Minireview

Radioimmunotherapy of Hematological Cancer: Problems and Progress

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Introduction

The optimistic and naive view of the early 1980s that mAbs\(^2\) were "magic bullets" has now been replaced by a more realistic understanding of the many obstacles to their effective use. Although some mAbs have produced significant antitumor responses in humans (1-6), a number of factors, including the weak cytotoxic activity of many murine mAbs, the difficulty in delivering mAbs to bulky disease, and the heterogeneity of antigen expression on tumor cells, have limited their utility. Because host effector mechanisms are not required for tumor cell killing, radioimmunotherapy has become a promising approach for the treatment of cancer. The use of radiolabeled mAbs may also partly overcome the problems of mAb penetration into solid masses and antigen heterogeneity, since cells in proximity to bound antibody may be killed by exposure to the local radiation field.

Some of the most encouraging results using radioimmunotherapy have been seen in hematological neoplasms. These diseases are ideally suited to the study of mAb therapies because of the accessibility of malignant cells in the blood, bone marrow, spleen, and lymph nodes. Additionally, the well-defined immunophenotypes of the various lineages and stages of hematopoietic differentiation have allowed antigenic targets to be identified (Table 1).

In this review, we consider the various issues that can affect the outcome of therapy with radiolabeled mAbs and examine new areas of investigation to improve therapeutic results. We then discuss some of the recent clinical trials for non-Hodgkin’s lymphoma and leukemia using radioimmunoconjugates.

Physical Obstacles to mAb Delivery

Several clinical trials have illustrated that tumor bulk can limit mAb targeting. In patients with lymphoma treated with an anti-CD21 mAb (OKB7), the percentage of injected dose within biopsied specimens correlated inversely with tumor bulk (7). In a subsequent trial, impaired targeting of anti-CD20 mAbs was reported in lymphoma patients with tumor burdens of over 500 mg or massive splenomegaly (8). Large tumor volumes are also reflected in leukemias with high numbers of circulating blasts. In this setting, mAbs will bind immediately to these blasts, resulting in rapid clearance of the antibody from the circulation. Therefore, mAb-based therapy of bulky disease will often be ineffective.

Other physical characteristics can prevent mAbs from reaching target cells (9). Variations in tumor vasculature can limit the distribution of mAbs to only well-perfused areas of tumor. Endothelial integrity and interstitial back-pressure can also interfere with mAb delivery (10). Within areas of reduced interstitial space, tumor cell volume can also inhibit mAb diffusion (11). Although several strategies to overcome these physical barriers have been investigated, they have met with limited success. Hyperthermia, radiation, and vasoactive agents have been used to increase blood flow to tumors; however, with these approaches, delivery to less-well-perfused areas has remained problematic (12, 13). The use of F(ab')\(2\), Fab, and genetically engineered single-chain Fv antibody fragments potentially offers increased tumor penetration because of the smaller size and lower molecular weight of these constructs (14). Nevertheless, the utility of these mAb fragments will likely be limited by rapid serum clearance, decreased binding avidity, and decreased molecular stability and activity when conjugated to radioisotopes.

Increasing Tumor:Normal Tissue Ratios

Because leukemia and lymphoma-associated antigens are not tumor specific, target antigens found on normal tissue can account for therapy-related toxicity, usually myelosuppression, and can interfere with delivery of mAb to tumor sites. Additionally, uptake of mAbs by normal tissues may occur, e.g., in liver cells and reticuloendothelial cells that bear carbohydrates, Fc receptors, or complement.

Various methods to minimize the nonspecific uptake of mAbs and to increase the ratio of tumor:Normal tissue irradiation are under investigation. Infusion of unlabeled mAbs either before or concomitantly with radiolabeled antibody may allow better access to tumor in some systems by blocking nonspecific binding sites. In clinical studies using the anti-CD20 mAb B1, when unlabeled antibody was given before \(^{131}\text{I}-\text{B}1\), less radioactivity was localized to normal tissues, predominantly the spleen, and greater tumor targeting was observed (15). Since improvement in biodistribution often requires the infusion of large doses of unlabeled antibody, high costs may make this approach impractical.

