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Treatment of Non-Hodgkin's Lymphoma (NHL) With Radiolabeled Antibodies (mAbs)

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Most patients with non-Hodgkin's lymphoma (NHL) achieve remission but, despite newer drugs, the natural history of this disease has not improved during the last 20 years. Less than one half of patients with aggressive NHL are cured, and few of those with low-grade NHL are curable. Furthermore, NHL becomes progressively more chemoresistant while remaining responsive to external beam radiation therapy. Radioimmunotherapy (RIT) is a logical strategy for the treatment of NHL because this disease is multifocal and radiosensitive. Because of their remarkable effectiveness for RIT, 2 anti-CD20 monoclonal antibodies (mAbs), one labeled with ^{111}In for imaging or ^{90}Y for therapy and a second labeled with ^{131}I for imaging and therapy, have been approved for use in patients with NHL. These drugs have proven remarkably effective and safe. Evidence for the importance of the radionuclide is manifested by the data in the randomized pivotal phase III trial of ^{90}Y-ibritumomab that revealed response rates were several times greater in the ^{90}Y-ibritumomab arm than in the rituximab arm. A second drug for RIT, ^{131}I-tositumomab, was compared in a pivotal trial with the efficacy of the last chemotherapy received by each patient. Once again, response rates were much higher for RIT. Both ^{90}Y-ibritumomab and ^{131}I-tositumomab require preinfusion of several hundred milligrams of unlabeled anti-CD20 mAb to obtain "favorable" biodistribution, that is, targeting of NHL. Response rates for other mAbs and radionuclides in NHL also have been high but these drugs have not reached the approval stage. These drugs can be used safely by physicians who have suitable training and judgment. Unlike chemotherapy, RIT is not associated with mucositis, hair loss, or persistent nausea or vomiting. Although hematologic toxicity is dose limiting, hospitalization for febrile neutropenia is uncommon. Randomized trials of RIT in different formulations have not been conducted, but there is evidence to suggest that the mAb, antigen, radionuclide, chelator, linker, and dosing strategy may make a difference in the outcome.
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Although most patients with non-Hodgkin's lymphoma (NHL) achieve remission, a cure occurs in only 25%.[1] Ironically, patients with aggressive NHL can be cured, whereas few with low-grade NHL are curable. Standard chemotherapy cures approximately 40% of patients with aggressive NHL,[2] but NHL becomes progressively more chemoresistant. However, most patients remain responsive to external beam radiation therapy; local disease can be eradicated. External beam radiation therapy is limited to locoregional disease, whereas NHL is usually multifocal.

Immunotherapy using mAbs has provided new treatment for NHL. Administered by intravenous infusion, mAbs target and attach to NHL cells and destroy these cells. This treatment is less toxic, and the duration of treatment is shorter than that of chemotherapy and radiation therapy. Side effects are mostly mild, self-limited, and can be decreased through medications given before and during the infusion. Serious side effects occur infrequently. The pivotal phase III trial of the anti-CD20 mAb, rituximab (Rituxan®, Genentech Inc, South San Francisco, CA; 375 mg/m^2 per week for 4 weeks), resulted in an overall response rate (ORR) of 48% and complete response (CR) rate of 6% in patients with relapsed low-grade or follicular NHL.[3] Rituximab has been less effective in aggressive NHL, but the combination of rituximab with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy in patients with CD20-positive aggressive NHL improved the CR rates compared with CHOP alone (76% versus 63%, $P = 0.005$).[4]

Radioimmunotherapy (RIT), systemic radiation targeted to malignant cells using mAbs, is a logical strategy for the treatment of NHL. NHL is suited to RIT because it is com-

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monly multifocal on presentation, often not cured by standard treatment, radiosensitive, and has remarkably specific antigens (Ags). Additionally, these patients are immunocompromised, making repeated dosing possible. RIT uses a radionuclide attached to the mAb to localize radiation. Targeting of the mAb allows it to find and attach itself to the surface of NHL cells, carrying the radionuclide to these cells. Radionuclide emissions destroy not only the NHL cell to which the mAb is attached but also surrounding cells to which mAbs have not bound. A disadvantage is that surrounding healthy cells also can be damaged.

^{90}Y-ibritumomab tiuxetan (Zevalin®; Biogen Idec Inc, San Diego, CA) was the first radiolabeled mAb to be approved for the treatment of patients with relapsed, low-grade B-lymphocyte NHL. ^{90}Y-ibritumomab tiuxetan comprises ibritumomab, a murine IgG1 anti-CD20 mAb, chelated via the chelator-linker, tiuxetan, to ^{90}Y for treatment. In a randomized pivotal trial in patients with relapsed or refractory, low-grade, follicular or transformed NHL, ^{90}Y-ibritumomab had ORR and CR rates significantly greater than those of rituximab.[5]

A second drug for RIT, ^{131}I-tositumomab (Bexxar®; Corixa Corp, Seattle, WA), also targets the CD20 Ag. In a pivotal trial in patients with refractory, low-grade NHL, ^{131}I-tositumomab was compared with the efficacy of the last chemotherapy received by each patient. Treatment with ^{131}I-tositumomab resulted in significantly improved response rates compared with the last chemotherapy (ORR 65% versus 28%; CR 17% versus 3%).[6] Promising results have been seen with 2 other radiolabeled mAbs, one against the CD22 Ag (epratuzumab; Lymphocide™; Immunomedics Inc, Morris Plains, NJ)[7,8] and the other against HLA-DR (Lym-1; Oncolym™; Peregrine Inc, Tustin, CA),[9,10] although neither has proceeded to pivotal phase III trials.

Historical Background of NHL and RIT

Trials of RIT began in the 1950s when ^{131}I-labeled rabbit polyclonal mAbs were given to patients with metastatic melanoma; CR occurred in 1 patient.[11] In the 1970s, Ettinger and coworkers[12] treated patients with cholangiocarcinomas and hepatomas with ^{131}I-anti-CEA and ^{131}I-antiferritin polyclonal Abs in combination with external beam radiation therapy and chemotherapy; a decrease in tumor size was observed in 6 of 9 patients. After the introduction of hybridoma technology in 1975,[13] mAbs of defined specificity could be produced in gram quantities. Carrasquillo and coworkers[14] then treated patients with radiolabeled mAbs to human melanoma associated Ag; 2 of 3 patients treated with higher doses showed an effect from treatment. Soon thereafter, DeNardo and coworkers[15] published the original description of RIT in a patient with NHL (Fig. 1).

Nadler and coworkers[16] were first to treat a patient with NHL with a mAb (Table 1). Miller and coworkers[17] generated antiidiotypic mAbs to treat individual patients with B-lymphocyte NHL; this trial was successful, although patients relapsed as the result of idiotypic variants. At about the same time, DeNardo and coworkers[15,18,19] used RIT successfully for patients with NHL and chronic lymphocytic leukemia. Since then, others have confirmed the potential of several different radiolabeled mAbs for treatment of NHL. Press and coworkers[21] took a straightforward approach to bone marrow toxicity. Patients with NHL were given ^{131}I-anti-CD20 mAbs in a single dose expected to cause marrow aplasia. Previously harvested autologous bone marrow was subsequently reinfused, thus permitting escalation of the radionuclide dose.

