Copper-2-Iminothiolane-6-[p-(Bromoacetamido)benzyl]-TETA-Lym-1 for Radioimmunotherapy of Non-Hodgkin’s Lymphoma

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Abstract

Copper-67 (67Cu) has ideal properties for radioimmunotherapy. The 62-h half-life is similar to the residence time of antibodies in tumor, and the therapeutic β emission of 67Cu is comparable to that of 131I. 67Cu, however, has γ emissions similar to 99mtechnetium that are favorable for imaging. The macrocyclic chelating agent 1,4,7,11-tetraazacyclotetradecane-N,N’,N″,N‴'-tetraacetic acid (TETA) binds 67Cu tightly and selectively, facilitating linkage to Lym-1, a mouse monoclonal antibody that preferentially targets malignant lymphocytes. The safety, efficacy, and practicality of 67Cu-2-iminothiolane (2IT)-6-[p-(bromoacetamido)benzyl]-TETA (BAT)-Lym-1 was assessed in this Phase I/II clinical trial for patients with non-Hodgkin’s lymphoma (NHL) who had failed standard therapy. Up to four doses of 67Cu-2IT-BAT-Lym-1, 25 or 50–60 mCi/m2 dose (0.93 or 1.85–2.22 GBq/m2, dose, respectively) were administered; the lower dosage was used when NHL was detected in the bone marrow. 67Cu-2IT-BAT-Lym-1 provided good imaging of NHL had favorable radiation dosimetry, and had a response rate of 58% (7 of 12). Hematological toxicity was dose-limiting, but no significant nonhematological toxicity was observed. The ability to image and treat NHL patients with a single radiopharmaceutical with useful physical properties makes 67Cu-labeled monoclonal antibody an option for future clinical trials, as this study showed that 67Cu-2IT-BAT-Lym-1 was safe, effective, and practical.

Introduction

Lym-1, a mouse MAb that preferentially targets the HLA-DR10 β-subunit expressed on most malignant B-cells (1, 2), has proven to be a useful vehicle for RIT of NHL (3–5). In a low-dose trial of 131I-Lym-1, 17 of 30 (57%) entries had durable responses, including three CRs (6). A maximum tolerated dose trial of 131I-Lym-1 produced responses in 11 of 21 (52%) entries, including 7 CR; all three patients in the highest dose cohort (3.7 GBq/m2) had durable CR (3). A time dependent proportional hazards model conclusively showed that response to 131I-Lym-1 was associated with improved survival in a multivariate analysis that adjusted for risk factors (7, 8). Thrombocytopenia was the dose limiting toxicity for 131I-Lym-1 RIT (9). 67Cu was first advocated for use in RIT by DeNardo and DeNardo (10) in 1983 and by Wessels and Rogus (11) in 1984, because of its useful physical and chemical properties. The 62-h half-life of 67Cu is similar to the residence time of many MABs in tumors (12, 13). The microdosimetry characteristics of 67Cu are similar to those of 131I (14). 67Cu emits abundant, therapeutically useful β particles of moderate energy and γ photons ideal for imaging studies but not too abundant to preclude outpatient, high-dose RIT (5). 67Cu has no proclivity for deposition in the skeleton or bone marrow (15).

To use 67Cu effectively, the macrocyclic chelating agent TETA was designed specifically to bind 67Cu selectively and tightly, enabling its conjugation to MAb (16). TETA binds 67Cu in preference to other metals; therefore, the resulting radiopharmaceutical can have a high specific activity (17). 67Cu-2IT-BAT-Lym-1 has exceptional structural stability, functional integrity, and product yields similar to those of 131I-Lym-1 (18, 19).

Four patients received both 67Cu-2IT-BAT-Lym-1 and 131I-Lym-1. Compared to 131I-Lym-1, 67Cu-2IT-BAT-Lym-1 had higher peak tumor concentrations, a longer mean biological t1/2 in NHL by a factor of 3.8, and a higher mean tumor concentration (% injected dose/g) by a factor of 2.8 at 48 h (20). 67Cu-2IT-BAT-Lym-1 delivered a lower radiation dose to the bone marrow than 131I-Lym-1 and similar radiation doses to normal organs, except the liver (5, 21, 22).