In an attempt to minimize irradiation of normal tissues, several groups of investigators have developed novel techniques in which circulating mAbs are cleared and isotopes are delivered to pretargeted mAbs. Most of these approaches have exploited the avidin-biotin system (16-19). In a similar strategy, mAbs conjugated to dihydrofolate reductase were later targeted with radiolabeled methotrexate, a high-affinity dihydrofolate reduc-
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Mediated killing because of low antigen density (26). In contrast, others have found that the binding of mAbs within antigen-rich areas of tumor could reduce the number of free antibodies available to diffuse deeper into the tumor and prevent uniform distribution (27, 28).

Although internalization of the antigen-antibody complex after binding can optimize delivery of some radioisotopes to tumor cell nuclei, antigen modulation can also shorten the tumor retention time of radioiodinated mAbs due to catabolism of the radioconjugate. Differences in the rates of endocytosis, intracellular degradation, and cell surface shedding of various mAbs can affect the selection of mAbs for radioimmunotherapy (29). The time to re-expression of antigenic targets on cell surfaces after modulation can affect the scheduling of subsequent mAb doses. For example, in patients with myeloid leukemia treated with trace-labeled 131I-M195, saturation of available CD33 sites was seen within 1 h after administration. Within 1 day, antigenic modulation had occurred, and re-expression of CD33 was detected by MY9 binding 48–72 h after M195 administration (24).

Reduction of Immunogenicity

Because most mAbs used clinically are derived from mice, they can generate a HAMA response. HAMA has been implicated in poor therapeutic results by neutralizing mAb on repeated doses and by enhancing clearance of mAb. Usually, no additional toxicities are seen; however, with large mAb doses, circulating immune complexes can lead to serum sickness.

A number of strategies have been explored to reduce the formation of HAMA. The use of immunosuppressive agents, such as cyclosporine, azathioprine, cyclophosphamide, and anti-T-cell mAbs, have met with variable results (30–32). Although plasmapheresis following an initial course of mAb therapy has allowed retreatment by reducing HAMA levels, enhanced mAb clearance was still noted (33). Therefore, in many clinical applications where repeated dosing is required, rodent mAbs will likely not be useful.

Chimeric and humanized mAbs are less immunogenic than their parental murine mAbs, but in some cases, their prolonged biological half-lives may result in nonspecific dose deposition and toxicity when used for radioimmunotherapy. The complementarity-determining region-grafted humanized version of the anti-CD33 mAb M195 (HuM195) produced no immune responses when given to 13 patients with myeloid leukemia in a Phase I trial. Furthermore, its pharmacokinetics were similar to murine M195, making it a suitable carrier for radioisotopes (34).

Isotope Selection

The choice of an appropriate isotope for radioimmuno-therapy depends on several factors, including the physical and biological half-life of the nuclide, its emission characteristics, labeling efficiency, and the stability of the immunonjugate (Table 2). Most clinical studies have used conjugates with 131I, a long-lived β particle emitter. Because of their relatively long range, β particles have the ability to kill target cells without antigen internalization and to kill surrounding tumor cells. These long-range emissions, however, may also destroy normal bystander cells. The γ emissions from 131I allow dosimetry studies to be performed easily, but treatment at high doses requires patient isolation, can result in significant radiation exposure, and is associated with acute radiation syndrome.

Table 1  Target antigens used in radioimmunotherapy of hematological malignancies

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Diseases</th>
<th>mAbs</th>
<th>Expression on malignant cells (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiotype immunoglobulin</td>
<td>B-cell NHL*</td>
<td>Anti-idiotype</td>
<td>&gt;95</td>
</tr>
<tr>
<td>HLA-DR</td>
<td>B-cell NHL, CLL</td>
<td>Lym-1</td>
<td>&gt;95</td>
</tr>
<tr>
<td>CD20</td>
<td>B-cell NHL, B1, 1F5, 2B8</td>
<td>OKB7</td>
<td>≥50</td>
</tr>
<tr>
<td>CD22</td>
<td>B-cell NHL, LL2</td>
<td>MB-1</td>
<td>≥70</td>
</tr>
<tr>
<td>CD37</td>
<td>B-cell NHL, OKT11</td>
<td>CTCL, CLL, T101</td>
<td>70–90</td>
</tr>
<tr>
<td>CD5</td>
<td>ATL, AML, CML</td>
<td>Anti-Tac</td>
<td>&gt;95</td>
</tr>
<tr>
<td>CD33</td>
<td>AML, CML, M195, HuM195</td>
<td>M95, Hum95, p67</td>
<td>&gt;95</td>
</tr>
<tr>
<td>CD45</td>
<td>AML, ALL, BC8</td>
<td>70–90</td>
<td></td>
</tr>
</tbody>
</table>

* NHL, non-Hodgkin’s lymphoma; CTCL, cutaneous T-cell lymphoma; ATL, adult T-cell leukemia/lymphoma.