McLaughlin and coworkers[3] demonstrated the efficacy of chimeric anti-CD20 mAbs for immunotherapy for patients with low-grade NHL in a pivotal trial that led to approval of rituximab. Thereafter ^{90}Y-ibritumomab and ^{131}I-tositumomab were approved for RIT.[5,6]

RIT with ANTI-CD20 mAbs

General

Anti-CD20 mAbs react with greater than 95% of B lymphocytes and greater than 90% of B-lymphocyte NHL. Rituximab, a chimeric mAb, works by enlisting immune systems to destroy NHL cells to which it binds and also causes direct NHL cell death by apoptosis. After pretreatment with rituximab to obtain "favorable biodistribution," ^{90}Y-ibritumomab, the mouse parent of rituximab attached to the radionuclide ^{90}Y, is used for RIT (Table 2). Preinfusion of unlabeled anti-CD20 mAb is essential because of the high density of Ag on normal lymphocytes; less unlabeled mAb is associated with poorer detection of known NHL.[21]

Another mouse mAb against the CD20 Ag has also been approved for the treatment of patients with NHL. ^{131}I -tositumomab requires pretreatment with 475 mg of unlabeled anti CD20 mAb to increase the radiation dose to NHL and reduce the radiation dose to normal tissue. More than one half of patients with low-grade or transformed low-grade NHL treated with a single nonmyeloablative dose of ^{131}I-tositumomab for salvage achieve a response, and many of these patients have CR. A phase II trial in previously untreated patients with NHL showed an ORR of 100% and toxicity rarely in excess of grade 2.[22] Press and coworkers[23] have shown that a single dose of ^{131}I-anti CD20 mAb was remarkably effective in patients with relapsed NHL when bone marrow transplantation (BMT) was used to permit administration of large doses of ^{131}I. Tumor doses ranged from 27 to 92 Gy. With a median follow up of 2 years, there was a 62% progression-free survival rate and 93% overall survival rate. Toxicity included 3 serious infections (1 of which led to death), and 3 cases of cardiopulmonary toxicity.

^{90}Y-Ibritumomab (Zevalin®)

The murine IgG1 mAb, ibritumomab, the parent of the chimeric mAb, rituximab, has been attached to the linker chelator tiuxetan (MX-DTPA) and ^{90}Y to form ^{90}Y-ibritumomab. Ibritumomab is a mAb to the CD20 Ag that is expressed on the surface of most normal and malignant B-lymphocytes. Tiuxetan is a second-generation metal chelator that is co-

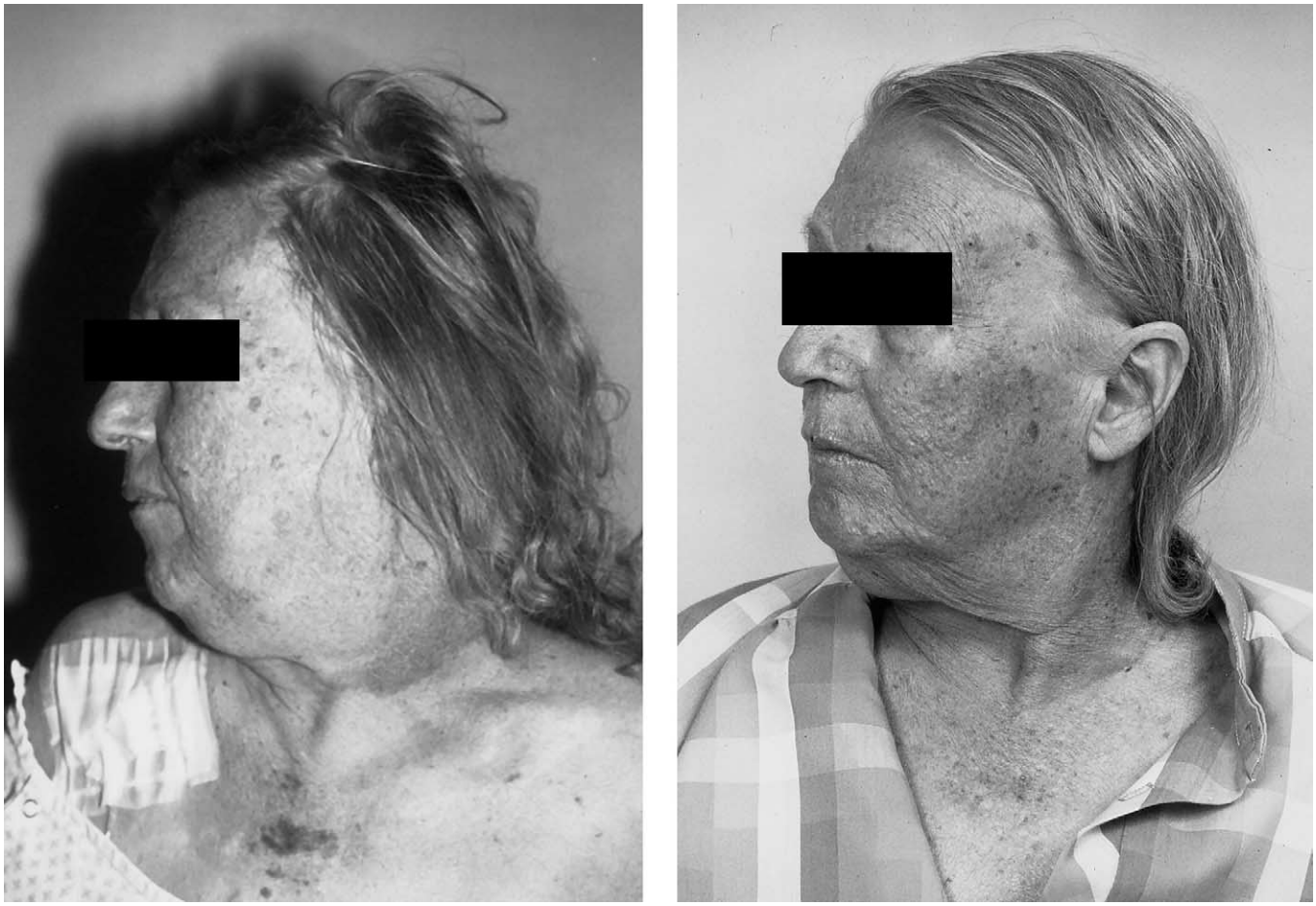

Figure 1 Photographs of patient reflect her moribund state and large NHL tumors before RIT and subsequent improvement after several therapy doses 1.1 or 2.2 GBq (30 or 60 mCi) of ^{131}I-Lym-1. (Reproduced with permission from DeNardo and DeNardo.[51])

valently bound to the mAb and chelates the radionuclides, ^{90}Y for treatment and ^{111}In for imaging. ^{90}Y is a pure beta emitter with a mean path length in soft tissue of approximately 5 mm. ^{90}Y-ibritumomab can be safely administered as an outpatient procedure, consisting of an infusion on day 1 for imaging and a second infusion for treatment within 1 to 2 weeks. Imaging is performed to confirm the expected biodistribution of the ^{111}In-ibritumomab. Biodistribution is evaluated by using a series of whole-body images that are obtained after the administration of ^{111}In-ibritumomab. Patients first receive an infusion of rituximab 250 mg/m^2 to decrease circulating B-lymphocytes and improve tumor targeting. If expected biodistribution is observed, patients proceed to the therapeutic dose of ^{90}Y-ibritumomab. The therapeutic dose also is preceded by an infusion of rituximab 250 mg/m^2. It has been shown that predosing with unlabeled mAb improves the biodistribution of the radiolabeled mAb, from visualization of 18% of NHL sites without a predose to visualization of 92% of NHL sites after administration of 1 or 2.5 mg/kg.[21]

In a dose escalation, phase I-II trial (7.4 to 14.8 MBq/kg; 0.2 to 0.4 mCi/kg), Knox and coworkers[21] treated patients with recurrent low- and intermediate-grade NHL with ^{90}Y-ibritumomab. The ORR after a single dose of ^{90}Y-ibritumomab was 67% in low-grade and 82% in aggressive NHL. The MTD was

Table 1 Highlights of Historical Background of RIT for Patients with NHL*

1980	Original description of immunotherapy using anti-CD20 mAbs, Nadler	(16)
1982	Original description of effective immunotherapy using anti idiotypic mAbs, Miller	(17)
1987	Original description of RIT in NHL (and CLL) using ^{131}I-Lym-1 mAbs, DeNardo	(15,18)
1989	Original description of myeloablative RIT using ^{131}I-anti CD20 MAbs, Press	(20)
1990	Original description of use of RIT using ^{90}Y anti idiotypic mAbs, Parker	(53)
1998	Approval of rituximab based on pivotal trial, McLaughlin	(3)
2002	Approval of ibritumomab tiuxetan based on pivotal trial, Witzig	(5)
2001	Approval of tositumomab based on pivotal trial, Kaminski	(6)
2000	Original description of pretargeted RIT, Weiden	(39)

*Reference numbers in parentheses.

