Phase 1 study of an anti-CD33 immunotoxin, humanized monoclonal antibody M195 conjugated to recombinant gelonin (HUM-195/rGEL), in patients with advanced myeloid malignancies

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ABSTRACT

We conducted a phase 1 study of an anti-CD33 immunotoxin, humanized monoclonal antibody M195 conjugated to recombinant gelonin (HUM-195/rGEL), in patients with relapsed, refractory myeloid leukemias. Twenty-eight patients received the construct intravenously at four dose levels (12, 18, 28 and 40 mg/m^2 per course) in a "3+3" study design. The dose-limiting toxicity was infusion-related allergic reaction including hypoxia and hypotension. The 28 mg/m^2 total dose was considered the maximally tolerated dose. Four patients developed a reduction in peripheral blood blasts of at least 50%. Three patients treated with the 10, 12 and 28 mg/m^2 doses showed a 38-50% reduction in bone marrow blasts. There was normalization of platelets in one patient treated with 40 mg/m^2. Pharmacokinetic analysis demonstrated that the highest blood levels achieved were 200-300 ng/mL which cleared with a half-life of ~20 hours. Antigenicity was low with one patient at the 12 mg/m^2 dose and one patient at the 18 mg/m^2 dose (2/23, <10%) developing antibodies to the recombinant gelonin component after 28 days. We concluded that HUM-195/rGel can be safely administered in a multi-dose cycle to patients with advanced myeloid malignancies and warrants further investigation.

Introduction

CD33 is a surface protein that is expressed in uni- and multi-potent hematopoietic colony-forming cells but not in their more primitive precursors.[1-3] Flow cytometrically sorted CD33$^-$ bone marrow cells or bone marrow cells depleted of CD33$^+$ cells by monoclonal antibody and complement can still give rise to multilineage colonies indicating the presence of a more primitive CD33$^-$ precursor cell.[2] Studies using samples from patients heterozygous for G6PD indicate that in most patients with acute myelogenous leukemia (AML), leukemic cells express CD33 while the normal hematopoietic progenitors do not.[4,5] Stem cell autografts from patients with AML treated *ex-vivo* with CD33 antibody are slow to engraft but hematopoietic reconstitution is possible from bone marrows depleted of CD33$^+$ cells indicating functional lack of expression of CD33 in normal hematopoietic progenitor cells.[6] Among hematologic malignancies, CD33 expression is almost exclusively restricted to myeloid malignancies.[7]

Based on this preferential expression of CD33 in leukemic progenitors, CD33-based therapeutic strategies have been pursued over the past two decades and have led in the past to the development of an antibody-drug conjugate designated gemtuzumab ozogamicin, a humanized anti-CD33 antibody conjugated to the small molecule toxin calicheamicin for use in older patients with AML in first relapse.[8,9] Concerns about increased toxicity of this conjugate, particularly when used in combination with chemotherapy, have led to its voluntary withdrawal from the market. Still, recent studies demonstrated the clinical efficacy of using gemtuzumab ozogamicin, in combination with chemotherapy, in specific subsets of patients.[10-12]

M195 is a monoclonal IgG2a antibody to CD33 derived from a mouse immunized with live human leukemic myeloblasts.[3,7] Flow cytometric studies showed that M195 reactivity is mostly restricted to myeloid blasts and myeloid progenitors and is absent in mature myeloid cells.[7] Pharmacokinetic studies in phase 1 trials have shown that M195 is rapidly internalized after binding to target cells and binding sites are saturated at doses above 5 mg/m^2.[13] The clinical activity of M195 was studied in a phase I trial of M195 labeled with therapeutic doses of ^{131}I.[14] However concerns exist regarding the use of radio-immune conjugates because of potential exposure of normal hematopoietic cells to radiation and the transient nature of the observed therapeutic effects of either the naked antibody or the radiolabeled agent.

The recombinant antibody HUM-195 is a complementarity determining region (CDR)-grafted fully humanized version of M195 with a human IgG1 framework.[15] Compared to M195, HUM-195 has higher avidity for binding CD33 and, in contrast to M195, can induce antibody-dependent cell-mediated cytotoxicity in addition to complement-mediated cytotoxicity.[15] HUM-195 demonstrated low immunogenicity in a phase 1 trial and dose-limiting toxicity (DLT) was not encountered

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with doses up to 10 mg/m^2 administered every 76-98 h for six doses.[16] Recombinant gelonin (rGel) is an engineered, bacterially-expressed recombinant version of gelonin toxin originally isolated from the seeds of *Gelonium multiflorum*. It is a single chain protein that inactivates the ribosomal 60S subunit by cleaving rRNA adenine N-glycoside bonds in a sequence-specific fashion and is a potent inhibitor of protein synthesis.[17] Unlike dual-chain toxins such as ricin, gelonin lacks a carbohydrate-binding domain and, by itself, cannot bind to or enter mammalian cells without a carrier such as an antibody or growth factor.

