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ORIGINAL REPORT

Phase I Trial of Anti-CD22 Recombinant Immunotoxin Moxetumomab Pasudotox (CAT-8015 or HA22) in Patients With Hairy Cell Leukemia

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See accompanying article on page 1888; listen to the podcast by Dr Bishop at www.jco.org/podcasts

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ABSTRACT

Purpose
To conduct a phase I dose-escalation trial assessing safety and response of recombinant immunotoxin moxetumomab pasudotox (CAT-8015, HA22) in chemotherapy-resistant hairy cell leukemia (HCL).

Patients and Methods
Eligible patients had relapsed/refractory HCL after ≥ two prior therapies and required treatment because of abnormal blood counts. Patients received moxetumomab pasudotox 5 to 50 μg/kg every other day for three doses (QOD ×3), with up to 16 cycles repeating at ≥ 4-week intervals if patients did not experience disease progression or develop neutralizing antibodies.

Results
Twenty-eight patients were enrolled, including three patients each at 5, 10, 20, and 30 μg/kg, four patients at 40 μg/kg, and 12 patients at 50 μg/kg QOD ×3 for one to 16 cycles each (median, four cycles). Dose-limiting toxicity was not observed. Two patients had transient laboratory abnormalities consistent with grade 2 hemolytic uremic syndrome with peak creatinine of 1.53 to 1.66 mg/dL and platelet nadir of 106,000 to 120,000/μL. Drug-related toxicities in 25% to 64% of the 28 patients included (in decreasing frequency) grade 1 to 2 hypoalbuminemia, aminotransferase elevations, edema, headache, hypotension, nausea, and fatigue. Of 26 patients evaluable for immunogenicity, 10 patients (38%) made antibodies neutralizing more than 75% of the cytotoxicity of 1,000 ng/mL of immunotoxin, but this immunogenicity was rare (5%) after cycle 1. The overall response rate was 86%, with responses observed at all dose levels, and 13 patients (46%) achieved complete remission (CR). Only 1 CR lasted less than 1 year, with the median disease-free survival time not yet reached at 26 months.

Conclusion
Moxetumomab pasudotox at doses up to 50 μg/kg QOD ×3 has activity in relapsed/refractory HCL and has a safety profile that supports further clinical development for treatment of this disease.

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INTRODUCTION

Hairy cell leukemia (HCL) composes 2% of all leukemias.[1] The purine analogs cladribine and pentostatin achieve high complete remission (CR) rates (70% to 95%), with most patients still in CR after 10 to 15 years.[2-7] However, the lack of plateau on the disease-free survival curves[3,6] and the high rates of minimal residual disease (MRD) after purine analogs,[8-11] even after more than 15 years of CR,[12] suggest lack of curability in many, if not most, patients. Declining CR rates with each course of purine analog[3,7] have resulted in an increasing number of patients with relapsed or refractory disease, for whom there are no approved therapies. In the largest trial of relapsed/refractory HCL, rituximab achieved an overall response rate of 26%, including a 13% CR rate.[13]

Major responses, including CRs, have been documented in patients with relapsed/refractory HCL using recombinant immunotoxins containing an Fv fragment fused to truncated *Pseudomonas* exotoxin.[14-18] BL22 (CAT-3888), targeting CD22, achieved CR rates of 47% to 61% in patients with HCL in phase I and II trials. The major adverse effect was a completely reversible hemolytic uremic

syndrome (HUS) observed in eight (12%) of 69 patients with HCL.[16-18] BL22 was less effective in patients with chronic lymphocytic leukemia,[17] probably because of low CD22 expression. We used hot-spot mutagenesis to increase the affinity of BL22,[19] and the resulting protein, called HA22, CAT-8015, or moxetumomab pasudotox, contains threonine-histidine-tryptophan instead of serine-serine-tyrosine in the antigen-binding site of the heavy chain. This resulted in a 14-fold increased binding affinity for CD22, as a result of lower off-rate, and a larger increase in cytotoxicity. Moxetumomab pasudotox has antitumor activity in murine xenograft studies and an acceptable safety profile in cynomolgus monkeys.[20] Phase I testing was undertaken to determine its safety and efficacy in HCL.