Table 2 Overview of anti-CD20 RIT Using ^{131}I-Tositumomab or ^{90}Y-Ibritumomab

Property	Tositumomab (Bexxar®)	Ibritumomab Tiuxetan (Zevalin®)
Labeled mAb	Mouse anti-CD20 mAb	Mouse anti-CD20 mAb
mAb predose	Mouse anti-CD20 mAb	Chimeric anti-CD20 mAb
Response and toxicity	Similar	Similar
Dosing	Dosimetry	Body weight and baseline platelet count
Radionuclide	^{131}I	^{90}Y
Radionuclide clearance	Faster*	Slower
Radionuclide half-life	8 days	2.7 days
Radionuclide emissions	Beta and gamma†	Beta‡

*May reduce radiation exposure to normal and NHL cells.
†Allows monitoring radiation that goes to the targeted sites in a process called dosimetry
‡May require ^{111}In as surrogate for imaging.

14.8 MBq/kg (0.4 mCi/kg); transient myelosuppression was the primary adverse event. Witzig and coworkers[24] determined that a dose of rituximab of 250mg/m^2 was adequate for improving targeting of ^{90}Y-ibritumomab and that the maximum tolerated single dose was 14.8 MBq/kg (0.4 mCi/kg) in patients with a platelet count of at least 150,000/mL and 11.1 MBq (0.3 mCi/kg) in those with a count between 100,000 to 149,000/mL. In a pivotal phase III trial, ^{90}Y-ibritumomab was compared with rituximab in patients with relapsed or refractory follicular, low-grade, or transformed NHL.[5] Patients were randomized to one treatment with ^{90}Y-ibritumomab 14.8 MBq/kg (0.4 mCi/kg) after infusion of rituximab 250 mg/m^2 or to rituximab 375 mg/m^2/wk for each of 4 weeks. ^{90}Y-ibritumomab produced significantly higher overall (80% versus 56%; $P = 0.002$) and complete (30% versus 16%; $P = 0.04$) response rates than did rituximab (Fig. 2).[5]

The CR/CRu rate was 34% in the ^{90}Y-ibritumomab patients and 20% in the rituximab patients ($P = 0.04$). The efficacy of ^{90}Y-ibritumomab also has been evaluated in patients with rituximab-refractory follicular NHL.[25] The ORR and CR were 74% and 15%, respectively.

Response rates with ^{90}Y-ibritumomab are high and the drug is well tolerated, with delayed, reversible myelosuppression being the dose-limiting toxicity.[5,25,26] Responses have been achieved in patients with bulky tumors, older patients, and those that have failed rituximab. Only patients with adequate bone marrow reserves and less than 25% lymphoma marrow involvement have been approved for treatment (Fig. 3). ^{90}Y-ibritumomab dosing is weight-based. The administered dose of ^{90}Y-ibritumomab usually is between 0.7 to 1.1 GBq (21-30 mCi) and is never more than 1.2 GBq (32 mCi). The risk of radiation exposure is minimal.[27] Imaging can be predicted by substituting ^{111}In.[28]

Unlike chemotherapy, ^{90}Y-ibritumomab RIT was not associated with severe mucositis, hair loss, or persistent nausea or vomiting. The nonhematologic toxicities resembled those of rituximab and were generally mild. Hematologic toxicities, including thrombocytopenia, neutropenia, and anemia, were common adverse events and often were prolonged (median duration, 22 days). The incidence of hospitalization because of febrile neutropenia was 2%.[29] ^{90}Y-ibritumomab has not been associated with an increased frequency of myelodysplastic syndrome or acute myelogenous leukemia over that of chemotherapy.

^{90}Y-ibritumomab is indicated for the treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-lymphocyte NHL, including patients with rituximab-refractory follicular NHL. A total of 152 patients with NHL have received treatment after receiving ^{90}Y-ibritumomab. Therapies given after ^{90}Y-ibritumomab have proven safe and effective. ORRs were comparable to those in patients with NHL not previously treated with ^{90}Y-ibritumomab.

^{131}I-Tositumomab (Bexxar®)

Another drug approved by the Food and Drug Administration for NHL RIT is ^{131}I-tositumomab, which targets the same CD20 Ag. Tositumomab, an IgG2a mouse mAb to which ^{131}I

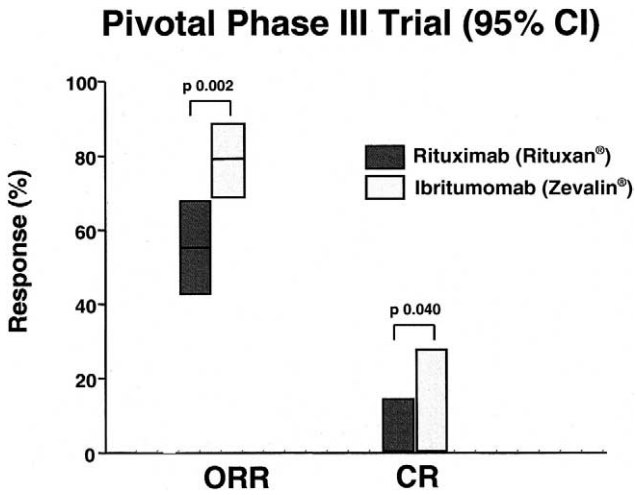

Figure 2 Results for the pivotal phase III trial of ^{90}Y-ibritumomab RIT and rituximab immunotherapy in relapsed/refractory low-grade, follicular, or transformed NHL. Patients randomized into the ^{90}Y-ibritumomab arm were given a tracer dose of 185 MBq (5 mCi) ^{111}In-ibtritumomab on day 0 and then a therapeutic dose of 14.8 MBq/kg (0.4 mCi/kg) ^{90}Y-ibritumomab on day 7. Both ibritumomab doses were preceded by an infusion of 250 mg/m^2 of rituximab. Patients randomized into the rituximab arm received a standard course of rituximab (375 mg/m^2 weekly × 4). The efficacy analysis performed on 143 patients enrolled in this trial showed an ORR of 80% for ^{90}Y-ibritumomab versus 56% for rituximab ($P = 0.002$). CRR was 30% for ^{90}Y-ibritumomab versus 16% for rituximab ($P = 0.04$). (Graphics generated from data in Witzig et al.[5])

