the blood is the SA, or anti-antibody method (19, 20). The clearance of antibody from the blood can be controlled by the investigator rather than by the properties of the injected antibody fragments. As shown in Fig. 4, it took 3 injections of 2.0 mCi of 125I-NP-4 F(ab')2 given over 6 days before the tumoricidal effect was similar to that of a single injection of 2.0 mCi of 125I-NP-4 whole IgG. Although the tumoricidal effects were similar, the toxicity of this injection was more. Thus, these data predict that at equal levels of toxicity, antibody fragments may be more tumoricidal than the whole IgG.

Myelotoxicity of radioiodinated antibodies is attributed mainly to the level of radioactivity in the blood that circulates through the marrow (10). Thus, faster clearance of the radioactivity from the blood should reduce the level of toxicity. However, faster clearance of the radiolabeled MAb from the blood may also reduce tumor uptake. This is demonstrated by comparing the biodistribution of NP-4 IgG to its F(ab')2 fragment (Table 1). From these studies, it is not unexpected that asingle 2.0-mCi injection of 125I-anti-AFP MAb delayed tumor growth for 7 days, but the tumor rapidly progressed in size thereafter (data not shown).

Management of radioactive materials at these higher dose levels is difficult. Therefore, a more practical approach to using antibody fragments would be dose fractionation. As shown in Fig. 4, it took 3 injections of 2.0 mCi of 125I-NP-4 F(ab')2 given over 6 days before the tumoricidal effect was similar to that of a single injection of 2.0 mCi of 125I-NP-4 whole IgG. Although the tumoricidal effects were similar, the toxicity of this injection schedule (Fig. 5) was most similar to that of a single 1.0 mCi injection of 125I-NP-4 IgG (Fig. 1), indicating that further escalation or increased frequency of doses could be given before reaching the MTD. Thus, these data predict that at equal levels of toxicity, antibody fragments may be more tumoricidal than the whole IgG.

Reduction in Myelotoxicity by the SA Method. Another method for increasing the rate of radioantibody clearance from the blood is the SA, or anti-antibody method (19, 20). The difference between this method and antibody fragments is that the clearance of antibody from the blood can be controlled by the investigator rather than by the properties of the injected antibody fragments.
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Fig. 5. Toxicity (A, loss in body weight; B, loss in pWBC) of 1, 2, or 3 injections of 2.0 mCi $^{131}$I-NP-4 F(ab')$_2$ given every 3 days.

Table 2 Radiation dose estimated from biodistribution studies with $^{131}$I-NP-4 IgG or F(ab')$_2$ in GW-39 tumor-bearing hamsters

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Liver</th>
<th>Kidney</th>
<th>Lung</th>
<th>Blood</th>
<th>Total NP-4</th>
<th>Blood doses of IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td>NP-4 IgG</td>
<td>NP-4 F(ab')$_2$</td>
<td>total rads adjusted to blood doses of IgG</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor</td>
<td>4784</td>
<td>840</td>
<td>6334</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>558</td>
<td>104</td>
<td>784</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>636</td>
<td>154</td>
<td>1161</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>968</td>
<td>136</td>
<td>1025</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>1305</td>
<td>173</td>
<td>1305</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Radiation doses were estimated from time-activity curves generated from the biodistribution data shown in Table 1, based on the injection of 2 mCi of $^{131}$I-NP-4 IgG or F(ab')$_2$.

material. For example, whole IgG can be used rather than fragments to permit optimal tumor accretion, and at this time, the excessive amount of radioantibody in the blood can be removed rapidly by complexation with an anti-antibody. However, upon rapid removal of radioantibody from the blood, there is also some decrease in the amount of radioantibody in the tumor (20). In order to determine whether this decrease in tumor uptake would impact negatively on the tumoricidal activity of radioantibody treatment, we have compared the tumoricidal activity and toxicity of a 2-mCi injection of $^{131}$I-goat anti-CEA alone or followed 48 h later by the rapid clearance of blood activity with the SA. As shown in Fig. 6, the tumor growth was unaffected by SA treatment in comparison to the radioantibody alone, but body weight loss was reduced nearly 2-fold. Thus, higher, more tumoricidal doses of radioantibody may be administered if a SA is used.