PATIENTS AND METHODS

Eligibility

Patients had a confirmed diagnosis of classic or variant HCL with measurable disease and ≥ two prior systemic therapies, including ≥ two courses of purine analog unless response to the first course lasted less than 2 years. Patients were excluded for poor hepatic, renal, or pulmonary function; pregnancy; therapy less than 3 weeks before enrollment; prior immunotoxin; hepatitis B or C or HIV infection; or pre-existing antibodies to moxetumomab pasudotox. Patients were treated between May 2007 and May 2009 at the National Institutes of Health, Bethesda, MD (n = 21); the Medical University, Lodz, Poland (n = 2); Northwestern University, Robert H. Lurie Comprehensive Cancer Center, Chicago, IL (n = 3); or Stanford University Medical Center (n = 2), Stanford, CA.

Study Design

Patients received moxetumomab pasudotox over 30 minutes every other day for three doses (QOD ×3). Hydroxyzine and ranitidine were used to prevent allergic reaction, acetaminophen was used to prevent fever, and 1 L of intravenous (IV) fluid was used before and after each dose to prevent hypovolemia during third spacing. Patients without progressive disease (PD) or high neutralizing antibody levels could be re-treated at the same dose at 4-week intervals for two cycles past achievement of CR without MRD. Dose escalation required zero of three or one of six patients at the current dose level with dose-limiting toxicity (DLT) by cycle 2, day 10, and patients with antibodies or PD preventing a second cycle were replaced. The maximum-tolerated dose (MTD) was defined as the highest dose level tested where DLT was observed in zero to one of six patients. DLT was defined as drug-related grade 3 or 4 toxicity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0) except for the following: hematologic toxicity either grade 3 or lasting ≤ 5 days and not requiring transfusions, or neutropenia lasting less than 1 week after starting growth factor therapy or lymphopenia; grade 3 electrolyte levels in patients with chronically low levels; grade 3 AST, ALT, alkaline phosphatase, and bilirubin; grade 3 fever; grade 3 hypertriglyceridemia or hypercholesterolemia or grade 4 hypertriglyceridemia lasting less than 2 months; and grade 3 hypoalbuminemia lasting ≤ 7 days in absence of capillary leak syndrome (CLS). DLT from CLS was defined as either grade 3 CLS-related hypotension requiring more than 20 mL/kg/h of IV fluid or symptomatic pulmonary edema requiring oxygen or a more than 10% decrease in oxygen saturation. DLT from HUS was defined as grade 3, including microangiopathic hemolytic anemia with schistocytes and either grade 4 thrombocytopenia or grade ≥ 2 creatinine elevation. Grade 2 HUS, defined as anemia with schistocytes and grade 1 creatinine elevation, was not considered a DLT.

Response Criteria

CR required absence of HCL in blood and bone marrow using nonimmunologic stains; no hepatosplenomegaly by physical examination or imaging; and resolution of blood counts to neutrophils ≥ 1,500/μL, platelets ≥ 100,000/μL, and hemoglobin (Hgb) ≥ 11 g/dL without growth factors or transfusions for ≥ 4 weeks; thereafter, bone marrow was obtained. CR with MRD was defined as HCL evident in bone marrow by immunohistochemistry or in blood by flow cytometry. Partial remission (PR) required ≥ 50% reduction in abnormal blood lymphocyte count, ≥ 50% reduction of lymphadenopathy, ≥ 50% reduction in abnormal hepatosplenomegaly by computed tomography or physical examinations, and achievement of normal blood counts as required for CR or a ≥ 50% improvement over baseline, including Hgb ≥ 9 g/dL if transfusion dependent before enrollment. PD required a ≥ 25% increase in adenopathy or new lymph nodes, a ≥ 25% increase in liver or spleen measured below the costal margin, a ≥ 25% HCL-related decrease in normal blood counts below levels required for CR, or a ≥ 50% increase in circulating abnormal lymphocytes. Stable disease was defined as lack of CR, PR, or PD.

