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A Phase I/II Dose Escalation Study of Apolizumab (Hu1D10) Using a Stepped Up Dosing Schedule in Patients with Chronic Lymphocytic Leukemia (CLL) and Acute Leukemia

Thomas S. Lin[1], **Wendy Stock**[2], **Huiping Xu**[3,*], **Mitch A. Phelps**[3], **Margaret S. Lucas**[1], **Sara K. Guster**[1], **Bruce R. Briggs**[4], **Carolyn Cheney**[1], **Pierluigi Porcu**[1], **Ian W. Flinn**[5], **Michael R. Grever**[1], **James T. Dalton**[3,**], **John C. Byrd**[1]

[1]Division of Hematology and Oncology, The Ohio State University, Columbus, OH

[2]Division of Hematology and Oncology, University of Chicago, Chicago, IL

[3]Division of Pharmaceutics, College of Pharmacy, The Ohio State University, Columbus, OH

[4]Department of Pathology, The Ohio State University, Columbus, OH

[5]Sarah Cannon Research Institute, Nashville, TN

Abstract

Apolizumab (Hu1D10), a humanized monoclonal anti-HLA-DR β-chain antibody, mediates apoptosis of CLL cells *in vitro*. We conducted a phase I/II dose-escalation study of thrice-weekly apolizumab (1.5, 3.0, 5.0 mg/kg/dose) for 4 weeks in relapsed CLL. Two of six patients at 5.0 mg/kg/dose developed treatment-related dose-limiting toxicity (aseptic meningitis, hemolytic uremia). Other toxicities included infusion toxicity, urticaria, and headache. Eleven patients were enrolled in a phase I/II expansion to evaluate the maximum tolerated dose (MTD) of 3.0 mg/kg/dose. In total, 23 patients were enrolled (22 CLL, 1 ALL). Nineteen CLL patients were treated at or above the MTD. One partial response was observed, and three patients had stable disease exceeding six months. Pharmacokinetic analysis demonstrated a dose-dependent C_{max} increase and serum antibody accumulation after week 1 of therapy. Given the toxicity and lack of efficacy in this and other trials in lymphoma and solid tumors, further development of apolizumab was discontinued.

INTRODUCTION

Major histocompatibility (MHC) class II antigens are expressed on limited subsets of immune effector cells and represent a potential target of monoclonal antibody therapy. Human leukocyte antigen (HLA)-DR is expressed on most hematologic malignancies,

Address for reprints: John C. Byrd, M.D., D. Warren Brown Professor of Leukemia Research, Professor of Medicine and Medicinal Chemistry, Interim Co-Director, Division of Hematology-Oncology, Department of Internal Medicine, Associate Director for Translational Research, The Comprehensive Cancer Center, The Ohio State University Columbus, Ohio, 43210, Phone: 614-293-9869, Fax: 614-293-7526, john.byrd@osumc.edu.

*Current address: Pfizer Pharmaceuticals, Groton / New London, CT

**Current address: GTx, Inc., Memphis, TN

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

except for multiple myeloma, and there is great interest in phase I/II clinical development of antibodies targeted against HLA-DR. Ligation by anti-HLA-DR antibodies induced apoptosis in leukemia and non-Hodgkin's lymphoma (NHL) cell lines, and in primary acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL) and NHL cells (1–7). Apolizumab (Hu1D10, Remitogen) is a humanized murine IgG1 monoclonal antibody which recognizes a polymorphic determinant on the HLA-DR beta chain (1, 2). The 1D10 antigen is expressed on normal B lymphocytes, dendritic cells, macrophages and some activated T lymphocytes, and in 50% of acute lymphocytic leukemia (ALL), 50–70% of NHL, and 80–90% of CLL (8). A phase I dose escalation study administered apolizumab weekly or daily for 5 consecutive days to 20 patients with NHL. This study demonstrated clinical activity; 4 of 8 patients with follicular NHL responded (1 CR, 3 PR) with a median time to response of 106 days (9–12). Infusion-related toxicity (fever, chills, nausea, vomiting, rash, headache, hypotension) was common but manageable, and most toxicities were grade 1 or 2. However, pharmacokinetic data from the phase I study indicated that weekly dosing is insufficient to maintain the 10 μg/ml trough concentration necessary for maximal apoptosis in CLL cells *in vitro* (11, 12). Higher or more intensive dosing may be necessary to maintain this target plasma concentration *in vivo* in CLL patients. Therefore, based on our experience with rituximab in CLL (13), we conducted a phase I dose escalation study of thrice-weekly apolizumab, using a "stepped-up" dosing schedule, in patients with relapsed and refractory CLL and acute leukemia.