RAIT Using IL-1 to Reduce Myelotoxicity. Several growth factors can cause the proliferation of myeloid cells and thereby reduce the toxicity of myelotoxic agents (21–23). Using the hamster-GW-39 human colonic tumor xenograft model, we have shown that IL-1 causes a 2- to 3-fold proliferation in the number of pWBC (12). As shown in Fig. 7, stimulating the proliferation of pWBC with IL-1 prior to radioantibody treatment does not prevent loss in pWBC, but there remains a higher level of pWBC in the circulation than if radioantibody is given alone. In addition, by administering IL-1 7 days after RAIT, the pWBC count was able to recover more quickly, opening the possibility that IL-1 treatment may also be used to rescue a host that is myelosuppressed by RAIT (12). Thus, RAIT doses may be escalated when IL-1 is used in combination with radioantibodies. This procedure is described in greater detail elsewhere in this supplement (24).

Discussion

As with any form of radiation therapy, hematotoxicity is a major concern. Thus, in concert with the developing technologies that will allow for the selective delivery of a variety of radionuclides to disseminated cancer via antibody ligands, we must also develop methods that will extend our ability to use these agents in vivo, and the control of hematotoxicity should be our first concern. In this regard, we have summarized 3 different approaches that may be used to reduce radioantibody-induced myelotoxicity.

The first approach is the most direct, namely, to determine optimal dosing and scheduling of radiolabeled antibodies. Although it is a time-consuming effort, this is the most important investigation when developing new therapeutic regimens. Sim-
ilar to other therapeutic agents, each MAb coupled to different radionuclides by different labeling methods may require individual attention to optimize its therapeutic ability in relationship to its toxicity, especially for each tumor system. Toxicity to normal tissues is the first concern in the adjustment of dose and schedule. Normal tissue toxicity will be governed by the rate of radioantibody removal from the body. Optimizing the rate of radioantibody removal from the body and tumor uptake are critical in maximizing RAIT treatment. Once the MTD has been determined, comparisons can be made of tumoricidal effects between different radiolabeled antibodies. For example, we have found that the F(ab')2 fragments of a MAb (Mu-9) directed against colon-specific antigen-p, another colorectal tumor-associated antigen (25), used in this same model system is more tumoricidal at the same dose and schedule than NP-4 F(ab)'; (18). Biodistribution studies have shown similar tumor and nontumor tissue uptake for these 2 antibody fragments over the first 3 days, but Mu-9 F(ab')2 has a higher retention in the tumor thereafter. Although this may be the principal reason for the improved therapy with Mu-9 F(ab')2, we cannot rule out that differences in the distribution of each fragment within the tumor may also have a role in this effect (18). Thus, the magnitude, duration, and distribution of radioantibody in the tumor will contribute to the tumoricidal activity of each antibody. We anticipate that the duration of radioantibody binding in the tumors will have less impact for radionuclides with a shorter physical half-life than those with a longer half-life. In addition, different coupling methods may influence radioantibody pharmacokinetics, which will require reevaluation of dosing. As we continue to develop a better understanding of how each of these factors contributes to RAIT, we may be better able to predict the biological behavior of different MAb conjugates.

F(ab')2 fragments appear to afford an advantage over whole IgG in RAIT. Their high rate of clearance and improved tumor/nontumor ratios in comparison to whole IgG seem to offset the reduced tumor uptake of F(ab')2. However, in order to yield equal doses to the tumor, higher amounts of radioantibody fragments are required. The need to escalate doses of radiolabeled antibody may increase the difficulty in patient management with regard to radiation safety concerns, as well as adding to the difficulty encountered in producing higher quantities of radiolabeled antibody. Fractionated dose scheduling provides an alternative approach for maximizing tumor doses, minimizing toxicity, reducing radiation safety concerns, and reducing the total amount of radioantibody required per injection. Of course smaller fractionated doses of 131I-labeled NP-4 IgG may be administered in a fashion similar to that for F(ab')2, but the longer clearance time of the IgG would require either a longer interval between doses or a smaller dose for each injection. Ceriani and Blank (26) showed that multiple injections of a 131I-labeled MAb against milk fat globule could arrest the growth of a human breast tumor xenograft, but it was important to have enough recovery time between injections. For RAIT, it may be critical for the first series of injections to impart the maximum tumoricidal effect, because tumor cells escaping death may have altered phenotypes that include altered antigen expression or increased resistance to radiation. Our studies have shown, however, that with large tumor masses, incomplete cell killing occurs after a single cycle of treatment with radiolabeled antibody. Even if these remaining surviving cells do not have altered phenotypes, we will still need to be concerned whether or not a second cycle treatment with radiolabeled antibody will have adequate uptake in the surviving cell fraction to kill these cells. Our data indicate that we may be able to achieve higher tumor doses in a shorter period of time with fractionated doses of F(ab')2 fragments than with whole IgG and thus may improve the ability of radiolabeled antibodies to kill a higher proportion of the tumor cell population.