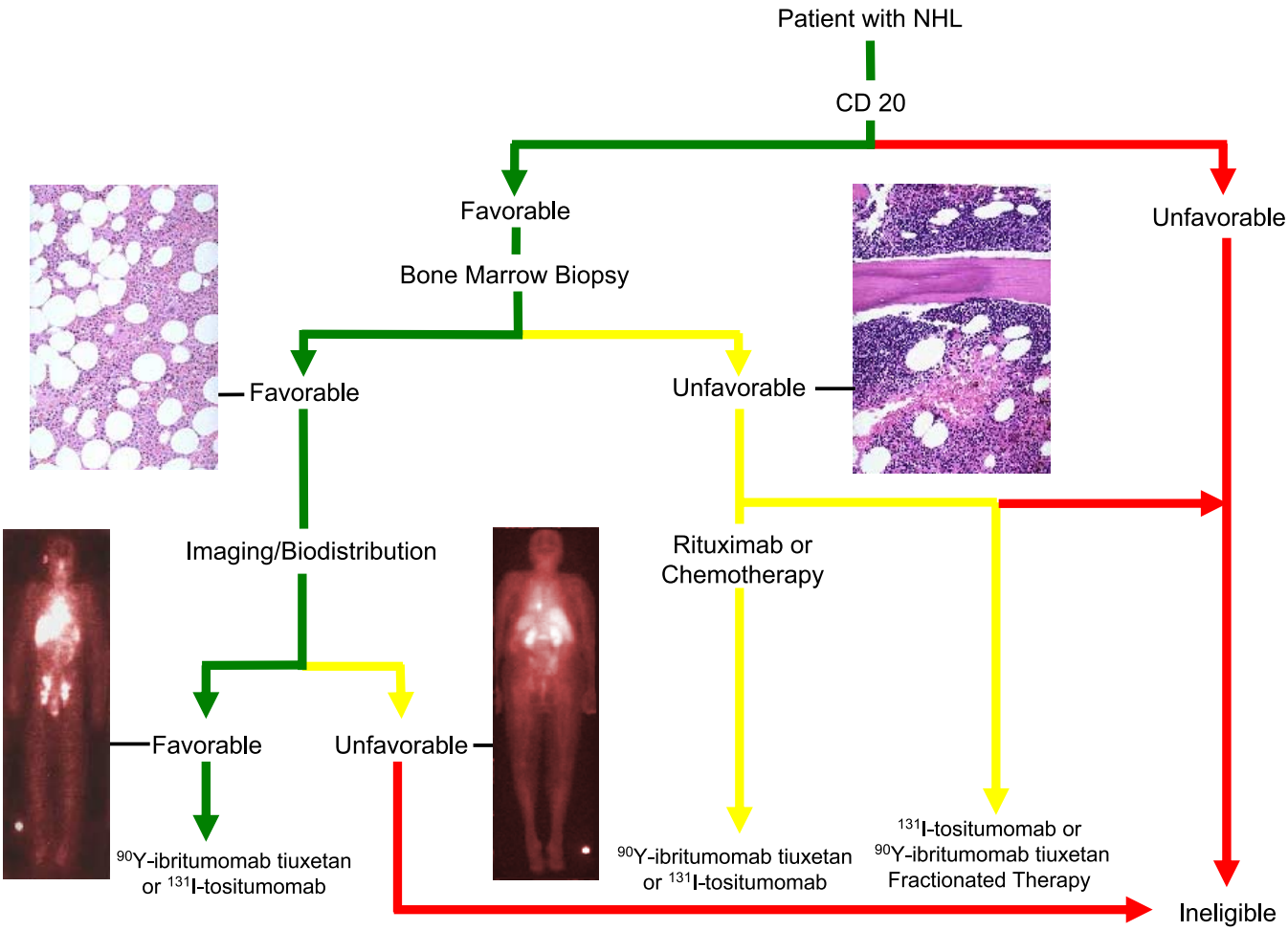

Figure 3 Proposed schematic for treating patients with NHL using ^{90}Y-ibritumomab or ^{131}I-tositumomab. Eligibility for either ^{90}Y-ibritumomab or ^{131}I-tositumomab requires that the patient is resistant/refractory to chemotherapy, has no human antibody against the mAb, has positive CD20 malignant cells, and has not more than 25% NHL involvement of the bone marrow by biopsy. A significant number of patients with NHL are ineligible for RIT because of extensive involvement of the bone marrow by NHL. Although not approved, patients who are ineligible because of extensive marrow involvement might meet this eligibility requirement by marrow cytoreduction using rituximab or chemotherapy before ^{90}Y-ibritumomab or ^{131}I-tositumomab. Alternatively, ^{131}I-tositumomab might be used because the residence time and range of ^{131}I in the marrow are shorter than those of ^{90}Y. If the bone marrow eligibility requirement is met then the patient must have a favorable (expected) biodistribution by imaging to proceed to ^{90}Y-ibritumomab therapy. Imaging is rarely the basis for ineligibility. The anterior image of the patient demonstrates favorable (expected) biodistribution and ^{111}In-ibritumomab uptake in enlarged pelvic and inguinal lymph nodes. The patient with unfavorable (altered) biodistribution shows excessive renal uptake of radionuclide, interpreted to be caused by documented hydronephrosis secondary to tumor obstruction. Both images were obtained about 68 hours after ^{111}In-ibritumomab. mAb, monoclonal antibody; NHL, non-Hodgkin's lymphoma; RIT, radioimmunotherapy. (Reproduced with permission from DeNardo et al.[52]) (Color version of figure is available online.)

is attached, produces beta emissions for treatment and gamma emissions for imaging and dosimetry.[30] In a pivotal phase III trial in patients with low-grade or transformed low-grade NHL, 65% of patients responded to ^{131}I-tositumomab, whereas only 28% of the same patients responded to their previous regimen of salvage chemotherapy (Fig. 4).[6] Overall, trials of ^{131}I-tositumomab in patients with follicular NHL have shown an overall response rate of 81% with a median duration of response of 11 months. There were complete responses in 39% of patients, with a median duration of 57 months. The hematologic toxicity that occurred with ^{131}I-tositumomab was reversible. Nonhematologic toxicities generally were transient and mild. Human Ab responses to this mouse mAb were detected in 56% and 12% of previously untreated and chemotherapy-treated patients, respectively. Personnel can be protected from exposure by observing universal radiation safety precautions. In addition, patients are given saturated solution of potassium iodide or Lugol's solution to prevent the uptake of ^{131}I by the thyroid.

RIT With Other mAbs

Other mAbs and radionuclides have been investigated but have not reached the approval stage. Among these are Lym-1

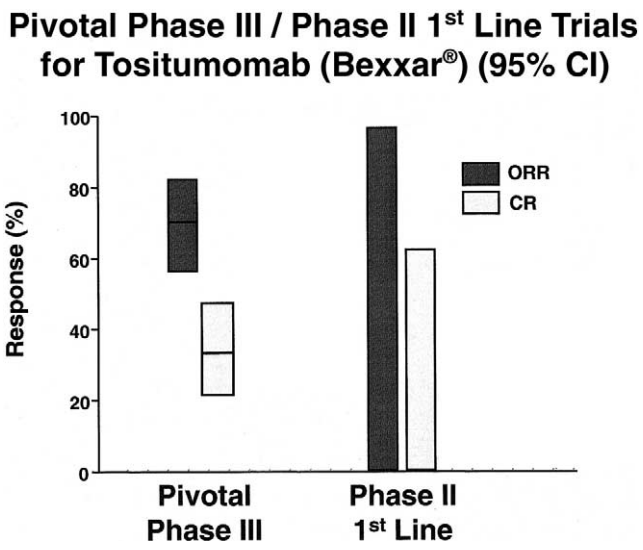

Figure 4 Results for the pivotal phase III trial of ^{131}I-tositumomab in chemotherapy-refractory, low-grade or transformed NHL. Patients who had not responded or had progressed after their most recent chemotherapy regimen were treated with ^{131}I-tositumomab at a dose contributing 75 cGy to the body. The patients had received a median of 4 previous chemotherapy regimens. Sixty-five percent of the patients had a response after ^{131}I-tositumomab compared with only 17 (28%) after their last chemotherapy ($P < 0.001$). Three of the patients had a CR after their last chemotherapy compared with 20% after ^{131}I-tositumomab ($P < 0.001$). In a phase II trial in patients with previously untreated low-grade NHL, ORR was 100% and highly durable. (Graphics generated from data in Kaminski et al.[6,22])

(Oncolym™), which targets HLA-DR10 β, and epratuzumab, which targets CD22.

Approximately 90% of B-lymphocyte NHL malignancies react with Lym-1. Lym-1, an IgG2a mAb with high affinity for a discontinuous epitope on the beta subunit of the human leukocyte Ag (HLA-DR), selectively binds a noncirculating Ag that is highly expressed on the surface of human malignant B-lymphocytes but less so on normal B-lymphocytes. The membrane Ag bound by Lym-1 is not significantly internalized after mAb exposure, nor is it shed into the blood of patients with NHL. ^{131}I-Lym-1, as a single agent, has had significant response rates in all grades of NHL (Fig. 5A). To use the favorable characteristics of radiometals for RIT, trials have been conducted with ^{67}Cu-2IT-BAT-Lym-1 and ^{111}In/^{90}Y-2IT-BAD-Lym-1. Patients given ^{67}Cu-2IT-BAT-Lym-1 (0.9 to 2.2 GBq/m2; 25 to 60 mCi/m2 per dose), the lower dose being used when NHL was detected in the bone marrow, had an ORR of 58%. Myelotoxicity was dose-limiting with ^{90}Y-2IT-BAD-Lym-1, just as it has been in studies of ^{131}I-Lym-1 and ^{67}Cu-2IT-BAT-Lym-1.

