Radioimmunotherapy for Acute Leukemia

John M. Burke, MD, Joseph G. Jurcic, MD, David A. Scheinberg, MD, PhD

Background: The use of monoclonal antibodies to deliver radioactive isotopes directly to tumor cells has become a promising strategy to enhance the antitumor effects of native monoclonal antibodies. In this article, we summarize the role of radioimmunotherapy in the treatment of leukemia.

Methods: The authors reviewed the published clinical trials of radioimmunotherapy in acute leukemia.

Results: Radioimmunoconjugates that emit β-particles, such as 131I-anti-CD33, 90Y-anti-CD33, 131I-anti-CD45, and 188Re-anti-CD66c, deliver significant doses of radiation to the bone marrow and may be particularly effective when used as part of a conditioning regimen for hematopoietic stem cell transplantation. Radioimmunoconjugates that emit short-ranged α-particles, such as 213Bi-anti-CD33, are better suited for the treatment of low-volume or residual disease.

Conclusions: Radiolabeled antibodies can be administered safely to patients with advanced leukemias and have significant antileukemic activity. Radiolabeled antibodies can potentially intensify the antileukemic effects of conditioning regimens when used in conjunction with hematopoietic stem cell transplantation. Whether or not radiolabeled antibodies improve the outcome of patients with leukemia remains to be demonstrated by randomized studies.

Introduction

Despite advances in therapy, only about 20%-30% of patients with acute myelogenous leukemia (AML) and 30%-40% of adults with acute lymphoblastic leukemia (ALL) achieve long-term disease-free survival. The most common cause of treatment failure is relapse. In addition, the toxicity of chemotherapy and complications of hematopoietic stem cell transplantation contribute significantly to mortality rates.

Treatment with monoclonal antibodies (MAbs) has the potential to improve efficacy and decrease toxicity by targeting therapy to specific cell types and sites of disease. Native MAbs can be used to focus an inflammatory response against a tumor cell. The binding of MAbs to a target cell can result in complement
activation, thereby initiating a number of biologically important effects that disrupt the integrity of the cell membrane. Cells with antibody and complement on their surfaces may also be engulfed, or opsonized, by macrophages. Another important mechanism for tumor cell killing by native MAbs is antibody-dependent cell-mediated cytotoxicity (ADCC), in which an effector cell expressing an Fc receptor binds to a cell-bound MAb and is triggered to kill the target cell. Monocytes, macrophages, natural killer cells, and neutrophils can affect antibody-dependent cell-mediated cytotoxicity.

Chimeric and humanized antibodies have been constructed to overcome the weak antitumor activity and the immunogenicity of many murine MAbs. These antibodies retain the binding specificity of the original rodent antibody determined by the variable region but can potentially activate the human immune system through their human constant region. Clinical trials have demonstrated that both rituximab, a chimeric anti-CD20 MAb, and Campath-1H, a humanized anti-CD52 MAb, have activity against chronic lymphocytic leukemia. However, the activity of native antibodies in acute leukemias is more limited. The humanized anti-CD33 MAb HuM195 has been shown to eliminate minimal residual disease detectable by reverse transcription-polymerase chain reaction (RT-PCR) in patients with acute promyelocytic leukemia (APL) and to produce rare complete remissions in patient with relapsed or refractory AML, but only in patients with low leukemic burdens.

In order to increase the antitumor effects of native antibodies, drugs and bacterial toxins have been conjugated to MAbs. For example, gemtuzumab ozogamicin consists of a humanized anti-CD33 antibody linked to calicheamicin, a potent tumor antibiotic. Gemtuzumab ozogamicin has produced remissions in 30% of carefully selected patients with relapsed AML. BL22 is a recombinant immunotoxin consisting of the variable domain of an anti-CD22 antibody fused to a fragment of Pseudomonas exotoxin. In a recent trial, BL22 resulted in an 81% response rate in patients with hairy cell leukemia refractory to cladribine. Table 1 lists the labeled and unlabeled antibodies that have been used to treat leukemias in recent trials.

In an alternative approach, antibodies can be used to target radioisotopes directly to sites of disease in order to increase the antitumor effects of native MAbs. This article reviews the role of radioimmunotherapy with both α-particles and β-particles in the treatment of leukemia.

### Isotope Selection

When selecting a radioisotope for clinical use, the characteristics of the isotope must be considered.