MATERIALS AND METHODS

Patient population.

Patients with relapsed and refractory CLL, AML and ALL were eligible for the phase I study. Patients had to be at least 18 years of age, have received at least one prior course of chemotherapy or immunotherapy, and be able to provide written, informed consent to participate in this institutional review board (The Ohio State University, University of Chicago, and Johns Hopkins University) approved protocol. CLL patients had to be Rai stage III/IV and/or require treatment for disease-related symptoms. AML/ALL patients had to be primary refractory or relapsed and not a candidate for potentially curative therapy such as stem cell transplantation. Patients could not have received immunotherapy within one month of study enrollment. Patients with active infection, organ dysfunction, thrombocytopenia (platelets 50,000/mm^3 or less), or Eastern Cooperative Oncology Group (ECOG) performance status greater than 3 were not eligible. The phase I/II dose expansion was limited to CLL and was conducted only at the Ohio State University; otherwise, entry criteria were the same.

1D10 antigen density.

1D10 antigen density was determined by fluorescence activated cell sorter (FACS) analysis of peripheral blood or bone marrow. Tumor cells were isolated from peripheral blood using ficoll density gradient centrifugation (Ficoll-Paque Plus, Pharmicia Biotech, Piscataway, NJ). FACS analysis was utilized, gating on CLL cells co-expressing CD19 (using FITC-conjugated anti-CD19) and the 1D10 antigen (using PE-conjugated anti-1D10). CLL cells stained with FITC-conjugated anti-CD19 and PE-conjugated anti-MSL-1 IgG1 (isotype-

specific anti-CMV antigen) served as negative controls. Mean fluorescence intensity (MFI) of 1D10 antigen expression was measured relative to MFI of negative control cells, and 1D10 antigen density was expressed as relative MFI. Patients with relative MFI ≥ 2 were eligible for treatment on this study. We obtained 1D10 antigen density on 77 CLL patients including those screened for the phase I study and CLL patients enrolled on another laboratory protocol. The range of MFI in CLL was 0.98–31.68. Sixty CLL patients (78%) had MFI ≥ 2.0 and were considered to have 1D10-positive tumor cells.

Treatment schedule.

Apolizumab was administered using a "stepped-up" dosing schedule. Patients received 0.15 mg/kg on day 1, 0.5 mg/kg on day 2, and the target dose of their cohort (1.5, 3.0 or 5.0 mg/kg) on day 3 and three times weekly for 4 weeks. Total doses of apolizumab were 17.15 mg/kg in cohort 1, 33.65 mg/kg in cohort 2, and 55.65 mg/kg in cohort 3. Patients received acetaminophen 650 mg PO and diphenhydramine 50 mg PO/IV 30 minutes prior to each dose of apolizumab. Patients who developed urticaria received cetirizine hydrochloride (Zyrtec) 5–10 mg PO prior to subsequent doses of apolizumab. On the phase I/II expansion, patients were given hydrocortisone 100 mg IV as premedication also.

Toxicity and Response.

Toxicity was assessed by NCI Common Toxicity criteria (CTCAE) v2.0 (14). Dose limiting toxicity (DLT) was defined as grade 4–5 infusion-related toxicity, reversible grade 3–5 or irreversible grade 2 non-hematologic toxicity, grade 4 thrombocytopenia lasting 1 week, grade 4 neutropenia lasting 2 weeks, or grade 4 neutropenic fever lasting 1 week. CLL response was assessed by NCI 96 criteria (15).

Pharmacokinetic analysis.