HUM-195/rGel is an immunotoxin created by conjugating rGel with HUM-195 via an N-succinimidyl-3-(2-pyridyl-dithio)-propionate linkage.[17,18] An analog of rGel was used which contained an engineered cysteine in the C-terminus, allowing site-specific conjugation of the toxin to the antibody component. The HUM-195/rGel conjugate has been examined in numerous *in vitro* models demonstrating impressive, specific cytotoxic effects.[18-20] In a bone marrow purging model using HL60 cells mixed with mobilized peripheral blood progenitor cells, incubation with HUM-195/rGel followed by freeze-thawing, simulating marrow purging, led to a 2-log reduction of leukemic cells from the normal progenitor cells.[19] Additional *in-vivo* models of leukemia also confirmed the conjugate's activity.[20] Here we report the results of the first in-human phase I study of HUM-195/rGel in patients with CD33-expressing myeloid malignancies.

Design and Methods

Objective

The primary objective of the study was to determine the safety and toxicity of the HUM-195/rGel immunotoxin in patients with relapsed or refractory myeloid malignancies and define a recommended dose for phase 2 studies. Secondary objectives were to examine the biological effects of HUM-195/rGel, including the ability to elicit antileukemic responses and human anti-gelonin antibody (HAGA) responses.

Eligibility

Patients aged ≥18 years with any of the following diagnoses in whom prior therapies had failed were eligible: relapsed or refractory AML, refractory anemia with excess blasts, chronic myelomonocytic leukemia, accelerated or myeloid blastic phase of chronic myelogenous leukemia or myeloproliferative disorders and >5% blasts in the blood or bone marrow. In addition, as assessed by flow cytometry, CD33 expression was required in ≥80% of blasts. Because of concerns associated with proliferative diseases, eligibility was restricted to patients with a white blood cell count <10x10^9/L in those with AML, myelodysplastic syndrome, chronic myeloid leukemia in myeloid blastic phase and myeloproliferative disorders and ≤30x10^9/L in those with chronic myeloid leukemia in accelerated phase. Other eligibility criteria included: (i) being off any cytotoxic chemotherapy for 2 weeks prior to enrollment and free from residual toxicity of grade ≥2 from prior therapies; (ii) serum creatinine ≤ 1.5 times the upper limit of normal laboratory values; and (iii) serum bilirubin ≤2.0 times the upper limit of normal and aspartate aminotransferase and/or alanine aminotransferase (ALT) levels ≤2.5 times the upper limit of normal laboratory values.

Treatment plan

HUM-195/rGel was administered intravenously in 100 mL of Plasmalyte or Isolyte along with 100 mg of albumin over 1 h. Premedication consisted of 50 mg hydrocortisone and ondansetron 8 mg intravenously. The planned dose escalation scheme is presented in Table 1. Each course included two infusions per week (72 to 96 h apart) for 2 weeks (for a total of 4 infusions) followed by a 2-week period of observation (making a total of 4 weeks per cycle). The time between infusions was designed to allow optimal re-expression of the CD33 antigen upon exposure of cells to the antibody component.[16]

Patients could receive a second cycle at the same dose 2 weeks after receiving the final dose of their first course provided that non-hematologic toxicities were less than grade 3 and one of the following conditions were fulfilled within 42 days from the start of the first cycle: (i) hematologic improvement: defined as at least a halving of marrow leukemia infiltrate (% blasts x % cellularity) or of peripheral blood leukemia burden (% blasts x white blood cell count), or (ii) doubling in platelet count to ≥30 x10^9/L, or doubling in absolute neutrophil count to >0.5x10^9/L, or (iii) reappearance of >10% blasts cells in a marrow that is ≥15% cellular or reappearance of >2x10^9/L circulating blasts, or (iv) an absolute peripheral blast count <25% greater than at baseline. For patients experiencing greater than grade 2 toxicity and requiring >42 days for recovery to normal or leukemic hematopoiesis as defined above, the dose for second cycle was reduced by one level.