Factors such as variability in tumor size and number of binding sites among patients, mAb specificity and binding avidity, immunoreactivity, mAb internalization after binding, and immunogenicity contribute to the difficult and poorly understood pharmacokinetics of radioiodinated mAbs. The number of available antigen sites will alter antibody pharmacokinetics and biodistribution. In a dose escalation trial of the trace-labeled 131I-anti-CD33 mAb M195 for myeloid leukemias, e.g., superior targeting to sites of disease as determined by gamma camera imaging was seen with a comparatively small mAb dose. This may be explained in part by the relatively low number of binding sites (approximately 10,000–20,000) on each leukemia cell (24).

The optimal binding avidity for therapeutic mAbs remains controversial, but most studies indicate that high avidity mAbs confer a therapeutic advantage, particularly for small tumors (25). Some leukemia cells may even be resistant to immunemediated killing because of low antigen density (26).

Tumor targeting to sites of disease as determined by gamma camera imaging was seen with a comparatively small mAb dose. This may be explained in part by the relatively low number of antigen sites on each leukemia cell (24). Other methods to remove circulating radiolabeled mAbs include extracorporeal immunoadsorption (21) and plasmapheresis (22). The administration of chelating agents, such as EDTA or DTPA, after treatment with 99mTc-labeled mAbs has also been shown to facilitate the excretion of circulating radioiodinated mAbs and to decrease bone uptake of released isotope (23).

Antibody Pharmacokinetics

Factors such as variability in tumor size and number of binding sites among patients, mAb specificity and binding avidity, immunoreactivity, mAb internalization after binding, and immunogenicity contribute to the difficult and poorly understood pharmacokinetics of radioiodinated mAbs. The number of available antigen sites will alter antibody pharmacokinetics and biodistribution. In a dose escalation trial of the trace-labeled 131I-anti-CD33 mAb M195 for myeloid leukemias, e.g., superior targeting to sites of disease as determined by gamma camera imaging was seen with a comparatively small mAb dose. This may be explained in part by the relatively low number of binding sites (approximately 10,000–20,000) on each leukemia cell (24).

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exposure to hospital staff, and poses a waste hazard. Although $^{131}$I has been useful in pilot studies, other promising isotopes should be evaluated in future trials.

$^{90}$Y is a pure $\beta$ emitter; its lack of $\gamma$ emissions allow outpatient administration of relatively high doses and reduce radiation exposure to hospital staff. Additionally, if the targeted antigen undergoes modulation (35), the $^{90}$Y radiometal is more likely to be retained intracellularly (35). Therapy with $^{90}$Y, however, poses several difficulties: (a) dissociation of $^{90}$Y from the mAb complex in vivo can result in the deposition of the isotope in bone; (b) unlike $^{131}$I, $^{90}$Y cannot be conjugated directly to a mAb but must be linked to the antibody by a chemical chelator; and (c) because of the absence of $\gamma$ emissions, biodistribution and dosimetry studies require the administration of mAb trace labeled with a second isotope, typically $^{131}$In, whose biodistribution is not identical to $^{90}$Y.

Individual clinical situations play an important role in isotope selection. Therapy with long-range $\beta$ emitters may be better for killing bulky disease, but the use of shorter ranged $\alpha$ particles may be more suitable for high specific activity labeling (46). This decrease in immunoreactivity is related directly to the number of tyrosine residues in the hypervariable region of the mAb and to the linear energy transfer of the $\beta$ particle. The clinical utility of $\alpha$ emitters may be limited by their short half-lives and difficult chemistry.