Plasma concentrations of apolizumab were determined using a sandwich enzyme-linked immunoadsorbent assay (ELISA) (16). A murine anti-Hu1D10 idiotype antibody was used as the solid-phase capture reagent, and binding of apolizumab to coated wells was detected with horseradish peroxidase (HRP)-conjugated sheep anti-human IgG antibody. The terminal elimination rate constant k was determined using linear regression of the terminal phase concentration versus time data after the final dose of apolizumab. Systemic clearance (CL) during the first dose was calculated as CL=Ro/C*(1-exp[-k*t]), where Ro was rate of apolizumab infusion, C was apolizumab concentration at end of infusion, and t was duration of infusion.

Statistical analysis.

Scatter plots of systemic clearance (CL) during the first dose versus relative MFI of 1D10 antigen density were done, and regression analysis was performed to determine the correlation coefficient.

RESULTS

Patient demographics.

Twenty-three eligible patients (7 female) were enrolled on the phase I/II trial. The phase I trial enrolled 18 patients (17 CLL, 1 ALL), including 12 subjects in the dose escalation and six additional subjects who were treated at the maximum tolerated dose (MTD). The phase I/II expansion enrolled 5 of 12 planned CLL patients prior to its closure due to discontinuation of the development of this drug by the pharmaceutical sponsor (see Discussion). Demographics of the 23 patients on this study are shown in Table I and include a median age of 58 years (range, 38–79), with a median of 3 prior therapies (range 1–11). Of the 22 CLL patients, 20 were refractory to fludarabine, 10 were Rai Stage 3–4, and median white blood cell (WBC) count at enrollment was 18,100/μl (range 2,800–168,600). Median MFI of 1D10 antigen density was 8.93 (range, 2.27–27.56) in the phase I group and 3.7 (range, 2.79–30.99) in the phase II group.

Toxicity.

Tables II and III summarize the number of patients who developed toxicity during the course of apolizumab therapy. In the phase I portion, all 18 patients developed infusion toxicity (10 fever, 9 nausea, 7 urticaria, 7 headache) during “stepped-up” dosing that resolved with subsequent treatments in patients in cohorts 1 and 2 (Table II), whereas infusion toxicity persisted in cohort 3 (5.0 mg/kg/dose). Infusion toxicity appeared to be related to cytokine release of TNF-α, IL-6, IL-8, and IL-10 but not IFN-γ or plasma nitric oxide (data not shown). Grade 3–4 infusion toxicity was uncommon, although 4 patients developed grade 3–4 dyspnea or hypoxia. Urticaria and pruritis generally did not improve after initial dose titration, but were manageable with antihistamines. No patient discontinued therapy due to urticaria or pruritus, and more severe immediate hypersensitivity symptoms were not observed. Four patients developed grade 3–4 thrombocytopenia, which was not related to platelet count at study entry (Tables II and III). In the phase I/II expansion, steroid premedication equivalent to 100 mg hydrocortisone was given as prophylaxis for infusion reaction. No rash or hives occurred in the phase II portion. One of 5 patients had grade 2 infusion reaction (fever, chills), and another reported headache.

Dose limiting toxicity (DLT).

DLT was assessed in the phase I study. All 6 patients in cohorts 1 and 2 completed therapy. Only 3 of 6 patients in cohort 3 completed therapy, due to progressive disease (PD, 1) and treatment related DLT (2), including aseptic meningitis and atypical hemolytic uremia syndrome (HUS). Aseptic meningitis was observed in a 65 year-old male after dose 7. This patient became disoriented, developed short term memory deficits, and complained of headache. Examination was notable only for a fever of 100.6 degrees. His neurological and cardiac examinations were unremarkable. Computed tomography and magnetic resonance imaging studies of the head were normal. Cerebral spinal fluid (CSF) was grossly hazy with a WBC count of 840 with 92% neutrophils, a decreased glucose of 47, and an elevated protein of 113. CSF cultures and infectious studies were negative, and no organisms or leukemia cells were seen. CSF after 24 hours of empiric antifungal, antiviral, and antibacterial therapy was clear, with a WBC count of 140 and 56% neutrophils. His

symptoms entirely resolved over a week. Apolizumab was detected in his CSF, and he was felt to have had aseptic meningitis due to the study drug.