Since it is likely that at least 2 cycles of radioantibody treatment will be required to optimize tumoricidal activity against large tumor masses, another advantage of the F(ab')2 may be the decreased likelihood for the development of a host immune response to fragments in comparison to whole IgG (27). However, if several injections of the F(ab')2 are required in comparison to a single injection of whole IgG, this possible advantage of F(ab')2 may be reduced. Although there are several evolving technologies that may reduce the concern over the development of human anti-mouse antibody by MAb-directed therapy techniques (e.g., human MAbs, or human-mouse chimeric MAbs), human anti-mouse antibody remains a formidable obstacle that can reduce the efficacy of RAIT (28).

Although antibody fragments may provide an improved RAIT with 131I-labeled MAbs, we have shown recently that NP-4 F(ab')2 labeled with 111In or 88Y had substantial uptake of radioactivity in the kidneys. Since other investigators have shown an increased kidney uptake of other MAb fragments labeled with radionuclides (29-31), we expect that renal toxicity may limit the application of radiometal-labeled fragments. However, since the kidney is less radiosensitive than the bone marrow, we cannot presently exclude the possibility that radiometal-labeled F(ab')2 fragments may have some application in RAIT. Renal uptake of monovalent Fab' fragments labeled with radiometals seems to be too excessive for therapeutic consideration.

The SA method provides an alternative for removing radioantibody from the blood in a controlled fashion. The advantages of the SA approach are: (a) whole IgG can be used to provide for the highest percentage uptake in the tumor; (b) radioantibody can be removed at a time of maximum tumor accretion, thereby maximizing tumor dose yet providing for reduced toxicity to normal tissues; and (c) radioantibody distribution patterns in the tissues may be altered to allow for less uptake in more radiosensitive tissues in comparison to less sensitive tissues. With regard to this latter issue, the SA method may be used to complex radiometal-labeled fragments in the blood, and these complexes then would be deposited principally in the liver and spleen (20), thereby potentially reducing kidney uptake. In principle, one would be depositing the radioactivity in the less radiosensitive liver rather than in the kidneys, but splenic doses may also increase. However, it is difficult to predict whether the radionuclide, once metabolized by the liver, would become entrapped in the kidneys. Although some studies using radiometal-labeled antibodies in combination with SA have been reported (32, 33), these have shown tissue distribution patterns only within 4 h after SA treatment. Thus, the timing of the SA injection in relationship to the radiolabeled antibody must be investigated to determine the feasibility of this approach. The need for a second injection of another antibody that may further stimulate the host to produce an antibody response and the possibility for complications arising from immune complex formation in vivo are the major problems facing the SA approach. However, these problems are not insurmountable, and if the SA method can provide an advantage over using antibody fragments, it may be useful for RAIT.

Agents that stimulate WBC proliferation may provide an-

other way of reducing the hematotoxicity induced by RAIT, but the selection of which agent to use and the optimal dosing of these agent(s) require further investigation. For example, we have found that daily injections of IL-1 provide a more sustained stimulation of WBC production than single injections and therefore may be better for RAIT treatments. When IL-1 has been used in conjunction with radiolabeled antibody, we have not observed any protection against the loss of body weight (12). This is not due to an IL-1 effect, because animals given ng quantities of IL-1 used for radioprotection without radiolabeled antibody do not have any weight loss. The loss in body weight may reflect transient toxicity to the gastrointestinal tract, but the mechanism of this toxicity has not been demonstrated.

Indeed, as we are better able to protect the marrow from the toxic side effects of RAIT, we will need to study more carefully the toxicity to other organs and to determine if there are any long-term effects.

In summary, as with any form of cancer treatment, RAIT has its potential benefits and problems. Our current studies with colorectal cancer and 131I-labeled anti-CEA antibodies indicate that RAIT may be curative for small tumors, but larger tumors are not killed completely. Thus, this form of RAIT may provide a significant means for systemic treatment of cancer in patients with minimal disease. As we continue to develop more potent radiolabeled antibody agents, we must devise methods to optimize radiolabeled antibody treatment schedules in order to widen the window between tumoricidal effects and host toxicity. We have only begun to discover how to optimize this procedure for radiolabeled antibodies, and with the evolving technologies for preparing antibodies with different types of radionuclides, similar concerns will need to be addressed.

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References


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