The results of 131I-Lym-1 clinical trials, preclinical studies, and the pharmacokinetics and dosimetry of 67Cu-2IT-BAT-Lym-1 were encouraging. Therefore, this Phase I/II trial of 67Cu-2IT-BAT-Lym-1 was conducted in patients with B-cell NHL who had failed standard therapy. Up to four doses of 67Cu-2IT-BAT-Lym-1, 25 or 50–60 mCi/m2/ dose (0.93 or 1.85–2.22 GBq/m2/dose, respectively) were administered; the lower dosage was used when NHL was detected in the bone marrow. 67Cu-2IT-BAT-Lym-1 provided good imaging of NHL had favorable radiation dosimetry, and had a response rate of 58% (7 of 12). Hematological toxicity was dose-limiting, but no significant nonhematological toxicity was observed. The ability to image and treat NHL patients with a single radiopharmaceutical with useful physical properties makes 67Cu-labeled monoclonal antibody an option for future clinical trials, as this study showed that 67Cu-2IT-BAT-Lym-1 was safe, effective, and practical.

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The abbreviations used are: HLA, human leukocyte antigen; CR, complete response; HAMA, human antimouse antibody; 2IT, 2-iminothiolane; LDH, lactate dehydrogenase; MAb, monoclonal antibody; MIRD, medical internal radiation dose; NHL, non-Hodgkin’s lymphoma; PBSC, peripheral blood stem cell; PR, partial response; RIT, radioimmunotherapy; TETA, 1,4,7,11-tetraazacyclotetradecane-N,N’,N″,N‴'-tetraacetic acid; BAT, 6-[p-(bromoacetamido)benzyl]-TETA.
Patients and Methods

**Patient Characteristics.** All patients had progressive disease after anthracycline-based chemotherapy (average, 2.6 chemotherapy regimens; range, 1–5); three patients had progressed after high-dose chemotherapy with PBSC support. Three patients had received local external beam radiotherapy, and another patient had received total body irradiation as part of a bone marrow transplantation conditioning regimen. The average age of the eight men and four women was 53 years (Table 1). Eleven of 12 patients had intermediate or high-grade NHL. Eight patients had Stage IV NHL, and four patients had Stage III NHL. Six patients had malignant involvement of the bone marrow, and 8 of 12 had elevated LDH values, a negative prognostic sign (23).

**Preparation of $^{67}$Cu-2IT-BAT-Lym-1.** Lym-1 (Techniclone, Inc., Tustin, CA) is an IgG2a mouse MAb with high affinity against a noninternalizing, discontinuous epitope of the HLA-DR10 β-subunit antigen on the surface membrane of malignant B-lymphocytes (1, 2). Lym-1 met United States Food and Drug Administration mouse MAb production guidelines for murine viral, Mycoplasma, fungal, bacterial contamination, endotoxin, DNA content, and general safety testing in animals.

BAT was conjugated to Lym-1 via 2IT (Sigma Chemical Co., St. Louis, MO) as described previously, resulting in the immunonoconjugate 2IT-BAT-Lym-1 (5, 19, 24). There were 3.7–5.8 TETA/Lym-1 as measured by metal binding assay. Ammonium citrate-buffered $^{67}$Cu (Brookhaven National Laboratory, Upton, NY, or Los Alamos National Laboratory, Los Alamos, NM) was added to 2IT-BAT-Lym-1. Sodium EDTA (Fisher Scientific, Pittsburgh, PA; 10 mm) was used to complex nonspecifically bound metal ions, and then $^{67}$Cu-2IT-BAT-Lym-1 was separated from $^{67}$Cu-EDTA by G-25 molecular sieving gel chromatography (Sigma) and formulated at 0.037 GBq (1 mCi/ml) in 4% human serum albumin/saline (18, 21).