Atypical hemolytic uremic syndrome (HUS) was observed in a 79 year-old female who was hospitalized after dose 11 for thrombocytopenia, anemia, hyperbilirubinemia, elevated lactic dehydrogenase, hematuria, and acute renal failure. The previous week she had received trimethoprim/sulfamethazole for a urinary tract infection and diarrhea. Haptoglobin was less than 20 mg/dL, but no spherocytes or schistocytes were observed on her peripheral blood smear. Renal ultrasound was normal. She died of myocardial infarction on the third day of hospitalization. Based upon the two DLTs observed at level 3, the cohort 2 dose (3.0 mg/kg/dose) was defined as the MTD of apolizumab in this patient population. No delayed toxicity was noted with apolizumab.

Response.

Table IV outlines the individual response in all patients. All patients were evaluated for response. Of the 22 CLL patients, 19 were treated at the MTD or above. One patient with del(17p13) achieved a partial response lasting four months. Stable disease for greater than 6 months was noted in three CLL patients.

Pharmacokinetic analysis.

Pharmacokinetic analysis was performed on 13 patients. Values of k ranged from 0.000799 to 0.003551 hr^{-1}, corresponding to apolizumab half-lives of 36 days and 8.1 days, respectively. Inter-subject variability in apolizumab half-lives and area under the curve (AUC) after the first dose of antibody appeared to be due to differences in clearance of antibody. Regression analysis indicated that MFI of 1D10 antigen density accounted for a portion of the variability in apolizumab systemic clearance. In fact, if one clear outlier is excluded from correlation analysis, a statistically significant ($p<0.001$) relationship between MFI and clearance is observed (data not shown).

DISCUSSION

Our results indicate that apolizumab can be administered safely to patients with relapsed CLL and ALL, using a “stepped-up” thrice-weekly dosing schedule similar to that previously employed for rituximab (13). Infusion toxicity was ubiquitous but manageable, and all patients treated at the first two cohort dose levels completed treatment. Pre-medication with cetirizine hydrochloride (Zyrtec) effectively prevented recurrent hives in patients who developed urticaria to apolizumab. “Stepped-up” dosing allowed apolizumab to be administered with acceptable toxicity up to 3.0 mg/kg/dose. However, prohibitive toxicity was observed at 5.0 mg/kg/dose, similar to the experience with weekly apolizumab in NHL (9). One high-risk patient with del(17p13) achieved a short-lived partial response, and three additional patients had clinical improvement with stable disease for greater than 6 months. Although further development of apolizumab was discontinued by the pharmaceutical sponsor due to limited clinical activity and potentially concerning HUS in this and other studies, the data derived from this clinical trial provide guidance to future development of other HLA-DR directed antibody treatment approaches.

Aseptic meningitis and atypical HUS constituted the two cases of DLT in this study; both toxicities have been described after therapy with other monoclonal antibodies (17, 18). Aseptic meningitis was observed with intravenous immunoglobulin (19), the anti-CD3 antibody muromonab (OKT3) (20) and the anti- TNF-α antibody infliximab (21, 22). Apolizumab was detected in the CSF of the patient who developed aseptic meningitis, and his symptoms resolved with discontinuation of therapy. HUS was observed in 2 of 16 patients who received the anti-CD22 immunotoxin RFB4(dsFv)-PE3 (BL22) (18). The mechanism by which apolizumab induced atypical HUS in our patient remains poorly defined. Endothelial cells express MHC class II molecules, which are up-regulated in endothelial dysfunction and autoimmune diseases (23). In addition, HLA-DR53 was found to be protective against HUS (24). It is unclear whether the patient who experienced atypical HUS expressed HLA-DR52, which does not protect against HUS (24), or had some medical condition that resulted in increased HLA-DR expression on her endothelial cells, thereby predisposing her to HUS upon exposure to apolizumab.