<table>
<thead>
<tr>
<th>Antibody (ref)</th>
<th>Antigen</th>
<th>Disease</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab³</td>
<td>CD20</td>
<td>CLL</td>
<td>Mediates ADCC, CMC, interrupts signaling pathway</td>
</tr>
<tr>
<td>Campath-1H⁴</td>
<td>CD20</td>
<td>CLL, PLL</td>
<td>Mediates ADCC, CMC</td>
</tr>
<tr>
<td>HuM195⁵⁻⁸</td>
<td>CD62</td>
<td>CLL, PLL</td>
<td>Mediates ADCC, CMC</td>
</tr>
<tr>
<td>Gemtuzumab ozogamicin⁹</td>
<td>CD33</td>
<td>AML, MDS, APL</td>
<td>Delivers calicheamicin</td>
</tr>
<tr>
<td>BL22¹⁰</td>
<td>CD33</td>
<td>AML</td>
<td>Delivers Pseudomonas exotoxin</td>
</tr>
<tr>
<td>¹³¹I-M195¹¹⁻¹³</td>
<td>CD33</td>
<td>AML, MDS, myeloblastic CML</td>
<td>Delivers β-particle emitter</td>
</tr>
<tr>
<td>¹³¹I-HuM195¹³</td>
<td>CD33</td>
<td>AML, MDS, myeloblastic CML</td>
<td>Delivers β-particle emitter</td>
</tr>
<tr>
<td>⁹⁰Y-HuM195¹⁴</td>
<td>CD33</td>
<td>AML, CML</td>
<td>Delivers β-particle emitter</td>
</tr>
<tr>
<td>²¹¹Bi-HuM195¹⁵</td>
<td>CD33</td>
<td>AML, CML</td>
<td>Delivers β-particle emitter</td>
</tr>
<tr>
<td>¹³¹I-p67¹⁶</td>
<td>CD33</td>
<td>AML</td>
<td>Delivers β-particle emitter</td>
</tr>
<tr>
<td>¹³¹I-BC8¹⁷⁻¹⁹</td>
<td>CD45</td>
<td>AML, ALL, MDS</td>
<td>Delivers β-particle emitter</td>
</tr>
<tr>
<td>¹⁸⁸Re-BW 250/183²⁰⁻²²</td>
<td>CD66</td>
<td>AML, ALL, CML</td>
<td>Delivers β-particle emitter</td>
</tr>
<tr>
<td>⁹⁰Y-anti-Tac²³</td>
<td>CD25</td>
<td>ATL</td>
<td>Delivers β-particle emitter</td>
</tr>
</tbody>
</table>

Particles have a relatively long range (0.8-5 mm) and a higher linear energy transfer (approximately 100 keV/µm). As few as one or two α-particles traversing the nucleus can destroy a target cell. Therefore, because of the short range of α-particles, radioimmunotherapy with α-emitters should result in less nonspecific toxicity to normal bystander cells and in more efficient single-cell killing than β-emitting constructs. This potential for specific antitumor effects makes targeted α-particle therapy an attractive approach for the treatment of cytoreduced or minimal residual disease.

Radioimmunotherapy With β-Particle Emitters

Radiolabeled Anti-CD33 Antibodies

CD33 is a 67-kD cell surface glycoprotein found on most myeloid leukemia cells and on committed myelomonocytic and erythroid progenitor cells. It is not found on lymphoid or nonhematopoietic cells. Three anti-CD33 MAbs have been used in the radioimmunotherapy of myeloid leukemias: M195, HuM195, and p67. M195 is a murine monoclonal IgG2a antibody that is derived from a mouse immunized with live human leukemic myeloblasts. HuM195 is a humanized antibody constructed by grafting the complementarity-determining region of M195 onto the constant region and variable framework of a human IgG1 antibody. HuM195 differs from the murine M195 in two important ways. First, HuM195 can mediate the killing of leukemia cells in vitro by human peripheral blood mononuclear cells, whereas M195 cannot. Second, while significant numbers of patients treated with murine M195 develop human antimouse antibodies that adversely affect the pharmacokinetics of the antibody and preclude re-treatment with it, patients treated with HuM195 do not develop significant immune responses.