Immunoreactivity of $^{67}$Cu-2IT-BAT-Lym-1, assessed by solid phase RIA against partially purified Raji cell homogenates (25) was at least 80% relative to unmodified Lym-1. For the 15 preparations of $^{67}$Cu-2IT-BAT-Lym-1 used for 22 patient doses, the mean ± SD of $^{67}$Cu associated with monomeric immunonoconjugate by both molecular sieving high-performance liquid chromatography (TSK 3000, Beckman, Fullerton, CA) and cellulose acetate electrophoresis (Gelman Sciences, Inc., Ann Arbor, MI) was $99 ± 1%$ (22, 26, 27).

**Study Design.** Patients were eligible if at least 20% of the malignant lymphocytes were Lym-1 reactive by immunohistochemistry, serum was negative for HAMA, liver function tests were less than 2 times normal, Karnofsky performance score was at least 70%, and absolute neutrophil and platelet counts were at least 1500/mm$^3$ and 100,000/mm$^3$, respectively. Patients with more than 25% of their marrow replaced by NHL were ineligible. Patients received no other cancer therapy for at least 4 weeks, had measurable disease, and signed an informed consent approved by the University of California, Davis Human Subjects and Radiation Use Committees under a United States Food and Drug Administration Investigational New Drug authorization. A history and physical examination was performed before the outpatient $^{67}$Cu-2IT-BAT-Lym-1 infusions, at about 1 week after each infusion and monthly for 3 months thereafter. Pharmacokinetics and radiation dosimetry were determined after each dose of $^{67}$Cu-2IT-BAT-Lym-1.

Diphenhydramine (50 mg) and acetaminophen (650 mg) were given 0.5 h before and 3 and 6 h after Lym-1 infusion. Unmodified Lym-1 (20 mg for patients 1, 2, and 3) or 5 mg of Lym-1 (an amount subsequently shown sufficient to block nonspecific binding sites and provide stable pharmacokinetics; Ref. 28), for patients 4–12, were injected at 0.5–1.0 mg/min prior to $^{67}$Cu-2IT-BAT-Lym-1. Patients 1, 2, and 3 received 2.22 GBq/m$^2$ (60 mCi/m$^2$) $^{67}$Cu-2IT-BAT-Lym-1; the next nine (Phase II) patients received 1.85 GBq/m$^2$ (50 mCi/m$^2$) doses of $^{67}$Cu-2IT-BAT-Lym-1 if pre-RIT bilateral bone marrow biopsies did not detect NHL, and 0.93 GBq/m$^2$ (25 mCi/m$^2$) if NHL was detected. Patients with grade III or IV hematological toxicity after a dose were treated with a 50% $^{67}$Cu dose reduction after the blood counts returned to grade I or better. Patient 1 received all four planned doses of RIT. The maximum administered dose was 15.7 GBq (patient 1), and the minimum was 1.6 GBq of $^{67}$Cu (patient 12; Table 1).

**Toxicity and Response Assessment.** Renal function tests, liver function tests, and quantitative HAMA assay were obtained at 4–6 weeks after RIT and then at 3–6 month intervals. Complete blood counts were obtained weekly during therapy until blood counts had recovered. National Cancer Institute Common Toxicity Criteria were used to classify data. Responses required a durability of 4 weeks and were classified as complete absence of disease, including negative bone marrow examination (CR), or decrease in the sum of the products of tumor dimensions by at least 50% or tumor volumes by at least 70% (PR).

**Pharmacokinetics and Radiation Dosimetry.** Blood samples were analyzed for $^{67}$Cu-2IT-BAT-Lym-1 content immediately, at 15, 30, 60, 120, and 360 min, and daily for up to 10 days after RIT. Blood radioactivity was counted in a gamma well counter (Amersham Pharmacia Biotech, Piscataway, NJ) and compared with a standard from the injected dose to obtain the concentration of $^{67}$Cu in the blood. Cumulated $^{67}$Cu in blood was obtained by fitting pharmacokinetic data to a biexponential function (29). High-performance liquid chromatography analysis using a molecular sieving column (TSK 3000, Beckman Instruments, Fullerton, CA) was performed on plasma to assess the stability of $^{67}$Cu-2IT-BAT-Lym-1.
Pharmacokinetic data were obtained as previously described (21, 30, 31). Planar images of conjugate views were acquired immediately, at 4 h, and daily for up to 10 days to measure the amount of $^{67}$Cu-2IT-BAT-Lym-1 in organs and tumors (30, 32). Cumulated activity in organs was obtained using a monoexponential analysis and converted to a radiation dose using the MIRD formula considering radiation from the target and the remainder of the body, except in two cases in which cumulated activity of the liver was calculated using a cubic spline function for a better fit (33, 34). The amount of $^{67}$Cu-2IT-BAT-Lym-1 in organs and tumors was quantified using geometric-mean dosimetry.