Table 2 Characteristics of selected radioisotopes for therapy

<table>
<thead>
<tr>
<th>Radioisotope</th>
<th>Half-life</th>
<th>Particulate energy (KeV)</th>
<th>Range of emission (mm)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{131}$I</td>
<td>8.1 days</td>
<td>810</td>
<td>0.8</td>
<td>Good local toxicity within range. High-energy, long-range $\gamma$ emissions allow imaging; nonspecific radiation to normal tissues.</td>
</tr>
<tr>
<td>$^{90}$Y</td>
<td>2.5 days</td>
<td>2200</td>
<td>5.3</td>
<td>High-energy $\beta$ emissions without $\gamma$ emissions.</td>
</tr>
<tr>
<td>$^{186}$Rh</td>
<td>3.7 days</td>
<td>2100</td>
<td>1.8</td>
<td>Emits both $\beta$ and $\gamma$ particles.</td>
</tr>
<tr>
<td>$^{212}$Bi</td>
<td>1 h</td>
<td>6100, 8800</td>
<td>0.04-0.10</td>
<td>Extraordinary potency within a localized range. Short half-life makes in vivo applications difficult.</td>
</tr>
<tr>
<td>$^{213}$Bi</td>
<td>47 min</td>
<td>8400</td>
<td>0.06-0.10</td>
<td>Same advantages and limitations as $^{212}$Bi.</td>
</tr>
<tr>
<td>$^{211}$At</td>
<td>7.2 h</td>
<td>5900</td>
<td>0.04-0.10</td>
<td>Requires cyclotron.</td>
</tr>
</tbody>
</table>

The identification of suitable chelating agents for radiometals has been a challenging task. Studies have shown that the use of the macrocyclic ligand DOTA can result in stable $^{90}$Y immunoconjugates and can significantly reduce bone uptake of radioyttrium (41). Because DOTA has been shown to be immunogenic (42), however, several DTPA-derived chelates have been evaluated. Although none have been tested in vivo as well as DOTA, the A isomer of cyclohexyl-DTPA was found to be a suitable chelate for $^{90}$Y (43). This chelate has also been used to generate bismuth-HuM195 conjugates for myeloid leukemias. These constructs have demonstrated dose-dependent and specific activity-dependent killing of HL-60 target cells in vitro (44).

Radiolabeling of mAbs can cause loss of biological function, especially when they are labeled at high specific activities (45). This decrease in immunoreactivity is related directly to the number of tyrosine residues in the hypervariable region of the mAb to which radioiodide attaches. Immunoreactivity of mAb fragments is lost at even lower specific activities because there are fewer constant region tyrosines (46). In general, although complementarity-determining regions account for less than one tenth of the entire mAb sequence, they typically contain 20–30% of the tyrosine residues in the mAb. In contrast, lysine residues, which bind ligands used for radiometal chelation, are more uniformly distributed. Therefore, radiometal chelates may be more suitable for high specific activity labeling (46).

Dosimetry

Dosimetric studies are performed routinely in most radioimmunotherapy trials. Most techniques are based on the Medical Internal Radiation Dose model (47) and use serial gamma camera imaging along with measurements of plasma, urine, bone marrow, and, occasionally, biopsied target tissue to estimate radiation doses to tumor, marrow (48), and other normal tissues. The validity of these predictions, however, is limited by the accuracy in measuring activity using gamma camera imaging and by the inability to visualize all sites of disease in patients. Single-photon emission computed tomography may increase the accuracy of planar imaging, especially when used in conjunction with computed tomography (49, 50). Nevertheless, the quantitative value of single-photon emission computed tomography remains unknown. Based on dosimetric data, models, like that developed to simulate the distribution of the...
anti-CD33 mAb M195 (51), may provide information about radiation doses delivered to tissues not directly sampled and may also be used to estimate total tumor burden and tumor burden in individual organs. In some trials, dosimetric studies have been used to select patients for therapy based on predictions of response and toxicity. Poor correlation between estimated radiation dose and tumor response, however, have often been observed (52), and this approach is not likely to be practical for widespread clinical use.