RESULTS

Patient Characteristics

Characteristics of the 28 patients enrolled are listed in Table 1. Patient age ranged from 40 to 77 years (median, 59 years), the male: female ratio was 4.6, and all patients had classic HCL except for two patients with variant HCL (one woman and one man). HCL cells assessed by four-color flow cytometry (n = 25) were bright-positive for CD20, CD22, and CD11c and positive for CD19 and CD103, and all patients except the two patients with variant HCL expressed CD25. Patients received one to seven prior courses of purine analog (median, two courses), including cladribine in all patients and pentostatin in 11 patients; one patient had just one prior purine analog (cladribine) as a result of refractoriness. Eleven (46%) of 24 patients were refractory to the last course of purine analog, based on failure to achieve blood counts consistent with CR for more than 1 year, and one patient (4%) had responded to a purine analog for more than 4 years. Of the 28 patients, 16 (57%) received prior rituximab. Spleen height (caudal-cranial diameter by imaging) ranged from 0 to 325 mm (median, 150 mm). Seven patients had prior splenectomy. Circulating HCL cells ranged from 0.8 to 60,000/μL (median, 53/μL).

Table 1. Patient Demographics and Clinical Characteristics

Demographic or Clinical Characteristic	Value
No. of patients	28
Age, years	
Median	59
Range	40-77
Male:female ratio	4.6
HCL, No. of patients	
Classic	26
Variant	2
Prior No. of purine analog courses	
Median	2
Range	1-7
Prior treatment with rituximab	
No. of patients	16
%	62
Prior splenectomy, No. of patients	7*
Spleen diameter, mm	
Median	150
Range	0-325
Circulating HCL cells by FACS/μL	
Median	53
Range	0.8-60,000

Abbreviations: FACS, fluorescence-activated cell sorting; HCL, hairy cell leukemia.
*Spleen height = 0.

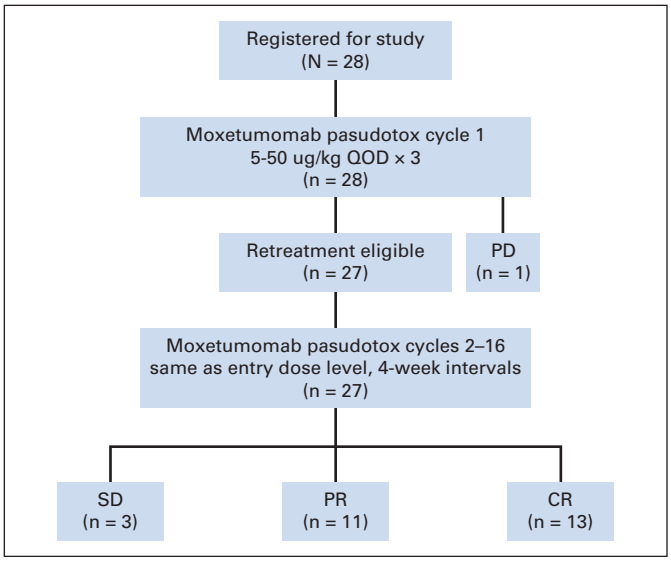

Fig 1. CONSORT flow diagram: disposition of study participants. After cycle 1, patients (except those with progressive disease [PD]) were re-treated with two to 16 additional cycles, limited to two past documentations of complete remission (CR) or earlier at the time immunogenicity was documented. In total, 114 cycles were administered to 28 patients, and re-treated patients achieved CR or partial remission (PR) or had stable disease (SD). QOD, every other day.

Dose Escalation

Twenty-eight patients received 114 cycles for a median of four cycles per patient (Fig 1). Three patients each received 5, 10, 20, and 30 μg/kg QOD $\times$3. Four patients received 40 μg/kg because one patient had PD after cycle 1 and was replaced per protocol. The remaining patients received 50 μg/kg QOD $\times$3, one dose level higher than the MTD of the parental molecule BL22,[17] because it was decided to expand this dose level as the MTD rather than escalate further.