Patients achieving at least a partial remission could continue therapy on the same schedule as above for 4 months or 2 months beyond complete remission, whichever was earlier. Intra-patient dose escalation during maintenance to a dose level that was already deemed safe was permitted for patients achieving partial remission.

Response definitions

Complete remission required normalization of the peripheral blood and bone marrow with ≤5% blasts, normocellular or hypercellular marrow, a granulocyte count of ≥1x10^9/L and a platelet count of ≥100x10^9/L. Disappearance of an abnormal karyotype was not necessary for complete remission in either AML or chronic myeloid leukemia in myeloid blastic phase. In this latter, a return to chronic phase was defined as complete remission except a white blood cell count ≥10x10^9/L. Partial remission was defined as above except for the presence of 6-25% marrow blasts. All other responses were considered failures.

Statistical design

Dose escalations were carried out with the standard "3+3" design. Occurrence of DLT in the first cycle in any patient was the trigger for the addition of at least three additional patients at that dose level. All patients who received therapy on study were considered evaluable for toxicity. DLT was defined as non-hematologic toxicity ≥ grade 3 (NCI common criteria, version 3.0) considered at least possibly related to the study drug. Hematologic DLT was defined as grade 3 or higher pancytopenia with a hypocellular

Table 1. Planned dose escalations.

Dose Level	HUM-195/rGel (mg/m^2/dose)	Total dose per course (mg/m^2)
1 (starting dose)	3	12
2	4.5	18
3	7	28
4	10	40
5	15	60
6	22	88

bone marrow and no marrow blasts lasting for 42 days or more. The DLT defining period was the first cycle.

The study was approved by the MD Anderson Cancer Center Institutional Review Board (Protocol N. DM98-342) and patients gave informed consent.

Results

Patients' characteristics

Twenty-eight patients were enrolled at four dose levels (12 at 3 mg/m^2, 3 at 4.5 mg/m^2, 6 at 7 mg/m^2 and 7 at 10 mg/m^2) and were evaluable for toxicity (Table 2). Twenty-two patients were evaluable for response. The median age of the patients was 67 years (range, 31-81 years) and 15 (54%) were female. All except one patient (with myelodysplastic syndrome/myeloproliferative disorder) had a diagnosis of AML and 12 (43%) had therapy-related or secondary AML. Cytogenetics were diploid in nine (32%) patients, seven (25%) had chromosome 5 and/or 7 abnormalities, six (21%) had chromosome 11 abnormalities and one had inversion 16 with additional trisomy 4 abnormality. The median number of prior therapies was two (range, 1-4) and three patients had prior exposure to gemtuzumab ozogamicin.

Treatment

Twenty-eight patients received 104 doses of HUM-195/rGel and 19 (68%) of them received at least four doses of the study drug. Nine (32%) patients did not receive the four doses planned in the first cycle due to disease progression (3 patients), progressive pneumonia, cardiac arrhythmia, congestive heart failure, early death, withdrawal of consent and allergic reaction (1 each). Two patients proceeded to receive cycle 2 of therapy: both had >50% reductions in peripheral blood blast percentage and one had improvements in absolute neutrophil count and platelet count in cycle 1. Both discontinued therapy beyond cycle 2 because of lack of marrow response.

Adverse events

Fatigue (32%), infusion-related chills and rigors (25%), fever (18%) and skeletal pain (21%) were the most frequent adverse events. Infusion-related allergic reaction with hypoxia was seen in three patients and was grade ≥3 in two patients at dose level 4 (10 mg/m^2). Grade ≤2 edema was seen in two patients and supraventricular tachycardia in another two patients (1 grade ≥3). Eleven patients developed neutropenic fever requiring hospitalization. Anginal chest pain relieved with sublingual nitroglycerine was seen in one patient at dose level 1 (3 mg/m^2). Elevations of liver enzymes were encountered in three patients (1 grade ≥3) at dose level 4 (10 mg/m^2).

There were three deaths (none related to the study drug) while on study, one due to progressive pneumonia with a presumably fungal etiology, one due to progressive disease, and one from a myocardial infarction on day 21 of cycle 1 at a dose of 7 mg/m^2. This last patient had hypertension as a predisposing factor.

Adverse events according to dose levels, irrespective of attribution, are summarized in Table 3. At the 10 mg/m^2 dose one patient developed an allergic reaction with shortness of breath and hypoxemia which was considered probably related to the study drug and was a DLT. Upon expansion of the cohort to six patients, another patient developed an allergic reaction with hypotension (grade 3). Thus this

Table 2. Patients' characteristics.