**Clinical Trials for Non-Hodgkin’s Lymphoma**

Encouraging results have been obtained with both myeloablative and nonmyeloablative radioimmunotherapy regimens in non-Hodgkin’s lymphoma (Table 3). mAbs reactive with CD20 (B1 and 1F5) and CD37 (MB-1) have been evaluated in myeloablative regimens. Patients whose tumors were estimated to receive greater radiation doses than normal tissues after biodistribution studies received therapeutic infusions of radioiodinated mAbs followed by autologous marrow reinfusion. Doses of $^{131}$I were escalated based on the predicted dose to normal organs. Dose-limiting second organ toxicity was cardiopulmonary toxicity. In this carefully selected population, durable remissions were observed (8). An additional 21 patients with relapsed B-cell lymphoma who had favorable biodistribution have undergone autologous marrow or peripheral progenitor cell transplantation after receiving $^{131}$I-labeled B1 at its maximum tolerated dose of 2700 cGy to normal organs. Eighteen patients responded, with a projected 4-year progression-free survival of 65% (53).

Lower doses of radiolabeled mAbs have also produced responses in patients with relapsed lymphoma. In a nonmyeloablative trial of $^{131}$I-labeled B1, patients were treated with escalating doses of trace-labeled mAb to determine an optimal dose for tumor targeting prior to receiving therapeutically labeled mAbs. These trace-labeled doses had antitumor activity in several patients, complicating the evaluation of the effects of radioimmunotherapy. Therapeutic doses of $^{131}$I were escalated based on the estimated whole-body radiation dose. Myelosuppression was dose limiting, and the maximum tolerated dose was 75 cGy in patients who had not previously received autologous marrow transplantation. Of 27 patients who received therapeutic doses of $^{131}$I-labeled B1, 21 had tumor regressions (15, 54).

Several other radiolabeled mAbs have demonstrated activity against B-cell lymphomas in clinical trials. Significant responses were seen in patients who received $^{90}$Y-labeled 2B8, another anti-CD20 mAb, without the need for hematopoietic progenitor cell rescue (55). Nonmyeloablative doses of $^{131}$I-Lym-1, directed against HLA-DR, have produced responses in patients with refractory lymphoma (56, 57) and reduced adenopathy in patients with CLL (58). Antitumor effects were observed with doses as small as 30 mCi $^{131}$I-labeled anti-CD22 mAb LL2 (59). Additionally, mixed tumor responses have been reported in patients receiving $^{131}$I-labeled OKB7, reactive with CD21 (60).

Fewer radioimmunotherapy trials have been performed in T-cell malignancies. In an early trial, $^{131}$I-labeled T101 (anti-CD5) produced responses in five patients with cutaneous T-cell lymphoma for up to 3 months (61). No objective responses were noted when radioiodinated T101 was given to patients with CLL, although transient decreases in circulating lymphocytes were observed (62). Nine of 18 patients with adult T-cell leukemia/lymphoma who received $^{90}$Y-labeled anti-Tac had sustained complete or partial remission for up to 8 months, with only modest hematopoietic toxicity (63).

### Table 3  Radioimmunotherapy trials in non-Hodgkin’s lymphoma

<table>
<thead>
<tr>
<th>Disease</th>
<th>Radiolabeled mAb</th>
<th>mAb dose (mg)</th>
<th>Isotope dose (mCi)</th>
<th>No. of patients</th>
<th>Response</th>
<th>HAMA (%)</th>
<th>Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-cell NHL</td>
<td>$^{131}$I-B1</td>
<td>58-1168</td>
<td>234-785</td>
<td>40</td>
<td>32 CR</td>
<td>20</td>
<td>Myelosuppression requiring AuBMT. Cardiopulmonary toxicity in 2.</td>
<td>8, 53</td>
</tr>
<tr>
<td>B-cell NHL</td>
<td>$^{131}$I-MF1</td>
<td>15-700</td>
<td>34-161</td>
<td>27</td>
<td>14 CR</td>
<td>18</td>
<td>Mild myelosuppression.</td>
<td>15, 55</td>
</tr>
<tr>
<td>B-cell NHL</td>
<td>$^{131}$I-MB-1</td>
<td>55-294</td>
<td>20-50</td>
<td>14</td>
<td>3 CR</td>
<td>0</td>
<td>Myelosuppression.</td>
<td>55; S. Knox, unpublished data</td>
</tr>
<tr>
<td>B-cell NHL</td>
<td>$^{131}$I-Lym-1</td>
<td>8-676</td>
<td>26-1044</td>
<td>54</td>
<td>11 CR</td>
<td>NR</td>
<td>Unlabeled mAb given prior to therapeutic dose. Thrombocytopenia; hypotension in 1.</td>
<td>56, 57</td>
</tr>
<tr>
<td>B-cell NHL</td>
<td>$^{131}$I-LL2</td>
<td>1.2-3.9</td>
<td>17.6-58.2</td>
<td>7</td>
<td>2 PR</td>
<td>14</td>
<td></td>
<td>59</td>
</tr>
<tr>
<td>B-cell NHL</td>
<td>$^{131}$I-OKB7</td>
<td>25</td>
<td>90-200</td>
<td>18</td>
<td>12 mixed responses</td>
<td>75</td>
<td></td>
<td>60</td>
</tr>
<tr>
<td>CTCL</td>
<td>$^{131}$I-T101</td>
<td>9.9-16.9</td>
<td>100-150</td>
<td>5</td>
<td>2 PR</td>
<td>100</td>
<td>Plasmapheresis allowed retreatment by reducing HAMA.</td>
<td>61</td>
</tr>
</tbody>
</table>