The bone marrow radiation dose was determined by each method. The first method addressed contributions from nonpenetrating 6VCu radiation were used to determine the radiation dose to marrow from marrow. The bone marrow radiation dose was determined by each of two methods. The first method addressed contributions from nonpenetrating radiation from bone and penetrating radiation from the total body, as previously described (31, 35). The second method addressed the marrow to marrow, nonpenetrating radiation dose extrapolated from the uptake of $^{67}$Cu-2IT-BAT-Lym-1 as imaged in three lumbar vertebrae (5, 37). Cumulated activity in bone marrow and the MIRD S value for nonpenetrating $^{67}$Cu radiation were used to determine the radiation dose to marrow from marrow.

**Assay for $^{67}$Cu-Ceruloplasmin ($^{67}$Cu-CP) and $^{67}$Cu-Albumin in Plasma.** Plasma samples obtained after $^{67}$Cu-2IT-BAT-Lym-1 infusion were assayed for $^{67}$Cu-CP by adding aliquots of antihuman CP (Sigma) in amounts sufficient to precipitate at least twice the normal concentration of circulating CP. The mixture was incubated at 37°C for 1 h and microcentrifuged at 10,000 rpm for 1 min. Supernatants and pellets were counted in a calibrated gamma well counter, and the percentage of $^{67}$Cu activity precipitated by the antibody was calculated. Similarly, plasma was assayed for $^{67}$Cu-albumin and $^{67}$Cu-transferrin with antihuman serum albumin and antihuman transferrin (Sigma), respectively (5).

**Results**

**Pharmacokinetics and Radiation Dosimetry.** The mean radiation doses ± SD for blood, body, bone marrow, and organs are seen in Table 2. The liver had the highest organ radiation dose from $^{67}$Cu-2IT-BAT-Lym-1. For 41 evaluable tumors, the doses ranged from 0.30 to 5.99 Gy/GBq. The highest cumulative tumor radiation dose was 70 Gy from four doses of $^{67}$Cu-2IT-BAT-Lym-1 (Table 1). Characteristic targeting of NHL by $^{67}$Cu-2IT-BAT-Lym-1 and prolonged retention of $^{67}$Cu in NHL is seen in Fig. 2. Fig. 3 shows the rise of blood $^{67}$Cu-CP as the percentage of $^{67}$Cu-2IT-BAT-Lym-1 in the blood decreases, due to transfer of $^{67}$Cu from $^{67}$Cu-2IT-BAT-Lym-1 to $^{67}$Cu-CP by the liver. No $^{67}$Cu was precipitated by antialbumin or antitransferrin.

**Response.** There was one CR and six PRs; the overall response rate 58% (7 of 12; Table 1). The patient who received...
Five patients received more than one dose of $^{67}$Cu-2IT-BAT-Lym-1. All four patients with normal pre-RIT LDH values responded; three of eight (38%) patients with elevated pre-RIT LDH values responded. One of the three patients who had previously had high-dose chemotherapy with PBSC support responded. The mean durations of the CR and PRs were 12 and 3 months, respectively.