Characteristics	Median	Range	N. (%)
Age (years)	65	31-80	
Sex			
Male			13 (46)
Female			15 (54)
Diagnosis			
De novo AML			15 (54)
Secondary AML			12 (43)
Myelodysplastic syndrome			1 (3)
Cytogenetics			
Diploid			9 (32)
-5/-7			7 (25)
11q			6 (22)
others			6 (22)
N. of prior therapies	2	1-4	
While blood cell count (x10^9/L)	3	(0.6-47.7)	
Platelets (x10^9/L)	19	(5-49)	
% CD33 in blasts	95	(80-99.6)	

Table 3. Adverse events by dose level irrespective of attribution.

	N. of patients= 28			
	12	3	6	7
	Dose levels			
Toxicities: Grade 1-2/3-4	3 mg/m^2	4.5 mg/m^2	7 mg/m^2	10 mg /m^2
Drug fever	5/0	0/0	0/0	0/0
Neutropenic fever	1/2	0/1	1/0	1/4
Nausea/vomiting	2/0		1/1	
Abdominal pain	1/0	0/0	1/0	0/0
Anorexia	0/1	0/0	0/0	1/0
Fatigue	2/0	0/0	1/0	5/1
Rigors	4/0	1/0	2/0	1/0
Allergic reaction	0/0	0/0	0/0	0/1
Gastrointestinal bleed	0/1	0/0	0/0	0/0
Pleural effusion	0/1	0/0	1/0	1/0
Rash	0/1	0/0	0/0	0/0
Erythema multiforme	0/0	0/0	0/0	1/0
Skeletal pain	0/1	2/0	2/0	3/1
Chest pain (non cardiac)	0/0	0/0	0/0	0/1
Headache	0/0	2/0	2/0	0/0
Supraventricular tachycardia	0/0	0/0	0/1	1/0
Sinus tachycardia	0/0	0/0	0/0	2/0
Myocardial infarction/angina	0/1	0/0	0/1*	0/0
Hypotension	0/0	0/0	0/1	0/1
Edema	0/0	0/0	1/0	2/0
Weight gain	0/0	0/0	1/0	0/0
Dyspnea	0/0	0/0	0/0	0/1
Stomatitis	0/0	0/0	0/0	1/0
Liver enzyme abnormalities	0/0	0/0	0/0	2/1
Hypophosphatemia	0/0	0/0	0/0	2/1

*Grade 5.

dose level was the DLT-defining level. With six patients enrolled at 7 mg/m^2 without encountering DLT, this dose level was considered the maximum tolerated dose.

Pharmacokinetics

Blood samples were obtained at various times after the end of infusion and were assessed for concentration of intact HUM-195/rGel using an enzyme-linked immunosorbent sandwich assay composed of a polyclonal anti-rGel capture antibody and an anti-human IgG detection antibody. Samples were drawn from patients during the first and fourth infusions. The pharmacokinetic clearance of intact HUM-195/rGel is shown for patients at the 10, 12 and 28 mg/m^2 dose levels (Figure 1). Values shown are the means±SEM for all patients at the given dose level. Overall, the kinetics fit a one-compartment model for clearance with a half-life of ~20 h. Clearance kinetics for individual patients were highly variable and this was likely due to adsorption of the immunoconjugate by various levels of CD33$^+$ tumor cells in each patient. In general, the blood levels achieved increased with increasing doses. There were no differences in clearance kinetics observed between the first and fourth infusions. The marked effective concentration zone (~200-450 ng/mL) represents the *in vitro* IC_{50} values for the immunoconjugate against various cell lines and specimens from patients.

Immunogenicity of HUM-195/rGel

The immunogenicity of HUM-195/rGel was assessed in samples of serum taken from the patients prior to drug administration and 28 days after the first injection. An enzyme-linked immunosorbent assay using rGel-coated plates and anti-human IgG polyclonal antibodies for detection was used to identify the presence of elicited anti-rGel antibodies. A positive signal was arbitrarily determined to be any sample with an optical density > 5 times that of the normal human control serum. No patients had pre-existing anti-rGel antibodies. One patient at the 12 mg/m^2 dose level and one patient at the 18 mg/m^2 dose level had high anti-rGel titers (~1:100,000) on day 28. No patients at the 28 or 40 mg/m^2 dose levels demonstrated anti-rGel antibodies.