Pharmacokinetic analysis suggests that systemic clearance of apolizumab is related to 1D10 antigen density, and that it may be possible to dose apolizumab according to an individual's 1D10 antigen density. The apparent relationship between 1D10 density and systemic clearance of apolizumab suggests that the antibody may undergo target-mediated disposition. This has been described for drugs that bind with high affinity to their pharmacological targets, particularly if that affinity is higher than the pharmacological dose of the drug (25, 26). If confirmed in a larger cohort of patients, this finding indicates that it may be possible to use HLA-DR density, as determined by MFI, as a surrogate marker to adjust the dose of anti-MHC class antibodies for an individual patient.

In summary, a "stepped-up" thrice-weekly dosing schedule allowed apolizumab to be administered with acceptable infusion toxicity. While one short-lived partial response was observed in a relapsed CLL patient with del(171p13), further development of apolizumab was discontinued due to limited clinical efficacy and potentially concerning HUS in this and other clinical studies of apolizumab.

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Table I.

Phase I and II Combined Patient Demographics (n=23)

Diagnosis, number	CLL	22	
	ALL	1	
CLL Patients (n = 22)			
Rai Stage	I	8	
	II	3	
	III	2	
	IV	8	
Median age, years (range)		58	(38–79)
Male : Female		15 : 7	
Median prior therapies, number (range)		3	(1–11)
Fludarabine-refractory, number		20	
Median WBC, /μl (range)		18,100	(2,800–168,600)
Median 1D10 density, MFI (range)		8.56	(2.27–30.99)

Legend: CLL (chronic lymphocytic leukemia); ALL (acute lymphocytic leukemia); WBC (white blood count); MFI (mean fluorescence index)

Table II.

Phase I Common toxicities (n=18)

TOXICITY	#PATIENTS	GRADE (#PTS)
Fatigue	11	1/2 (10), 4 (1)
Fever	10	1/2 (9), 3 (1)
Hyperglycemia	10	1/2 (8), 3 (2)
Nausea	9	1/2 (9)
Anemia	8	1/2 (8)
Thrombocytopenia	8	1/2 (4), 3/4 (4)
Headache	7	1/2 (7)
Urticaria	7	1/2 (7)
Cough	6	1/2 (6)
Chills / Rigors	6	1/2 (6)
Hypocalcemia	5	1/2 (5)
Hypotension	4	1/2 (4)
Infection (not neutropenic)	4	2 (3), 3 (1)

Table III.

Phase I Grade 3–5 toxicity (n=18)

TOXICITY	#PATIENTS	GRADE(S)
Bone pain	1	3
Cardiac ischemia	1	5
Dyspnea/hypoxia	4	3, 3, 3, 4
Earache	1	3
Fatigue	1	4
Fever	1	3
Hemolysis	1	3
Hyperglycemia	2	3, 3
Hypophosphatemia	1	3
Infection (neutropenic/unknown)	2	3, 3
Pneumonitis	1	3
Thrombocytopenia	4	3, 4, 4, 4

Table IV.

Response of individual patients (n= 23)

DOSE LEVEL	PATIENT	RESPONSE	DURATION
Level 1 (1.5 mg/kg/dose)	Pt #1	Stable Disease	3 months
	Pt #2	Stable Disease	8 months
	Pt #3	Stable Disease	5 months
Level 2 (3.0 mg/kg/dose)	Pt #4	Partial Response	4 months
	Pt #5	Stable Disease	8 months
	Pt #6	Stable Disease	5 months
Level 2 expansion	Pt #13	Stable Disease	5 months
	Pt #14	Progression	N/A
	Pt #15	Stable Disease	6 months
	Pt #16	Progression	N/A
	Pt #17	Stable Disease	5 months
	Pt #18	Progression	N/A
	Pt #19	Progression	N/A
	Pt #20	Stable Disease	4 months
	Pt #21	Stable Disease	1 month
	Pt #22	Progression	N/A
	Pt #23	Progression	N/A
Level 3 (5.0 mg/kg/dose)	Pt #7	Progression	N/A
	Pt #8	DLT (Non-Eval)	N/A
	Pt #9	DLT (Non-Eval)	N/A
	Pt #10	Progression	N/A
	Pt#11 *	Stable Disease	1.5 months
	Pt #12	Stable Disease	2 months

* Acute lymphoblastic leukemia (ALL) patient