NHL, non-Hodgkin’s lymphoma; CTCL, cutaneous T-cell lymphoma; CR, complete remission; PR, partial remission; MR, minor response; NR, not reported; AuBMT, autologous bone marrow transplant.
HuM195 as well as the pan-leukocyte anti-CD45 mAb BC8 (67) have been conducted. Biodistribution studies with trace-labeled 131I-BC8 demonstrated that 20 of 23 patients would receive more radiation to the marrow than to other normal organs. Greater radiation doses were achieved in patients with AML in relapse than in those who were in remission because of higher uptake and longer retention of radionuclide in the marrow. These 20 patients received therapeutically labeled 131I-BC8, delivering up to 3000 cGy to the marrow, followed by cyclophosphamide (120 mg/kg), total-body irradiation (1200 cGy), and infusion of either matched, related bone marrow, or autologous bone marrow. Sixteen patients achieved complete remission, and 11 have remained in remission from 8+ to 41+ months (67).

Radiolabeled M195 and HuM195 have also displayed significant activity against myeloid leukemias. In a Phase I trial, patients with relapsed or refractory myeloid leukemias were treated with escalating doses of 131I-labeled M195 up to 210 mCi/m². This agent was capable of killing as much as 1 kg of leukemia in some patients, Profound myelosuppression was seen at doses of 135 mCi/m² or greater, allowing eight patients to proceed to BMT. Twenty-six patients achieved complete remission, and 11 have remained in remission from 8+ to 41+ months (67).

<table>
<thead>
<tr>
<th>Disease</th>
<th>Radiolabeled mAb</th>
<th>mAb dose (mg)</th>
<th>Isotope dose (mCi)</th>
<th>No. of patients</th>
<th>Response</th>
<th>HAMA (%)</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>131I-p67</td>
<td>0.05–0.5/kg</td>
<td>110–330</td>
<td>4</td>
<td>4 CR</td>
<td>NR</td>
<td>Given with Cy/TBI prior to AuBMT or AlloBMT; 3 patients achieved durable remissions.</td>
<td>64</td>
</tr>
<tr>
<td>AML/ALL</td>
<td>131I-BC8</td>
<td>0.5/kg/dose</td>
<td>76–400</td>
<td>20</td>
<td>18 CR</td>
<td>NR</td>
<td>Given with Cy/TBI prior to AuBMT or AlloBMT; 4 patients died prior transplant; 4 relapsed; 1 did not engraft.</td>
<td>67</td>
</tr>
<tr>
<td>AML/blastic CML</td>
<td>131I-M195</td>
<td>2–3/m²/dose</td>
<td>50–210/m² (in 2–4 doses)</td>
<td>24</td>
<td>3 CR</td>
<td>37</td>
<td>Hepatic toxicity was seen in 1 patient; 23 patients had decreases in circulating blasts; 17 had decreases in marrow blasts; 5 patients received AlloBMT; 3 received AuBMT.</td>
<td>65</td>
</tr>
<tr>
<td>AML/blastic CML</td>
<td>131I-M195 131I-HuM195</td>
<td>1.5–4/m²/dose</td>
<td>120–230/m² (in 3–4 doses)</td>
<td>27</td>
<td>26 CR</td>
<td>38 (in 131I-M195 patients only)</td>
<td>Given with Bu/Cy prior to first or second AlloBMT; 10 deaths due to infection or GvHD among patients receiving first transplant; 6 patients relapsed.</td>
<td>66</td>
</tr>
<tr>
<td>APL (post-remission therapy)</td>
<td>131I-M195</td>
<td>2/m²/dose</td>
<td>50–70/m² (in 2 doses)</td>
<td>7</td>
<td>8 mo. median duration of CR</td>
<td>71</td>
<td>Given in second CR for residual disease after remission induction with all-trans RA. Prolongation of DFS compared to RA alone was seen.</td>
<td>68</td>
</tr>
<tr>
<td>CLL</td>
<td>131I-Lym-1</td>
<td>1–8</td>
<td>20–65 (multiple courses given)</td>
<td>5</td>
<td>5 PR</td>
<td>20</td>
<td>Decreased adenopathy in all patients and reduction of lymphocytosis in 2 were seen.</td>
<td>58</td>
</tr>
<tr>
<td>ATL</td>
<td>61Y-anti-Tac</td>
<td>5–15</td>
<td>NR</td>
<td>18</td>
<td>9</td>
<td>NR</td>
<td>Modest myelosuppression.</td>
<td>63</td>
</tr>
</tbody>
</table>