α-Particles are helium nuclei emitted from the decay of radioisotopes. There are approximately 100 radioisotopes that decay with α-particle emissions. Compared with β-particles, α-particles have a shorter range (50-80 µm) and a higher linear energy transfer range (50-80 µm) and a higher linear energy transfer including its half-life and the type of particle(s) it emits. The physical properties of several commonly used isotopes for the clinical radioimmunotherapy of leukemia are summarized in Table 2.

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Particle(s) Emitted</th>
<th>Half-life</th>
<th>Particulate Energy (keV)</th>
<th>Mean Range of α- or β- Particle Emission (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iodine-131</td>
<td>β, γ</td>
<td>8.0 d</td>
<td>970</td>
<td>0.8</td>
</tr>
<tr>
<td>Rhenium-188</td>
<td>β, γ</td>
<td>17 h</td>
<td>2,120</td>
<td>2.4</td>
</tr>
<tr>
<td>Yttrium-90</td>
<td>β</td>
<td>64 h</td>
<td>2,280</td>
<td>2.7</td>
</tr>
<tr>
<td>Bismuth-213</td>
<td>α</td>
<td>46 min</td>
<td>5,982</td>
<td>0.05-0.08</td>
</tr>
<tr>
<td>Actinium-225</td>
<td>α</td>
<td>10.0 d</td>
<td>5,935</td>
<td>0.05-0.08</td>
</tr>
</tbody>
</table>

Most clinical studies have used 131I, a long-lived β-particle emitter. The emissions from 131I allow dosimetry studies to be performed easily, but treatment at high doses requires patient isolation and can result in radiation exposure to hospital staff. More recently, the use of radiometals, such as 90Y and 186Re, has been investigated. 90Y is a pure β-emitter; its lack of γ-emissions allows outpatient administration of high doses. Therapy with 90Y, however, poses several difficulties. Dissociation of 90Y from the MAb complex in vivo can result in deposition of the isotope in bone. Unlike 131I, which binds directly to tyrosine residues, 90Y must be linked to the antibody by a chemical chelator. Furthermore, due to the absence of γ-emissions, biodistribution and dosimetry studies require administration of MAb trace-labeled with a second isotope, typically 111In, whose biodistribution is not identical to 90Y.
In a phase I study at the Fred Hutchinson Cancer Research Center (FHCRC), 131I-p67 was investigated in patients with advanced AML. Nine patients received a tracer dose of 131I-p67, and the biodistribution and estimated radiation absorbed dose to various organs were determined. The half-life of 131I-p67 in the marrow was 9 to 41 hours. This short half-life presumably resulted from internalization of the 131I-p67-CD33 complex with subsequent cleavage of 131I from the antibody and excretion from the marrow space. Of the 9 patients, only 4 had “favorable biodistribution,” defined as a higher dose of radiation delivered to the marrow and spleen than to other organs. These 4 patients then received therapeutic doses of 131I-p67 (110 to 330 mCi) together with cyclophosphamide (120 mg/kg) and total body irradiation (12 Gy) as conditioning regimen for allogeneic bone marrow transplantation. Although the therapy was well tolerated, 3 of the 4 patients eventually relapsed. Because of the short half-life of 131I-p67 in the marrow and the unfavorable biodistribution in many patients, the investigators have since focused on the 131I-anti-CD45 radioimmunoconjugate discussed below.

90Y-HuM195 — Compared with other β-particle emitters, 131I has several disadvantages. First, because of long-ranged γ emissions, patients must be hospitalized and isolated. Second, the long physical half-life of 131I (8.1 days) delays the time from treatment to stem cell infusion in patients undergoing transplantation. Third, when IgG is labeled with high doses of 131I, the ability of the antibody to bind to the target antigen is dramatically reduced. This occurs because approximately one third of the tyrosine residues, to which 131I bonds, are in the hypervariable regions of M195 and HuM195. Therefore, multiple infusions of 131I-M195 or 131I-HuM195 are needed to deliver adequate radiation doses to the marrow for ablation.