Both mLL2 and hLL2 (epratuzumab) are anti-CD22 mAbs that are rapidly internalized on binding to B-lymphocytes Humanized ^{90}Y-epratuzumab (^{90}Y-hLL2; Lymphocide™) has shown high tumor-to-normal organ radiation dose ratios and response rates in patients with relapsed/refractory NHL (Fig. 5B).[8,31-36] A variety of trials have been conducted using (1) mLL2 or hLL2; (2) any of several radionuclides; (3) single or multiple doses; (4) nonmyeloablative or myeloablative approaches; and (5) phase I-II or phase II trials. Response rates and toxicities for RIT have been similar to those for other anti-lymphoma mAbs described here, except that response rates for ^{131}I-anti-CD22 mAbs have been less.[30,37]

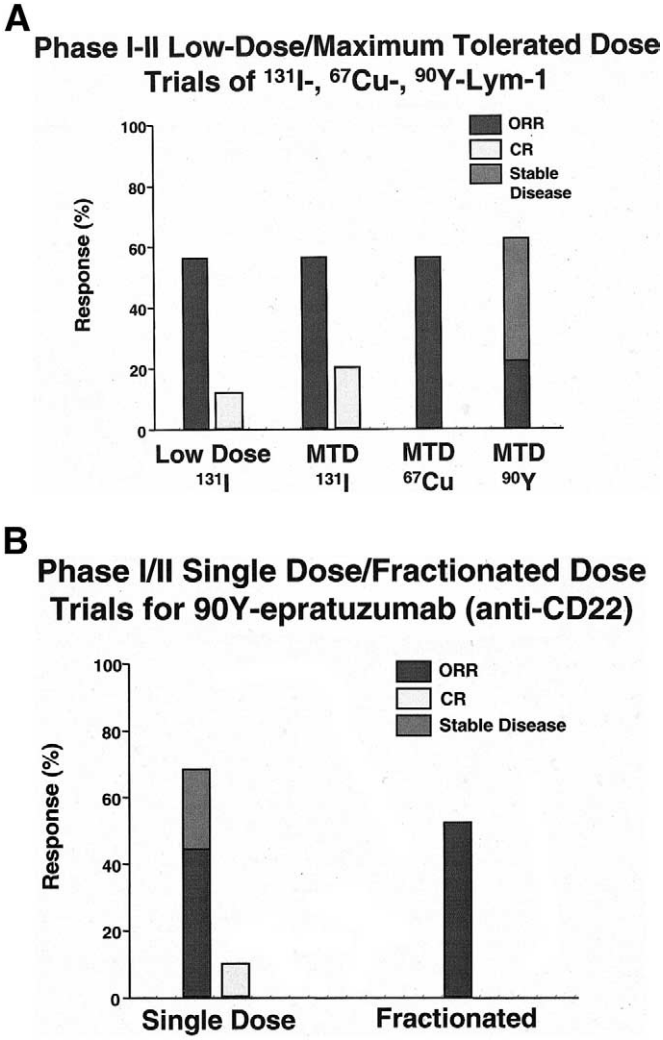

Figure 5 (A) Lym-1, a mouse mAb that targets a discrete epitope of HLA-DR-10β expressed on malignant B-lymphocytes, was studied labeled with ^{131}I, ^{67}Cu, or ^{90}Y. The first of a series of phase I-II, fractionated trials in patients with NHL, using multiple 1.1 or 2.2 GBq (30 or 60 mCi) doses of ^{131}I-Lym-1, showed a 57% ORR. Standard dose escalation trial in cohorts of patients with NHL reached a maximum tolerated dose (MTD) of ^{131}I-Lym-1 of 3.7 GBq/m^2 (100 mCi/m^2) for each of the first 2 doses of ^{131}I-Lym-1 given 4 weeks apart and produced an ORR of 52% and CR rate of 33%; 100% of the cohort entered at the MTD dose level had CRs. When labeled with ^{67}Cu or ^{90}Y, the efficacy was similar to those for ^{131}I-Lym-1. (Graphics generated from data in DeNardo et al.[9,10]) (B) Epratuzumab, humanized anti-CD22 mAb, has been studied in phase I-II trials labeled with ^{90}Y, ^{131}I, or ^{186}Re and in a phase II trial labeled with ^{90}Y. Response rates for ^{90}Y-epratruzumab were similar to those for CD20 and HLA-DR mAbs. The response rates for ^{131}I and ^{186}Re-labeled anti-CD22 mAb were lower than those for ^{90}Y because this mAb is internalized. (Graphics generated from data in other sources.[8,32,33,35])

Toxicity

RIT has proved safe. Treatment-related deaths and hospitalizations for toxicity have been rare. Patients prefer RIT to alternative therapies.

Allergic Reactions

Approximately one fifth of patients developed fevers, rigors, chills, and diaphoresis during and after infusions of mAbs.[38] The reactions typically lasted no more than a few hours. Pruritus and urticaria were observed in as many as 18% of patients. Bronchospasm and anaphylaxis were observed in 2% and 1% of patients, respectively. Rapid infusions and the administration of a large quantity of mAbs, particularly those targeting white blood cells, increase the likelihood of an allergic reaction. To reduce the risk of an allergic response, patients are commonly medicated with acetaminophen and diphenhydramine before and during the infusion of mAbs.

Human Antimouse mAbs

After exposure to mAbs that are foreign proteins, patients may develop human Abs against the foreign protein. A human antimouse Ab (HAMA) response is commonly induced by mouse mAbs and can result in rapid clearance of subsequently administered mAbs from the circulation, reducing tumor uptake and therapeutic efficacy. There is considerable variability in the development of a HAMA response among patients. Chimeric and humanized Abs induce distinctly less Ab responses in patients.

Myelosuppression

Because of the radiosensitivity of bone marrow, myelosuppression, manifested most commonly by thrombocytopenia, has been dose-limiting. Despite occasionally severe thrombocytopenia and neutropenia, bleeding and infection have been rare. In high-dose RIT with BMT, Press and coworkers[23] reported severe postural hypotension, life-threatening congestive cardiomyopathy and hemorrhagic pneumonitis in individual patients after a single infusion of ^{131}I-CD20 mAb that delivered 27 Gy or more to the lungs. When increasing doses of ^{90}Y labeled mAb have been administered to dogs, hepatotoxicity has occurred because of retention of ^{90}Y in the liver after mAb catabolism. Because ^{131}I is rapidly cleared, serious hepatic toxicity has been reported less often than pulmonary toxicity in trials in which high levels of ^{131}I have been delivered.

Concepts

General

The exquisite specificity and unlimited variability of mAbs has ushered in a revival of the concept of the "magic bullets" of Paul Ehrlich. mAbs bind with high specificity and affinity to Ags. Indeed, mAbs are specific for a discrete region, or epitope, of the Ag, thus leading to less cross-reactivity with nonmalignant tissues than polyclonal Abs.

In an effort to improve the results for unconjugated mAbs, mAbs have been conjugated with radionuclides. Radionuclides provide the following advantages: (1) beta emissions kill adjacent cells, regardless of whether they express the target Ag ("bystander" effect); and (2) radiation is not subject to drug resistance. RIT can be regarded as "smart" radiation therapy because systemic, tumor targeted RIT, can deliver as much as 50 times more radiation to malignant cells than that to the normal cells. The highest response rates have been achieved in patients with B-lymphocyte NHL. Beta emissions have ranges of 100 to 500 cell diameters providing a bystander effect on nearby cells that can overcome sources of heterogeneity. To reduce radiation to normal tissues, researchers have used pretargeted RIT. The method encompasses a delivery system in which the radionuclide is injected separately from the mAb, thereby minimizing exposure of normal tissues to circulating radionuclide. Weiden and coworkers,[39] using a streptavidin/biotin 3-step pretargeting approach with an anti-CD20 mAb in patients with NHL, obtained tumor to whole body ratios that were 2 to 3 times higher than those achieved with conventional anti-CD20 RIT.

Does the Radionuclide Make a Difference?