Responses

No complete or partial remission was achieved. Four patients had greater than 50% reductions in peripheral blood blasts (from 21% to 8%, 11% to 1%, 10% to 0%, and 69% to 32%) although they had no substantial reduction in bone marrow blasts. Interestingly four patients had substantial reductions in the percentage of CD33$^+$ bone marrow blasts in follow-up flow cytometry studies (96% to 57%, 94% to 1%, 85% to 15%, and 99% to 0%). An improvement in absolute neutrophil count to ≥1x10^9/L was seen in three patients and doubling of the platelet count (to >50x10^9/L) was also recorded in three patients. According to protocol-defined criteria, treatment was considered a failure in all other patients.

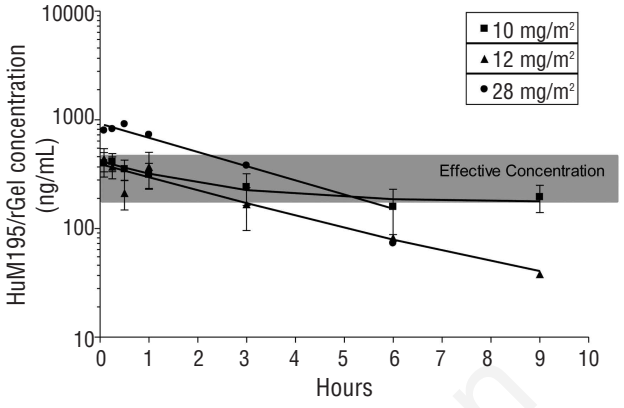

Figure 1. Serum pharmacokinetics of HUM-195/rGel. Values shown are the means±standard error of mean for all patients at the given dose level.

Discussion

Our study has defined 7 mg/m^2 given intravenously over 1 h twice weekly for 2 weeks in a 4-week cycle as the maximum tolerated dose for HUM-195/rGel. Apart from infusion reactions, which are commonly seen in patients being treated with humanized antibodies, no seriously concerning toxicities were seen. The significant paucity of liver enzyme abnormalities is of note. Furthermore, other toxins such as pseudomonas exotoxin and ricin A-chain cause a vascular leak syndrome,[21] while this was not a general observation in patients treated with the rGel conjugate. Also, other toxins have been found to be highly immunogenic while the immunogenicity of the rGel immunotoxin appeared to be low.[21]

There was modest evidence of clinical activity, with reductions in peripheral blood blast counts in some patients and improvements in neutrophil and/or platelet counts in others. Given the heavily pre-treated, relapsed/refractory patient population included in this study, the limited evidence of response is not surprising. It is also possible that the schedule could be optimized to favor greater clinical benefit. For example, schedules with more frequent administration (e.g., thrice weekly), or with a shorter off period (e.g., 2 weeks on, 1 week off) could be explored. Interestingly, the flow cytometrically detected reduction in CD33 positivity in the blasts of some patients at the end of first cycle may indicate sustained antigen occupancy by the immunotoxin. Supersaturating doses of unconjugated HUM-195 have been explored and multiple infusions of doses up to 12, 24, and 36 mg/m^2/day have been administered in a 4-h infusion schedule with toxicities limited to infusion-associated chills and rigor.[22] At these doses, antigen site occupancy was seen for 4 weeks and the average plasma half-life of HUM-195 was approximately 1 week, compared to 38 h seen in previous studies. Whether using a slower infusion schedule than the one reported in our study could enable higher doses of HUM-195/rGel to be delivered for better responses needs investigation.

There is a recent resurgence of interest in CD33-based immunotoxins because of the favorable outcomes seen in different cohorts of patients treated with gemtuzumab ozogamicin administered with chemotherapies.[10-12] In contrast, the data for unconjugated naked anti-CD33 antibody are less favorable, indicating the need for conjugation with toxins.[23] The ideal toxin for conjugation with anti-CD33 antibody remains to be defined and improvement in linker technology is expected to result in products with less collateral damage and organ toxicity. In conclu-

sion, HUM 195/rGel was well tolerated at doses of up to 7 mg/m^2 administered twice weekly for 2 weeks every 4 weeks (28 mg/m^2 total). There was modest evidence of clinical activity in this population of refractory patients. Additional studies with alternative schedules and combination with chemotherapy are warranted to determine the potential clinical role of HUM-195/rGel in patients with CD33$^+$ myeloid malignancies.

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