90Y offers several advantages over 131I for myeloablation. After internalization of antigen-antibody complexes into target cells, radiometals such as 90Y are better retained within these cells. Furthermore, because 90Y is a pure β-emitter, large doses can be given safely in the outpatient setting with fewer consequences for medical personnel or patients’ families. In a phase I trial at MSKCC, 90Y-HuM195 was studied in patients with relapsed or refractory AML. Nineteen patients were treated with escalating doses of 90Y-HuM195 (0.1 to 0.3 mCi/kg). Transient low-grade liver function abnormalities occurred in 11 patients. Myelosuppression lasted 9 to 62 days, and the maximum tolerated dose without stem cell rescue was 0.275 mCi/kg. Biodistribution and dosimetry studies were performed by co-administering 131I-HuM195. Up to 56 Gy and 75 Gy were delivered to the marrow and spleen, respectively. Thirteen patients had reductions in bone marrow blasts, and 1 patient achieved a complete remission lasting 5 months. All patients treated with 0.3 mCi/kg had hypocellular bone marrow biopsies performed 2 or 4 weeks after treatment, without evidence of leukemia. These results suggest that 90Y-HuM195 will be useful as conditioning before stem cell transplantation. Clinical trials investigating this agent as
part of preparative regimens for autologous and non-myeloablative allogeneic stem cell transplantation are now underway.

**Radiolabeled Anti-CD45 Antibodies**

CD45 is a tyrosine phosphatase expressed on virtually all leukocytes, including myeloid and lymphoid precursors in bone marrow and mature lymphocytes in lymph nodes. It is also expressed on most myeloid and lymphoid leukemic cells, but not on mature erythrocytes or platelets. Unlike CD33, it does not internalize after antibody binding. BC8 is a murine IgG1 anti-CD45 antibody. In a phase I trial at FHCRC, 44 patients with advanced acute leukemia or myelodysplasia received a biodistribution dose of $^{131}$I-BC8. Thirty-seven of the 44 had favorable biodistribution of the radiolabeled antibody. Thirty-four of these patients then received a therapeutic dose of $^{131}$I-BC8 followed by the conditioning regimen of cyclophosphamide (120 mg/kg) plus total body irradiation (12 Gy) before autologous or autologous transplant. An estimated radiation dose to the liver of 10.5 Gy was the maximum tolerated dose that could be administered with cyclophosphamide and total body irradiation. Of the 25 patients with AML or MDS, 7 survived disease-free at a median follow up of 65 months after transplantation. Of the 9 patients with ALL, 3 survived disease-free at 19, 54, and 66 months. The estimated maximum tolerated supplemental dose of radiation added by $^{131}$I-BC8 was 24 Gy to the bone marrow and 50 Gy to the spleen.

Subsequently, a phase I/II trial of $^{131}$I-BC8 together with busulfan and cyclophosphamide prior to matched related allogeneic transplantation was begun in patients with AML in first remission. Ninety percent of patients had a favorable biodistribution of the radiolabeled antibody. These patients were then treated with therapeutic doses of $^{131}$I-BC8, delivering 3.5 Gy (4 patients) or 5.25 Gy (all subsequent patients) to the liver, half the maximum tolerated dose defined in the phase I study. Toxicities attributable to the $^{131}$I-BC8 were minimal. In an encouraging preliminary report, 18 of 24 patients treated with therapeutic doses were alive and disease-free at a median of 42 months after transplant. These studies indicate that $^{131}$I-BC8 can be administered safely to patients and can increase the dose of radiation delivered to the marrow when given as part of a conditioning regimen before hematopoietic stem cell transplantation.

**Radiolabeled Anti-CD66c Antibodies**

CD66c, also known as nonspecific cross-reacting antigen (NCA), is a glycoprotein expressed on myeloid cells but not on leukemia cells. $^{188}$Re-BW 250/183 is a murine monoclonal IgG1 antibody directed at CD66c. $^{188}$Re is a radiometal with a 17-hour half-life. It emits both β and γ radiation, which allows biodistribution and dosimetry studies to be performed easily.