The choice of radionuclide for RIT depends on the type of radiation emitted, its path length in tissue, its elimination, and its half-life. For diagnostic purposes, the most important types of decay are gamma emissions that can be detected by imaging. In contrast, beta particles deposit their energy in the vicinity of the decay. Alpha particles deposit energy over a shorter range than beta particles so that nearby cells are spared. Auger electrons have an even shorter range of energy deposition, so that intranuclear deposition is optimal for cell killing. Beta particles have a small probability of releasing enough energy along their track to produce DNA breaks. Approximately 200 DNA double-strand breaks per cell are required to sterilize 99% of a malignant cell population. High linear energy transfer alpha radiation is densely ionizing and more efficiently produces DNA breaks. Because of their short range in tissues, alpha (and Auger electrons) have little bystander effect.

^{131}I is eliminated from tissues as the mAb is catabolized. If the Ag undergoes internalization within the NHL cell after mAb binding, "dehalogenation" is a problem. Radiometals like ^{90}Y are retained (residualized) in tissues once the mAb has been catabolized. A residualizing radionuclide increases tumor radiation dose but also potentially increases the radiation dose to normal tissues, such as the liver, where proteins are catabolized. An additional disadvantage of ^{90}Y is that, if freed from the chelated mAb, it accumulates in bone, thereby increasing radiation to the marrow. DeNardo and coworkers[40] compared the radiation dosimetry of ^{67}Cu, ^{131}I and ^{90}Y labeled-Lym-1 in patients with NHL. The therapeutic index (ratio of radiation doses to tumor and normal tissues) was most favorable for ^{67}Cu.

Does the Ag Make a Difference?

Several of the many Ags that are present on NHL cells have been targeted in trials of radiolabeled mAbs. These include

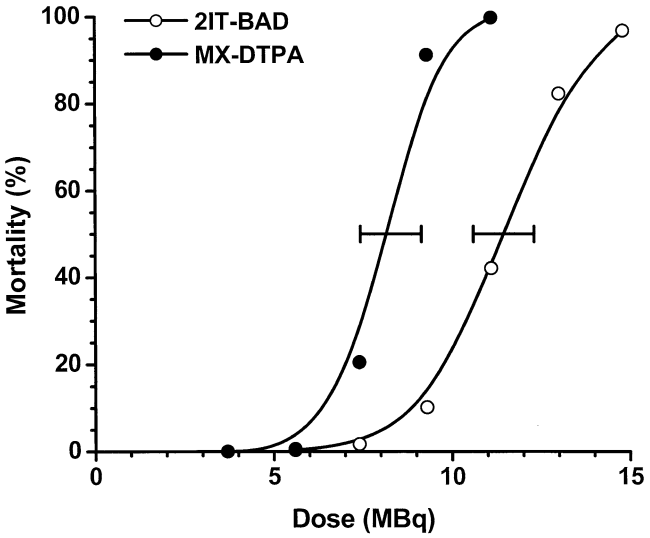

Figure 6 Survival of mice given ^{90}Y-MX-DTPA (●) or 2 to 2IT-BAD (○) chelated mAb. All drug mortality occurred within 30 days after treatment. Predicted probability of mortality rate was calculated using logistic regression analysis. Data points represent 9 to 19 mice; bars, 95% confidence interval. The $LD_{50/30}$ for ^{90}Y-MX-DTPA chelated mAb was 8.1 MBq (218 μCi) and that for ^{90}Y-DOTA chelated (2IT-BAD) was 11.4 MBq (309 μCi). Whole-body autoradiography of mice revealed substantially greater uptake of ^{90}Y in the skeleton when MX-DTPA was used as the chelator. (Graphics generated from data in DeNardo et al.[44])

CD19, CD20, CD22, CD37, MHC class II allele HLA-DR10, and immunoglobulin idiotype Ags. CD20, CD22, and HLA-DR Ags are restricted to B-lymphocytes and are present on approximately 90% of B-lymphocytic NHL and normal B lymphocytes but not on stem cells, pre-B-lymphocytes, and plasma cells. HLA-DR and CD20 Ags are present at high densities on malignant lymphocytes, whereas CD22 is less abundant. In addition to high densities on malignant lymphocytes, CD20 Ag also is found in high densities on normal B lymphocytes; therefore, a larger anti-CD20 mAb dose is required to target NHL tissue. Because Lym-1 has preferential reactivity with malignant lymphocytes, only small amounts of Lym-1 are required to achieve optimal targeting of NHL.

Does the mAb Make a Difference?

For immunotherapy, chimeric or humanized mAbs, because of their slower clearance rates, are preferred but, for RIT, slow blood and body clearance can be a disadvantage. The choice of mAb for RIT depends to some extent on the radionuclide used; a mouse mAb is cleared from the patient faster than a chimeric or humanized mAb.

Anti-CD20 mAbs are cytotoxic for both malignant and mature lymphocytes. RIT, using rituximab, induces lymphopenia. Because B-lymphocyte precursors do not express CD20 Ag, B-lymphocytes return to normal at about 6 months after treatment. Anti-HLA-DR and CD22 mAbs also have been shown to be cytotoxic for malignant B lymphocytes.[41,42] Additionally, mAbs against a common Ag may bind to different epitopes of the Ag, thereby having quite different characteristics. Another issue concerns human antiglobulin Ab responses. An Ab response in the patient may make it difficult to continue to treat the patient. If repeat doses are anticipated, a chimeric or humanized mAb may be favored.

Does the Chelator Make a Difference?

Radionuclides like ^{131}I are covalently bound to mAbs, usually on a tyrosine residue, whereas metallic radionuclides are bound by a chelate that has been conjugated to lysyl residues of the mAb. Although mAb specific, the addition of less than 4 chelators does not seem to alter immunoreactivity.[43] Recently developed macrocyclic chelators for radiometals, such as ^{111}In and ^{90}Y, provide greater stability in vivo. DeNardo and coworkers[44] investigated the effect of 2 different ^{90}Y chelators, methylbenzyldiethylene-triaminepentaacetic acid (MX-DTPA) and bromoacetamidobenzyl-1,4,7,10-tetraazocyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid (DOTA). The LD_{50} in mice was higher when the latter was used as the ^{90}Y chelator compared with MX-DTPA (Fig. 6). For both chelators, bone marrow toxicity was the cause of death. Whole-body autoradiography revealed greater uptake of ^{90}Y in the skeleton when MX-DTPA was used as the chelator. Similarly, Griffiths and coworkers[33] examined the effects of different chelating agents conjugated to the anti-CD22 mAb, epratuzumab. Each conjugate was labeled with ^{90}Y and the biodistribution compared in normal and lymphoma-bearing mice. Two DTPA derivatives were compared with DOTA. The DTPA chelates lost 3% to 4% of ^{90}Y over the first few days. ^{90}Y uptake in bone was significantly lower when DOTA was used as the chelator.

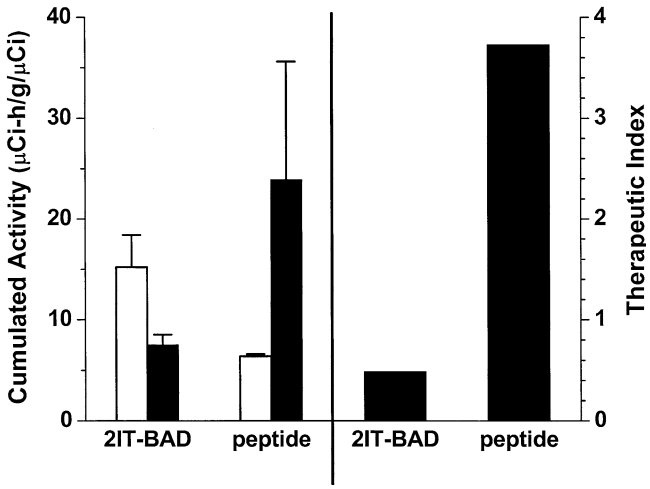

Figure 7 Cumulated activities (μCi-h/g/μCi) for ^{111}In-2IT-BAD and peptide-linked Lym-1 for liver (□) and tumor (■). When compared with 2IT-BAD, liver cumulated activity for DOTA-peptide Lym-1 was consistently reduced, whereas the tumor cumulated activities were maintained. The tumor-to-liver therapeutic index for DOTA-peptide-Lym-1 (cathepsin B degradable) was much higher than that for 2IT-BAD nondegradable linked Lym-1. Cumulated activities were obtained using nonlinear regression to analyze monoexponential activity concentrations obtained from the pharmacokinetic studies (error bars represent SE). (Graphics generated from data in DeNardo et al.[45])

Does the Linker Make Any Difference?