Serious Adverse Events

Patients were assessed before treatment and on days 1 through 8, 11, 14, 21, and 28 of each cycle. No DLTs were observed. Two patients had reversible laboratory changes suggestive of mild HUS. After the third cycle of 30 μg/kg QOD $\times$3, one patient had a decrease in platelet count to a nadir of 120,000/μL on day 11 and Hgb to a nadir of 10.1 g/dL on day 12, along with increases in creatinine to 1.53 mg/dL, lactate dehydrogenase to 326 U/L, and bilirubin to 1.3 mg/dL on days 9 and 10. A second patient after cycle 5 of 50 μg/kg QOD $\times$3 had a nadir platelet count of 106,000/μL and a peak creatinine of 1.66 mg/dL on day 10. Lactate dehydrogenase and bilirubin peaked on day 8, with values of 238 U/L and 1.0 mg/dL, respectively. These two patients received IV fluid and diuretics, and the abnormalities resolved without plasmapheresis or blood products. The latter patient, who a prior history of stroke, had presented with grade 3 dyspnea and grade 4 pneumonia and pulmonary embolism before cycle 5, considered to be unlikely drug related, and symptoms resolved with enoxaparin before cycle initiation. The only other serious adverse events were grade 2 hypoxia and bronchospasm in a patient receiving 30 μg/kg QOD $\times$3 after the second of four cycles, which were considered related to infection. There was no correlation between dose and percentage of patients at each dose level with serious toxicity ($r = 0.04$, $P = .7$).

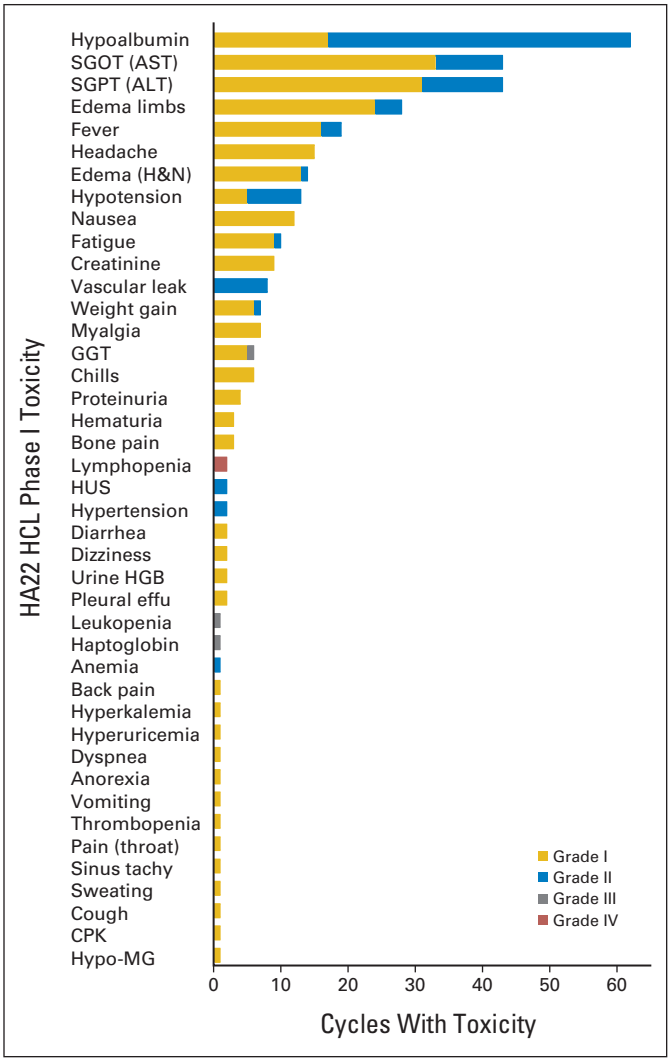

Fig 2. Toxicity of moxetumomab pasudotox. Incidence of toxicity by cycle is shown by grade for all 114 cycles administered to 28 patients. CPK, creatine phosphokinase; effu, effusion; GGT, γ-glutamyltransferase; HCL, hairy cell leukemia; H&N, head and neck; HGB, hemoglobin; HUS, hemolytic uremic syndrome; Hypo-MG, hypomagnesemia; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