A phase I dosimetry trial showed that administration of $^{188}$Re-BW 250/183 resulted in a favorable biodistribution in 11 of 12 patients, with significant amounts of radiation delivered to the marrow. In a subsequent trial at the Ulm University Hospital in Germany, 36 patients with high-risk AML or myelodysplastic syndrome were treated with $^{188}$Re-BW 250/183 prior to hematopoietic cell transplantation. After treatment with radiolabeled antibody, patients received one of three preparative regimens: total body irradiation (12 Gy) plus cyclophosphamide (120 mg/kg), busulfan (12.8 mg/kg) plus cyclophosphamide (120 mg/kg), or total body irradiation (12 Gy) plus thiotepa (10 mg/kg) and cyclophosphamide (120 mg/kg). Antithymocyte globulin was used to prevent graft rejection in patients receiving grafts from unrelated or mismatched related donors. Thirty-one patients received allogeneic grafts (mostly T-cell-depleted), 1 received a syngeneic graft, and 4 received autologous grafts. Favorable biodistribution of $^{188}$Re-BW 250/183 occurred in all patients. The mean therapeutic dose of radiolabeled antibody administered was 11.1 GBq (300 mCi). The median dose delivered to the bone marrow was 14.9 Gy (range 8.1 to 28 Gy). Besides the toxicity normally associated with the conventional preparative regimens, no additional toxicity attributable to the radiolabeled antibody occurred. However, 6 patients developed nephrotoxicity between 6 and 12 months after the transplant. The authors note that nephrotoxicity after bone marrow transplantation may be an effect of radiation. Engraftment occurred in all patients and was not delayed. Disease-free survival was 45% at the median follow-up of 18 months. Disease-free survival was higher in patients undergoing transplantation while in remission (67%) than in those undergoing transplantation while not in remission (31%). Nine of 35 evaluable patients relapsed. Eight patients died from transplant-related toxicity. This study suggests that $^{188}$Re-BW 250/183, similar to $^{90}$Y-HuM195 and $^{131}$I-BC8, may deliver significant doses of radiation to the marrow without excessive toxicity.

**Radiolabeled Anti-CD25 Antibodies**

The interleukin-2 receptor (IL-2R) consists of at least three IL-2 binding subunits: IL-2Rα (also known as CD25 or Tac), IL-2Rβ, and IL-2Rγ. Normal lymphocytes do not express IL-2Rα. However, in patients with human T-cell leukemia virus I (HTLV-I)-associated adult
Radioimmunotherapy With α-Particle Emitters

Preclinical Studies

The high linear energy transfer and short particle path length of α decays offer the potential for selective killing of tumor cells. The specificity and efficacy of targeted α-particle radioimmunotherapy with 212Bi, 213Bi, and 211At have been reported in several experimental models. In one of the first reports suggesting the feasibility of this approach, 212Bi conjugated to a tumorspecific MAb 103A was used against murine erythroleukemia. Targeting of the construct to neoplastic spleens was seen within 1 hour after injection. When 212Bi-103A was injected on day 13 after inoculation with leukemia cells, reductions in splenomegaly and the absence of liver metastases were noted. When administered on day 8, no histological evidence of erythroleukemia developed. Similarly, administration of 212Bi-anti-Tac after inoculation of nude mice bearing CD25-expressing lymphoma cells led to prolonged tumor-free survival and prevented the development of tumors in some animals. Treatment of established tumors, however, failed to produce responses. The explanation for the failure of 212Bi-anti-Tac to produce responses in established bulky tumors is that most of the 212Bi had decayed by the time that adequate amounts of radiolabeled antibody were taken up into the tumor cells.

213Bi has a half-life of 45.6 minutes and emits an α-particle of 8 MeV. Additionally, a 440 keV photon emission accompanies 26.5% of 213Bi decays, allowing detailed biodistribution and dosimetry studies to be performed. The isotope has been prepared from a 225Ac/213Bi generator and conjugated to HuM195 using the bifunctional chelating agent 2-(4-isothiocyanato-benzyl) diethylenetriamine pentaacetic acid (SCN-CHX-A-DTPA). Intravenous injections of up to 10 mCi/kg of 213Bi-HuM195 were safe in mice. The application of bismuth-labeled HuM195 in vitro resulted in dose-dependent and specific activity-dependent killing of CD33 positive HL60 cells. Approximately 50% of target cells were killed when only two bismuth atoms were bound to the cell surface.

213Bi-HuM195

A phase I dose escalation trial was conducted at MSKCC to determine the toxicity, biodistribution, dosimetry, and biological activity of 213Bi-HuM195. Eighteen patients with relapsed or refractory AML or chronic myelomonocytic leukemia were treated with 0.28 to 1 mCi/kg of 213Bi-HuM195. Treatment was well tolerated, and dose-limiting toxicity was not observed. Transient grade 1 or 2 liver function abnormalities occurred in 6 patients. Myelosuppression lasting 8 to 34 days was seen in all patients. Gamma camera imaging showed localization of 213Bi to expected areas of leukemic involvement, including the bone marrow, liver, and spleen, within 5 to 10 minutes after injection. The absorbed dose ratios between these sites and the whole body were 1,000-fold greater than those seen with β-emitting constructs in this antigen system.