Table 4

Radioimmunotherapy trials in leukemia

"CR, complete remission; APL, acute promyelocytic leukemia; ATL, adult T-cell leukemia; PR, partial remission; NR, not reported; AuBMT, autologous bone marrow transplant; AlloBMT, allogeneic bone marrow transplant; Cy/TBI, cyclophosphamide/total body irradiation; Bu/Cy, busulfan/cyclophosphamide; RA, retinoic acid; GvHD, graft-versus-host disease; DFS, disease-free survival.

mg/kg) and cyclophosphamide (120 mg/kg), followed by infusion of HLA-compatible bone marrow. Twenty-seven patients with relapsed/refractory AML, accelerated/blastic CML, or second phase CML were treated. Few toxicities could be attributed to 131I-M195 or 131I-HuM195. Twenty-six patients achieved a documented complete remission, and seven patients remain in an unmaintained complete remission. Only six patients relapsed, including one with isolated central nervous system disease 32 months after treatment. Although these studies suggest that radioimmunotherapy may potentially intensify antileukemic therapy before BMT without increased toxicity or impairment of engraftment, randomized trials will be needed to demonstrate a benefit to this approach.

The role of nonmyeloablative doses of 131I-labeled M195 given in the setting of minimal residual disease has been studied in seven patients with relapsed acute promyelocytic leukemia who attained a second complete remission with all-trans retinoic acid. Effects of therapy on residual disease were monitored by a reverse transcriptase-PCR assay. Two patients converted briefly to negative reverse transcription-PCR determinations following treatment with 131I-labeled M195. Patient outcomes in this trial compared favorably to earlier approaches used for the treatment of relapsed acute promyelocytic leukemia, including BMT (68). Therapy, however, was limited by significant myelosuppression and a high incidence of HAMA formation, which prevented retreatment. In an attempt to exploit the cytotoxicity of unconju-
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gated HuM195 (26, 69), we are examining its role in the treatment of minimal residual disease in several trials, including a large multicenter randomized study.

Conclusions

Treatment programs that combine radioimmunotherapy with other treatment modalities have yielded the most encouraging results. Two applications of radioimmunotherapy appear to be promising: (a) cytoreduction prior to marrow transplantation and (b) elimination of residual disease.

Because of the difficulties in targeting large volume disease, the elimination of minimal residual disease may be a more suitable use of some mAb therapies. It is likely that in this setting, a single course of rodent mAbs will not be adequate therapy. Therefore, the use of immunologically active and less immunogenic “humanized” mAbs or conjugates with short-range α particle emitters may provide more specific tumor cell kill and avoid the nonspecific effects of β emissions.

Myeloablative doses of radiolabeled mAbs have already demonstrated significant activity when used in several transplant preparative regimens (8, 53, 66, 67). Continued Phase I and II trials using this approach will be of limited utility. Comparative trials that definitively answer whether radioimmunotherapy improves patient outcomes in this setting should be initiated soon.

References


Radioimmunotherapy of hematological cancer: problems and progress.

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