Therapy-Related Adverse Events With Moxetumomab Pasudotox

To determine the safety of moxetumomab pasudotox, all adverse events at least possibly related to therapy were analyzed. As shown in Figure 2, hypoalbuminemia (54% of cycles) and elevated aminotransferases (AST, 38%; ALT, 38%) were observed most commonly, all grade 1 to 2. Other common events occurring in $\geq$ 5% of cycles, including limb (25%) and head & neck (12%) edema, headache (13%), hypotension (11%), nausea (11%), fatigue (9%), weight gain (6%), and myalgias (6%), were considered mild manifestations of CLS, which itself was reported in 7% of cycles as defined by more than 5% weight gain. Grade 3 to 4 γ-glutamyltransferase, leukopenia, haptoglobin, and lymphopenia were not considered dose limiting. Thus, moxetumomab pasudotox had an acceptable safety profile in patients at 5 to 50 μg/kg QOD $\times$3, without DLT.

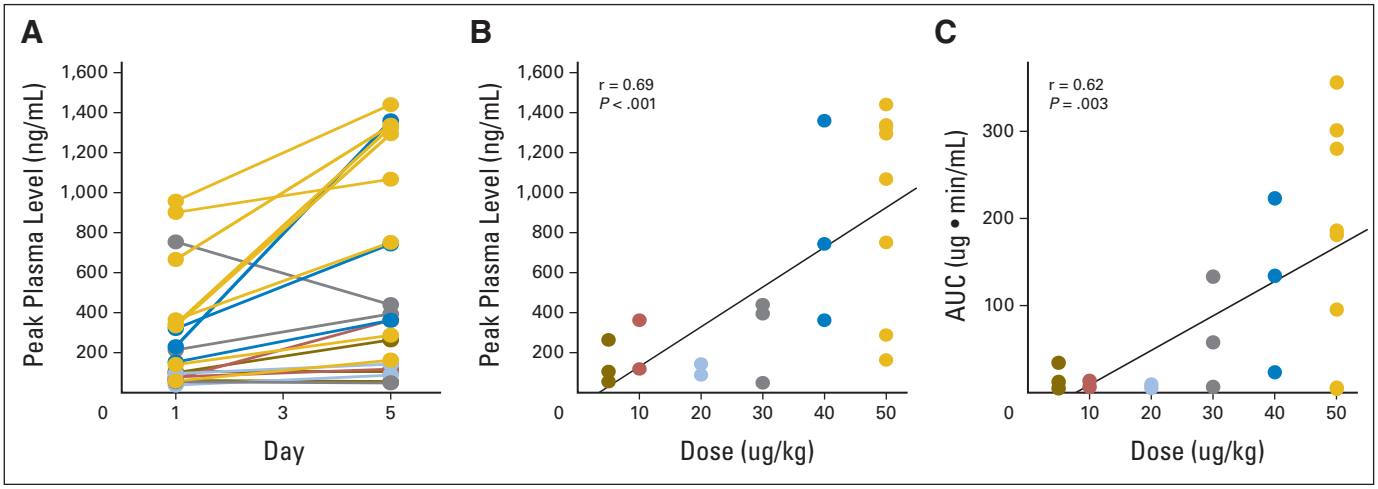

Fig 3. Pharmacokinetics of moxetumomab pasudotox. (A) Peak plasma levels on cycle 1 are compared between dose 1 (day 1) and dose 3 (day 5). (B) Peak plasma levels and (C) areas under the curve (AUCs) are shown for cycle 1, day 5 at each of the dose levels.