**Toxicity.** All three patients who received a 2.2 GBq/m$^2$ dose had grade IV granulocytopenia (average duration, 17 days; Table 3). Only two of five patients who received a 1.85 GBq/m$^2$ dose had as much as grade III granulocytopenia, and the average duration was 14 days. Granulocytopenia did not exceed grade I in any patient treated with 0.93 GBq/m$^2$. All three patients who received a 2.2 GBq/m$^2$ dose had grade IV thrombocytopenia, with an average duration of 51 days. Four of five patients who received a 1.85 GBq/m$^2$ dose had grade III or IV thrombocytopenia, with an average duration of 43 days. Only one of four patients treated with 0.93 GBq/m$^2$ had grade IV thrombocytopenia (duration, 7 days). Despite myelotoxicity, significant bleeding or infection did not occur. Anemia was neither dose-limiting or as prominent as the granulocytopenia and thrombocytopenia. No grade III or IV nonhematological toxicity occurred.

One patient completed the planned four doses of $^{67}$Cu-2IT-BAT-Lym-1. Further RIT to complete four doses was prevented in the remaining 11 patients by death from NHL (patients 5, 6, and 12), noncompliance (patient 11), and disease progression (patients 2, 4, 8, and 10). Five of 12 patients (42%) became HAMA positive (greater than 5 μg/ml) an average of 51 days after first exposure to $^{67}$Cu-2IT-BAT-Lym-1, and further RIT was prevented by HAMA in three patients.

**Discussion**

Lym-1, a mouse IgG$\alpha_\mu$ MAb, binds a variant HLA-DR10 antigen that is preferentially expressed on malignant B-lymphocytes (1, 38). Relatively small milligram amounts of radio-labeled Lym-1 provide optimal imaging and effective radionuclide delivery, as demonstrated in this Phase I/II RIT trial wherein TETA-chelated $^{67}$Cu was targeted to NHL in all 12 patients. Unmodified Lym-1 is ineffective for treatment of NHL (39, 40); however, despite the fact that 11 of 12 patients had stage III or IV intermediate or high-grade NHL, the response rate for $^{67}$Cu-2IT-BAT-Lym-1 was 58%. RIT with $^{131}$I-Lym-1 showed similar potential in the preceding Phase I/II clinical trials (3, 6, 9). $^{131}$I has been used for RIT because it is inexpensive, widely available, and easily attached to MAb. However, $^{131}$I has some suboptimal characteristics too; therefore, preclinical and clinical trials have been undertaken with radiometals in an attempt to improve the efficacy and safety of RIT.

Stable chelation of radiometals is a requirement for their effective use. Early attempts to use acyclic $^{67}$Cu chelators did not result in radiopharmaceuticals stable enough to be used clinically (41). In pioneering studies, the macrocyclic chelating agent TETA was designed specifically to bind $^{67}$Cu for conjugation to MAb through the bifunctional TETA derivative, BAT (16, 19, 26). The result is $^{67}$Cu-2IT-BAT-Lym-1, which has exceptional stability and immunoreactivity (18, 19). Because TETA binds copper selectively, in preference to other metals even when they are present in great excess (e.g., zinc, from which $^{67}$Cu is made, and the ubiquitous elements calcium and magnesium), $^{67}$Cu-2IT-BAT-Lym-1 of high specific activity can be rapidly and consistently prepared (17). The product yield of $^{67}$Cu-2IT-BAT-Lym-1 (90%) is comparable to that of $^{131}$I-Lym-1 (27). TETA also effectively chelates $^{64}$Cu, and the positron emissions of $^{64}$Cu are good for imaging (42, 43). However, the 12.7-h $t_{1/2}$ of $^{64}$Cu ($^{64}$Cu, 62 h) decreases the
therapeutic advantage conferred by the longer tumor residence time of the radiometal-labeled MAb (12, 31). Anti-TETA immune responses were noted in 15% of the patients, but anti-TETA did not occur in the absence of a concurrent anti-Lym-1 HAMA; thus, the rare anti-TETA response never altered therapeutic plans (44).

Copper-67 was first advocated for RIT in 1983 by DeNardo and DeNardo (10) because of its exceptional physical and biochemical properties. Copper-67 emits photons with energies (185 keV, 47%; 93 keV, 17%) similar to those of 99mTc, thereby making 67Cu better suited for gamma camera imaging and radiation dosimetry than 131I. A clinical study in which patients were sequentially injected with 131I-Lym-1 and 67Cu-2IT-BAT-Lym-1 demonstrated better imaging of 67Cu than 131I (21). 67Cu-2IT-BAT-Lym-1 provided approximately twice the counting efficiency (counts/s/GBq) of 131I-Lym-1. The decay characteristics of 67Cu permit doses of radioactivity more than 10 times greater (for equivalent radiation safety requirements) than those of 131I, which has more abundant high-energy γ emissions (45).