Thirteen of 15 evaluable patients had reductions in peripheral blood leukemia cells, and 14 of the 18 patients had decreases in the percentage of bone marrow blasts. No complete remissions were observed. Because of the nature of α-particle radiation, complete remission at 30 days after treatment would have required the individual targeting and killing of 99.9% of the leukemia cells. Given that the patients treated on this study had tumor burdens of up to 1012 cells, each with an average CD33 density of 10,000 per cell, roughly 1016 leukemic binding sites were available to HuM195. Since approximately 1 in 2,700 molecules of HuM195 carried the radiolabel at dosimetry, and biological activity of 213Bi-HuM195. Eighteen patients with relapsed or refractory AML or chronic myelomonocytic leukemia were treated with 0.28 to 1 mCi/kg of 213Bi-HuM195. Treatment was well tolerated, and dose-limiting toxicity was not observed. Transient grade 1 or 2 liver function abnormalities occurred in 6 patients. Myelosuppression lasting 8 to 34 days was seen in all patients. Gamma camera imaging showed localization of 213Bi to expected areas of leukemic involvement, including the bone marrow, liver, and spleen, within 5 to 10 minutes after injection. The absorbed dose ratios between these sites and the whole body were 1,000-fold greater than those seen with β-emitting constructs in this antigen system. Thirteen of 15 evaluable patients had reductions in peripheral blood leukemia cells, and 14 of the 18 patients had decreases in the percentage of bone marrow blasts. No complete remissions were observed. Because of the nature of α-particle radiation, complete remission at 30 days after treatment would have required the individual targeting and killing of 99.9% of the leukemia cells. Given that the patients treated on this study had tumor burdens of up to 1012 cells, each with an average CD33 density of 10,000 per cell, roughly 1016 leukemic binding sites were available to HuM195. Since approximately 1 in 2,700 molecules of HuM195 carried the radiolabel at the specific activities injected, it was difficult to deliver one to two 213Bi atoms to every leukemia cell, even if optimal antibody targeting were assumed. Nevertheless, this trial is the first proof-of-concept for systemic targeted α-particle immunotherapy in humans and provides the rationale for the continued investigation of this approach in a variety of cancers where minimal residual disease or micrometastatic disease may be present.
More recently, $^{225}$Ac has been conjugated to a variety of MAbs using the bifunctional chelate SCN-DOTA. $^{225}$Ac has a 10-day half-life and decays by $\alpha$ emission through three atoms, each of which also emits an $\alpha$-particle. In vitro, $^{225}$Ac coupled to internalizing MAbs specifically killed leukemia, lymphoma, breast, ovarian, neuroblastoma, and prostate cancer cells at doses 1,000 times less than $^{213}$Bi-containing radioimmunoconjugates. In xenograft models of disseminated human lymphoma and solid prostate carcinoma, single doses at nanocurie levels of tumor-specific constructs prolonged survival and cured a substantial fraction of animals without toxicity. Therefore, in this strategy, $^{225}$Ac-SCN-DOTA serves as an atomic nano-generator that delivers a cascade of four $\alpha$-particles to the inside of a cancer cell by an internalizing antibody. A phase I trial of $^{225}$Ac-HuM195 in advanced myeloid leukemias is planned.

Conclusions

Radioimmunotherapy for leukemia is a promising strategy designed to increase the efficacy of native MAbs, decrease the toxicity of therapy by targeting radiation to specific cell types or organ systems, and ultimately improve the long-term outcome for patients with leukemia. Radioimmunotherapy with $\beta$-particle emitters may be most effective for the treatment of bulky disease or as part of a conditioning regimen for hematopoietic stem cell transplantation, whereas radioimmunotherapy with $\alpha$-particle emitters may be better suited for the treatment of small-volume or minimal residual disease. The phase I and phase II studies described above have demonstrated that radiolabeled antibodies have activity in refractory leukemias, can be administered safely, and can increase the dose of radiation delivered to the marrow when given as part of a conditioning regimen before hematopoietic stem cell transplantation. Whether or not radiolabeled antibodies improve outcome compared with standard chemotherapy agents or conditioning regimens remains to be demonstrated by randomized phase III clinical trials. Future research must also define optimal combinations of MAb and radionuclide in various clinical settings.

References