Pharmacokinetics of Moxetumomab Pasudotox in Patients With HCL

Plasma levels of moxetumomab pasudotox were determined by a cytotoxicity assay.[16-18] As shown in Figure 3A, plasma levels increased significantly ($P < .001$) between days 1 and 5 of cycle 1, correlating with decreasing tumor burden for most patients. Peak plasma level measured on day 5 of cycle 1 correlated with dose level (Fig 3B, $r = 0.69$, $P < .001$). Drug exposure over time, represented by area under the curve, was often too low to measure on day 1. As shown in Figure 3C, the area under the curve measured on day 5 correlated with dose ($r = 0.62$, $P = .003$), although there was significant variability associated with differences in tumor burden. Plasma levels achieved were two to three orders of magnitude higher than the IC_{50} values, the calculated concentrations of moxetumomab pasudotox needed for 50% inhibition of protein synthesis.[19,21] Thus, dosing on protocol resulted in plasma levels sufficient to kill HCL cells from patients.

Immunogenicity of Moxetumomab Pasudotox

Because the recombinant immunotoxin contains a bacterial toxin, immunogenicity was expected. To quantify antitoxin-binding antibodies in patients receiving moxetumomab pasudotox, serum samples before each cycle were tested by an enzyme-linked immunosorbent assay (ELISA), which showed that 17 (65%) of 26 evaluable patients made antibodies after a median of two cycles. A positive result was usually known after the cycle was finished and would prevent further re-treatment per protocol. We also measured neutralizing antibodies using a cytotoxicity assay as previously described.[16-18] In previous studies, patients with up to 75% neutralization of 1,000 ng/mL of immunotoxin could be re-treated because blood levels were high enough to exceed antibody levels and improve response status or remove MRD. Immunogenicity positive by this test was lower than that detected by ELISA, with 10 (38%) of 26 evaluable patients having neutralizing antibodies. Moreover, in only one patient (5%) was neutralization detected after cycle 1. Neutralizing antibodies were detected in five (25%) of 20, one (8%) of 13, and one (11%) of nine patients after two, three, and four cycles, respectively, but not in five patients receiving five to 16 cycles each. Thus, neutralizing antibodies were less common than binding antibodies after moxetumomab pasudotox, and this allowed most of the patients to be re-treated to increase the chance and degree of response.

Patient Response

We evaluated responses after all 114 cycles of moxetumomab pasudotox were administered to 28 patients. As shown in Table 2, we observed major responses at all dose levels, with the overall response ranging from 67% to 100% at each dose level with no apparent correlation with dose. The CR rate was 46%, with CRs observed at doses as low as 10 μg/kg $\times$3. The PR rate was 39%, for an overall response rate of 86% in the 28 patients. Because patients had to achieve resolution of cytopenias (neutrophils $\geq$ 1,500/μL, platelets $\geq$ 100,000/μL, and Hgb $\geq$ 11 g/dL) lasting $\geq$ 4 weeks for CR, the bone marrow biopsy to document CR was performed only after this 4-week period. The number of cycles required for documentation of the 13 CRs was two to five cycles (median, three cycles). A total of 10 consolidation cycles were administered to five patients achieving CR. The other eight patients achieving CR did not receive consolidation cycles because of immunogenicity in six patients and grade 2 HUS in two patients. With limited numbers of patients, there was no relationship between dose level and CR rate, time or number of cycles to achieve CR, or the number of consolidation cycles given. One patient, treated at 30 μg/kg QOD $\times$3, was transfusion dependent for platelets and RBCs before

Table 2. Response at Different Doses Levels

Dose Level (μg/kg QOD $\times$3)	No. of Patients	% of Patients		
		CR	PR	ORR
5	3	0	100	100
10	3	67	33	100
20	3	67	0	67
30	3	33	33	67
40	4	50	25	75
50	12	50	42	92
Total	28	46	39	86

Abbreviations: CR, complete response; ORR, overall response rate; PR, partial response; QOD $\times$3, every other day for three doses.

enrollment, with platelet counts as low as 4,000/μL, and after four cycles of moxetumomab pasudotox, the patient achieved a negative bone marrow biopsy, meeting all criteria for CR except that the platelet count remained less than 100,000/μL. This patient did not experience relapse after more than 33 months since the last dose of moxetumomab pasudotox but is recorded as a PR rather than a CR per protocol, even though failure to achieve a platelet count more than 100,000/μL was probably related to prior chemotherapy rather than lack of immunotoxin efficacy.