Copper-67 emits therapeutically effective β particles (mean energy, 141 keV; $E_{\text{max}} = 577$ keV) similar to those of 131I (46, 47), and the microdosimetry of 67Cu and 131I are similar (Ref. 14; Fig. 4). However, MAbs labeled with radiometals, including 67Cu, exhibit prolonged retention in tumors at a higher radiation dose rate than 131I (13, 48–50). Despite the long $t_{1/2}$ of 131I, its clearance from tumors can reduce the tumor radiation dose and, potentially, efficacy (51, 52). 67Cu-radiolabeled MAbs have higher tumor-to-nontumor dose ratios than their iodinated counterparts (13, 53). Unlike some radiometals, 67Cu is not deposited in skeleton or bone marrow (15). These physical and chemical attributes contribute to the good therapeutic index of 67Cu.

Both 67Cu and 131I are capable of rather uniform tumor irradiation, thus ameliorating the problem of inhomogeneous penetration of NHL by the MAb (54, 55). Fractionating RIT into a series of doses, as was done in this study, is another strategy for achieving more uniform tumor radiation, as well as for increasing the total administered radiation dose (28, 56). The maximum tolerated single dose of 67Cu-2IT-BAT-Lym-1 was 2.22 GBq/m² (60 mCi/m²; Ref. 5), and in the present study, as high as 15.7 GBq were received by a patient who ultimately achieved a CR.

The liver stores copper and then excretes most of it into bile for elimination in feces (15). However, a small amount of copper is transferred to CP in the liver, and then Cu-CP is secreted into the blood. After infusion of 67Cu-2IT-BAT-Lym-1, the percentage of total plasma radioactivity precipitated by antihuman CP increased daily, and 67Cu-CP in the plasma peaked on day 4, resulting in a positive or flat slow phase of blood 67Cu clearance starting 3 days after 67Cu-2IT-BAT-Lym-1. These data suggest that the liver metabolized 67Cu-2IT-BAT-Lym-1 and transferred some 67Cu to CP. There was no evidence for release of free 67Cu; immunoprecipitation of albumin (the major carrier protein of copper) and CP showed 67Cu recycled only into CP. Cleavable peptide linkers that reduce the radiation dose to liver will be used for the next generation of radioimmunoconjugates (57).

The Phase II study of 67Cu-2IT-BAT-Lym-1 shows that doses of 67Cu greater than 1.85 GBq/m² result in hematological toxicity of substantial degree and duration, when given without PBSC support. There was minimal toxicity with the 0.93 GBq/m² doses, despite the fact that these patients had NHL detected by bone marrow biopsy. The observed myelosuppression is the result not only of radiation but also the extensive prior chemotherapy. On the other hand, the notable absence of nonhematological toxicity makes it likely that doses could be increased substantially if PBSC support was used.

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<tr>
<th>Table 3</th>
<th>Maximum hematologic toxicity after one or multiple doses of 67Cu-2IT-BAT-Lym-1</th>
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<td>Planned dose level</td>
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<td>No. of doses</td>
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<tr>
<td>Granulocyte toxicity grade</td>
<td>IV</td>
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<tr>
<td>Platelet toxicity grade</td>
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* Maximum grade of granulocytopenia during the entire course of the patient's RIT.
* Maximum grade of thrombocytopenia during the entire course of the patient's RIT.
of whom had intermediate or high-grade NHL. Imaging of $^{67}$Cu was excellent and the response rate was 58%. $^{67}$Cu, a novel therapeutic radionuclide, was stably bound by the macrocycle, TETA. The results were consistent with the exceptional combination of desirable physical and biochemical properties of $^{67}$Cu for RIT. Few trials have been done with $^{67}$Cu because it is neither inexpensive or routinely available, however, this clinical study attests to its utility for future RIT trials.

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References


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