In myeloablative strategies, the liver usually is dose-limiting for radiometal labeled mAbs. The radiation dose to the liver can be reduced by attaching the chelated radiometal to the mAb using a degradable peptide linker. Cathepsin cleavage in hepatocytes leads to a radioactive moiety that can be rapidly excreted by the kidney. DOTA-peptide-Lym-1 has a tetra peptide linker that is susceptible to cathepsin B, an enzyme in hepatocytes. The pharmacokinetic and dosimetric properties of ^{111}In- and ^{90}Y-labeled DOTA-peptide-Lym-1 were compared with those for the same radiolabeled mAbs with a nondegradable linker (2-iminothiolane (2-IT)-2-[*p*-(bromoacetamido)benzyl]-DOTA) in athymic mice bearing human NHL xenografts (Fig. 7).[45] Liver concentration, cumulated activity, and radiation dose of the DOTA-peptide-Lym-1 were less than one half those of the corresponding 2-iminothiolane (2-IT)-2-[*p*-(bromoacetamido)-benzyl]-DOTA drugs.

Do Dosing, Imaging, and Dosimetry Make a Difference?

The amount of radionuclide administered and the manner in which it is administered affect RIT. There are 2 broad algorithms for selecting the dose of radionuclide. ^{90}Y-ibritumomab and ^{131}I-tositumomab use different algorithms. A fixed-dose approach, based on body weight and bone marrow status, is used for ^{90}Y-ibritumomab whereas the dose of ^{131}I-tositumomab varies, depending on the body pharmacokinetics and weight of individual patients. ^{90}Y-ibritumomab is administered using an empirically selected radionuclide dose, based on observations of dose-limiting toxicity in a similar population of patients. It is assumed that a little pharmacokinetic variability exists between patients. The individualized approach to dosing used for ^{131}I-tositumomab requires predictive dosimetry and is preferred in cases in which there is interpatient variability. In other forms of radiation therapy, treatment planning for an individual patient has been shown to be important for optimal response and morbidity.

Radioimmunoimaging demonstrates mAb distribution in the patient. To image, a gamma-emitter is necessary. Dosimetric analyses are useful in the course of drug development to evaluate safety, toxicity, and efficacy. Radiation dosimetry also can be used to assess the results of treatment and for treatment planning for individual patients. Treatment planning for an individual patient ("patient-specific dosimetry") should be an ultimate goal.

Once the radionuclide dose has been determined, the dosing schedule must be considered. There are 2 approaches to administering RIT: a single large dose or multiple smaller doses of radionuclide can be given. Press and coworkers[20] administered almost a Curie of ^{131}I-anti-CD20 mAb to patients with NHL in a myeloablative strategy followed by autologous stem cell transplantation, showing remarkably good efficacy. A single dose of ^{131}I- or ^{90}Y-labeled mAb also has been shown to be effective in nonmyeloablative strategies.[46,47] An alternative approach involves the administration of multiple doses, often referred to as "fractionation."[48] The rationale for fractionated RIT is based on evidence that the radiation dose to the tumor, and the dose tolerated by normal tissues, can be increased.[9,49,50] Another advantage of fractionating the total radionuclide dose is better distribution of the microscopic radiation dose because of reduced heterogeneity of mAb targeting over several doses. Tumor control is less with nonuniform radiation because some regions of the tumor may be under-dosed. Fractionation also permits toxicity to be controlled by titration in the individual patient. Fractionation also can be used to reduce toxicity, when patients with bone marrow NHL are to be treated.[48]

With external beam treatment, radiation is intermittently pulsed at a high, constant dose rate (about 60 Gy/h) to a limited region of the body. With RIT, radiation is continuously delivered at a low dose rate that decreases because of physical and biologic decay. Dose rates as low as 0.05 Gy/h can stop the growth of radiosensitive NHL cells. Additionally, mAbs themselves may, in some cases, exert anti NHL effects.

References

1. Armitage JO: Treatment of non-Hodgkin's lymphoma. N Engl J Med 328:1023-1030, 1993
2. Fisher RI, Gaynor ER, Dahlberg S, et al: Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 328:1002-1006, 1993
3. McLaughlin P, Grillo-Lopez AJ, Link BK, et al: Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: Half of patients respond to a four-dose treatment program. J Clin Oncol 16:2825-2833, 1998
4. Coiffer B, Lepage E, Briere J, et al: CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 346:235-242, 2002
5. Witzig TE, Gordon LI, Cabanillas F, et al: Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. J Clin Oncol 20:2453-2463, 2002
6. Kaminski MS, Zelenetz AD, Press OW, et al: Pivotal study of iodine I 131 tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. J Clin Oncol 19: 3918-3928, 2001
7. Juweid M, Sharkey RM, Markowitz A, et al: Treatment of non-Hodgkin's lymphoma with radiolabeled murine, chimeric, or humanized LL2, an anti-CD22 monoclonal antibody. Cancer Res 55:5899s-5907s, 1995
8. Juweid ME, Stadtmauer E, Hajjar G, et al: Pharmacokinetics, dosimetry and initial therapeutic results with ^{131}I- and ^{111}In-/^{90}Y-labeled humanized LL2 anti-CD22 monoclonal antibody (MAb) in patients with relapsed/refractory non-Hodgkin's lymphoma (NHL). Clin Cancer Res 5:3292s-3303s, 1999
9. DeNardo GL, DeNardo SJ, Lamborn KR, et al: Low-dose fractionated radioimmunotherapy for B-cell malignancies using ^{131}I-Lym-1 antibody. Cancer Biother Radiopharm 13:239-254, 1998
10. DeNardo GL, DeNardo SJ, Goldstein DS, et al: Maximum tolerated dose, toxicity, and efficacy of ^{131}I-Lym-1 antibody for fractionated radioimmunotherapy of non-Hodgkin's lymphoma. J Clin Oncol 16: 3246-3256, 1998
11. Beierwaltes WH: Radioiodine-labeled compounds previously or currently used for tumor localization., in Agency IAE (ed): Proceedings of an Advisory Group Meeting on Tumor Localization with Radioactive Agents. Panel Proceedings Series. Vienna, Austria, International Atomic Energy Agency, 1974
12. Ettinger DS, Dragon LH, Klein J, et al: Isotopic immunoglobulin in an integrated multimodal treatment program for a primary liver cancer. A case report. Cancer Treat Rep 63:131-134, 1979