Duration of Response

Patients were observed with routine blood counts and bone marrow biopsies while still in CR to make sure they maintained the minimum normal blood counts. As shown in Figure 4A, the median disease-free survival has not been reached, with 10 (80%) of 13 patients remaining in CR for a median of 29 months. Only one patient experienced relapse before 1 year. Eight of 10 patients remaining in CR were assessed for MRD by flow cytometry of blood and immunohistochemistry of the bone marrow biopsy. Both tests are associated with early relapse when positive.[18,22] Seven of these eight patients remaining in CR achieved negative MRD status by these studies. Thus, in the majority of patients, CRs produced by moxetumomab pasudotox were durable and without evidence of MRD. As shown in Figure 4B, the duration of overall response (CR + PR) has also not been reached, with 15 (63%) of 24 patients still responding after 13 to 43 months (median, 30 months).

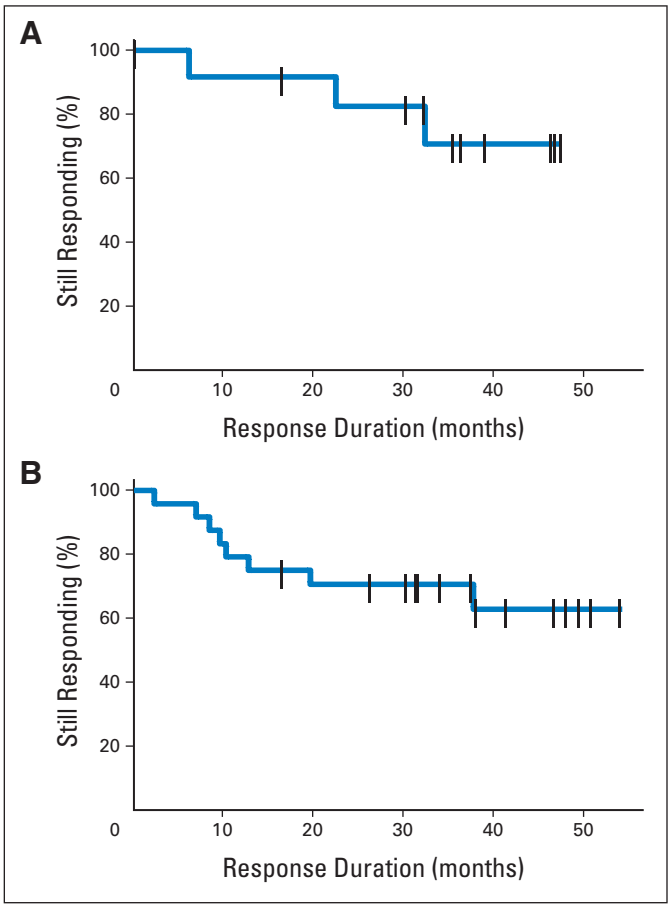

Fig 4. Duration of response. Percentage of patients originally achieving (A) complete remission (CR; n = 13) and (B) CR plus partial remission (n = 24) who maintained at least that level of remission. The vertical bars show the response duration of patients who still meet criteria for response.

Relationship Between Response and Clinical Factors

Clinical factors were examined to determine correlation with response. The ability to achieve CR with moxetumomab pasudotox was not related to the number of prior courses of purine analog ($P = .75$) or to the duration of response to the last course of purine analog ($P = .36$). With respect to tumor burden and distribution at the time of enrollment, we noted that zero of seven patients with prior splenectomy achieved CR with moxetumomab pasudotox, whereas 13 of 21 patients with spleens up to 325 mm in height (caudal-cranial diameter) achieved CR ($P = .007$, Fisher's exact test). Thus, splenic involvement may be an easier target than dense bone marrow involvement that might occur after splenectomy. Moreover, the patient with a 325-mm spleen had the shortest disease-free survival (Fig 4A); patients with more durable CRs had spleen heights of 115 to 175 mm before enrollment. Thus, like BL22,[18] moxetumomab pasudotox induced CRs in 46% to 47% of patients overall, but in 56% to 62% of patients who had not had prior splenectomy. Nevertheless, 86% of patients with prior splenectomy responded.

DISCUSSION

To determine whether moxetumomab pasudotox, a high-affinity derivative of the previously reported anti-CD22 recombinant immunotoxin BL22 (CAT-3888), could be administered safely and effectively, we performed a phase I trial in 28 patients with HCL. We were able to administer moxetumomab pasudotox at doses up to 50 μg/kg QOD $\times$3 without DLT. We observed responses in 86% of patients, and 46% of patients achieved CR. The majority of the CRs were durable and without evidence of MRD. CRs were achieved only in patients without prior splenectomy.

HUS from BL22[16-18] was originally felt to be CD22 mediated because it has not been observed with PE38-containing immunotoxins targeting other antigens.[15,23-25] Although the glomerulus was not found to be CD22$^+$, there was concern that moxetumomab pasudotox would cause HUS at lower dose levels than BL22 because of its higher binding affinity to CD22.[19] The lack of dose-limiting HUS in patients receiving moxetumomab pasudotox suggests that BL22-related HUS involved nonspecific (off-target) binding unrelated to CD22 and may have been at least partially avoided by increasing the affinity of the immunotoxin for CD22. Nevertheless, patients receiving moxetumomab pasudotox must continue to be monitored for this potential adverse effect.

We found that patients at all dose levels responded to moxetumomab pasudotox, and CRs were observed even at 10 μg/kg QOD $\times$3. Although Table 2 does not show a dose-response relationship, the number of patients treated at each dose level was not adequate to rule out increased response with higher dose levels. We observed PRs but not CRs in the seven patients with prior splenectomy, possibly because tumor cells may be more tightly packed in bone marrow so that the immunotoxin may have difficulty reaching them. These results suggest that patients with multiply relapsed HCL might best avoid splenectomy before undergoing experimental therapy with moxetumomab pasudotox. Of 15 patients not achieving CR, 12 (80%) developed antibodies based on ELISA, and treatment had to be stopped. A

potential effect of higher doses in patients developing antibodies is that high plasma levels overcome (or titrate out) neutralizing antibodies, allowing one or more additional cycles. In patients who achieve a near CR, an additional cycle with therapeutic plasma levels despite neutralizing antibodies could make the difference between durable CR and PR.

We believe these phase I results support a pivotal trial in which patients with multiply relapsed HCL are randomly assigned between moxetumomab pasudotox and best alternative therapy (ie, rituximab or cladribine). Expected immune effects of these alternative agents include prolonged B- and T-cell depletion with rituximab and cladribine, respectively.[26-28] We have observed neither of these immune effects with moxetumomab pasudotox, probably because its short half-life allows CD22-negative lymphocyte precursors to replenish the normal B cells otherwise depleted and because normal T cells lack CD22. The lack of toxicity observed during primary or secondary immunogenicity supports re-treatment with moxetumomab pasudotox until maximal response without regard to or measurement of neutralizing antibodies. At this time, additional patients with HCL are receiving the 50 μg/kg QOD $\times$3 dose level to gain more experience with safety and efficacy. Moreover, multicenter trials are under way using moxetumomab pasudotox for chronic lymphocytic leukemia and non-Hodgkin's lymphoma in adults and acute lymphoblastic leukemia in children.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Administrative support: Robert Lechleider
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GLOSSARY TERMS

Immunotoxin: A molecule containing an antibody or antibody fragment connected to a protein toxin. Immunotoxins bind to cell surface antigens via the antibody domain, and after being internalized into the cell, the toxin mediates catalytic cell death. Recombinant immunotoxins refer to proteins in which the Fv is linked to the toxin by a peptide.

Neutralizing antibody: Antibody produced by the patient that abrogates the cytotoxicity of the immunotoxin.

Purine analog: Antimetabolites that mimic the structure of naturally occurring purines.