13. Kohler G, Milstein C: Continuous culture of fused cells secreting antibody of predefined specificity. Nature 256:495-497, 1975
14. Carrasquillo JA, Krohn KA, Beaumier P, et al: Diagnosis of and therapy for solid tumors with radiolabeled antibodies and immune fragments. Cancer Treat Rep 68:317-328, 1984
15. DeNardo SJ, DeNardo GL, O'Grady LF, et al: Treatment of a patient with B cell lymphoma by I-131 Lym-1 monoclonal antibodies. Int J Biol Markers 2:49-53, 1987
16. Nadler LM, Stashenko P, Hardy R, et al: Serotherapy of a patient with a monoclonal antibody directed against a human lymphoma-associated antigen. Cancer Res 40:3147-3154, 1980
17. Miller RA, Maloney DG, Warnke R, et al: Treatment of B-cell lymphoma with monoclonal anti-idiotype antibody. N Engl J Med 306:517-522, 1982
18. DeNardo SJ, DeNardo GL, O'Grady LF et al: Pilot studies of radioimmunotherapy of B cell lymphoma and leukemia using I-131 Lym-1 monoclonal antibody. Antibody Immunoconj Radiophar 1:17-33, 1988
19. DeNardo GL, DeNardo SJ, O'Grady LF et al: Fractionated radioimmunotherapy of B-cell malignancies with ^{131}I- Lym-1. Cancer Res 50: 1014-1016, 1990 (suppl)
20. Press OW, Eary JF, Badger CC, et al: Treatment of refractory non-Hodgkin's lymphoma with radiolabeled MB-1 (anti-CD37) antibody. J Clin Oncol 7:1027-1038, 1989
21. Knox SJ: Radioimmunotherapy of the non-Hodgkin's lymphomas. Semin Radiat Oncol 5:331-341, 1995
22. Kaminski M, Tuck M, Regan D: High response rates and durable remissions in patients with previously untreated, advanced-stage, follicular lymphoma treated with tositumomab and iodine I-131 tositumomab (Bexxar). Blood 100:356a, 2002
23. Press OW, Eary JF, Appelbaum FR, et al: Phase II trial of ^{131}I-B1 (anti-CD20) antibody therapy with autologous stem cell transplantation for relapsed B cell lymphomas. Lancet 346:336-340, 1995
24. Witzig T, White C, Wiseman G, et al: Phase I/II trial of IDEC-Y2B8 radioimmunotherapy for treatment of relapsed or refractory CD20 B-cell non-Hodgkin's lymphoma. J Clin Oncol 17:3793-3803, 1999
25. Witzig TE, Flinn IW, Gordon LI, et al: Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. J Clin Oncol 20:3262-3269, 2002
26. Wiseman GA, Leigh B, Erwin WD, et al: Radiation dosimetry results for Zevalin radioimmunotherapy of rituximab-refractory non-Hodgkin lymphoma. Cancer 94:1349-1357, 2002
27. Wiseman GA, Leigh B, Witzig T et al: Radiation exposure is very low to family members of patients treated with yttrium-90 Zevalin TM anti-CD20 monoclonal antibody therapy for lymphoma. Eur J Nucl Med 28:1198, 2001
28. Wagner HN, Wiseman GA, Marcus CS, et al: Administration guidelines for radioimmunotherapy of non-Hodgkin's Lymphoma with ^{90}Y-labeled anti-CD20 monoclonal antibody. J Nucl Med 43:267-272, 2002
29. Witzig TE, White CA, Gordon LI: Safety of yttrium-90 ibritumomab tiuxetan radioimmunotherapy for relapsed low-grade, follicular, or transformed non-Hodgkin's lymphoma. J Clin Oncol 21:1263-1270, 2003
30. Vose JM, Colcher D, Gobar L, et al: Phase I/II trial of multiple dose ^{131}Iodine-MAb LL2 (CD22) in patients with recurrent non-Hodgkin's lymphoma. Leuk Lymphoma 38:91-101, 2000
31. Goldenberg DM, Horowitz JA, Sharkey RM, et al: Targeting, dosimetry, and radioimmunotherapy of B-cell lymphomas with iodine-131-labeled LL2 monoclonal antibody. J Clin Oncol 9:548-564, 1991
32. Sharkey RM, Brenner A, Burton J, et al: RIT of non-Hodgkin's lymphoma with 90Y-DOTA humanized anti-CD22 IgG (90Y-Epratuzumab): Do tumor targeting and dosimetry predict therapeutic response? J Nucl Med 44:2000-2018, 2003
33. Griffiths GL, Govindan SV, Sharkey RM, et al: ^{90}Y-DOTA-hLL2: An agent for radioimmunotherapy of non-Hodgkin's lymphoma. J Nucl Med 44:77-84, 2003
34. Linden O, Tennvall J, Cavallin-Stahl E, et al: Radioimmunotherapy using ^{131}I-labeled anti-CD22 monoclonal antibody (LL2) in patients with previously treated B-cell lymphomas. Clin Cancer Res 5:3287s-3291s, 1999
35. Linden O, Tennvall J, Cavallin SE, et al: Durable response to 90Y-epratuzumab (hLL2) in B-cell lymphoma failing chemotherapy by using dose-fractionation schedule. Blood 98:2524, 2001
36. Postema EJ, Raemaekers JM, Oyen WJG, et al: Final results of a phase I RIT trial using 186Re-Epratuzumab for the treatment of patients with non-Hodgkin's lymphoma. Clin Cancer Res 9:3995s-4002s, 2003
37. Juweid ME: Radioimmunotherapy of B-cell non-Hodgkin's lymphoma: From clinical trials to clinical practice. J Nucl Med 43:1507-1529, 2002
38. Dillman RO, Beauregard JC, Halpern SE, et al: Toxicities and side effects associated with intravenous infusions of murine monoclonal antibodies. J Biol Response Modifiers 5:73-84, 1986
39. Weiden PL, Breitz HB, Press O, et al: Pretargeted radioimmunotherapy (PRIT) for treatment of non-Hodgkin's lymphoma (NHL): Initial phase I/II study results. Cancer Biother Radiopharm 15:15-29, 2000
40. DeNardo GL, Kukis DL, Shen S, et al: ^{67}Cu-versus 131I-labeled Lym-1 antibody: Comparative pharmacokinetics and dosimetry in patients with non-Hodgkin's lymphoma. Clin Cancer Res 5:533-541, 1999
41. Liu C, DeNardo GL, Tobin E, et al: Antilymphoma Effects of Anti-HLA-DR and CD20 monoclonal antibodies (Lym-1 and Rituximab) on human lymphoma cells. Cancer Biother Radiopharm 19:545-561, 2004
42. Leonard JP: Immunotherapy of non-Hodgkin's lymphoma with hLL2 (Epratuzumab, an anti-CD22 monoclonal antibody) and HuID10 (Apolizumab). Semin Oncol 29:81-86, 2002
43. Kukis DL, DeNardo GL, DeNardo SJ, et al: Effect of the extent of chelate substitution on the immunoreactivity and biodistribution of 2IT-BAT-Lym-1 immunoconjugates. Cancer Res 55:878-884, 1995
44. DeNardo GL, Kroger LA, DeNardo SJ, et al: Comparative toxicity studies of yttrium-90 MX-DTPA and 2-IT-BAD conjugated monoclonal antibody (BrE-3). Cancer 73:1012-1022, 1994
45. DeNardo GL, DeNardo SJ, Peterson JK, et al: Preclinical evaluation of cathepsin-degradable peptide linkers for radioimmunoconjugates. Clin Cancer Res 9:3865-3872, 2003 (suppl)
46. Kaminski MS, Estes J, Zasadny KR, et al: Radioimmunotherapy with iodine (131)I tositumomab for relapsed refractory B-cell non-Hodgkin lymphoma: Updated results and long-term follow-up of the University of Michigan experience. Blood 96:1259-1266, 2000
47. Wiseman GA, White CA, Witzig TA, et al: Final dosimetry results of IDEC-Y2B8 phase I/II ^{90}Yttrium radioimmunotherapy trial on non-Hodgkin's lymphoma (NHL). J Nucl Med 40:64P, 1999
48. DeNardo GL, Schlom J, Buchsbaum DJ, et al: Rationales, evidence and design considerations in multiple dose (fractionated) radioimmunotherapy. Cancer 94:1332-1348, 2002
49. DeNardo GL, DeNardo SJ, Kukis DL, et al: Maximum tolerated dose of ^{67}Cu-2IT-BAT-Lym-1 for fractionated radioimmunotherapy of non-Hodgkin's lymphoma: A pilot study. Anticancer Res 18:2779-2788, 1998
50. Meredith RF, Khazaeli MB, Liu T, et al: Dose fractionation of radiolabeled antibodies in patients with metastatic colon cancer. J Nucl Med 33:1648-1653, 1992
51. DeNardo GL, DeNardo SJ: Radioimmunotherapy, in Haynie TP (ed): Nuclear Medicine: Oncology (ed 1). Reston, VA, Society of Nuclear Medicine, 2000, pp 39-74
52. DeNardo GL, Kennel SJ, Siegel JA, et al: Radiometals as payloads for radioimmunotherapy for lymphoma. Clinical Lymphoma 5:5-10, 2004 (suppl)
53. Parker BA, Vassos AB, Halpern SE, et al: Radioimmunotherapy of human B-cell lymphoma with Y-90-conjugated antiidiotype monoclonal antibody. Cancer Res 50:1022s-1028s, 1990 (suppl)