A phase I multidose study of dacetuzumab (SGN-40; humanized anti-CD40 monoclonal antibody) in patients with multiple myeloma

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ABSTRACT

This first-in-human, phase I study evaluated the safety, maximum-tolerated dose, pharmacokinetics, and antitumor activity of dacetuzumab in 44 patients with advanced multiple myeloma. Patients received intravenous dacetuzumab, either in 4 uniform weekly doses (first 4 cohorts) or using a 5-week intrapatient dose escalation schedule (7 subsequent cohorts; the last 3 cohorts received steroid premedication). An initial dose of 4 mg/kg dacetuzumab exceeded the maximum-tolerated dose for uniform weekly dosing. Intrapatient dose escalation with steroid premedication appeared effective in reducing symptoms of cytokine release syndrome and the maximum-tolerated dose with this dosing schema was 12 mg/kg/week. Adverse events potentially related to dacetuzumab included cytokine release syndrome symptoms, non-infectious ocular inflammation, and elevated hepatic enzymes. Peak dacetuzumab blood levels increased with dose. Nine patients (20%) had a best clinical response of stable disease. The observed safety profile suggested that dacetuzumab may be combined with other multiple myeloma therapies. Two combination trials are ongoing.

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Key words: multiple myeloma, dacetuzumab, SGN-40, CD40, immunotherapy.

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Introduction

Multiple myeloma (MM) accounts for approximately 1% of cancers worldwide and 10% of all hematologic cancers.[1-3] The regional incidence of MM varies,[2] but is relatively high in the United States, where 19,920 new cases were expected to be diagnosed and 10,690 deaths were anticipated for 2008.[4]

With the introduction of novel therapies in the past decade, response rates and, more importantly, survival have improved dramatically.[5] In a study of 387 MM patients who relapsed after stem cell transplantation, treatment with thalidomide, lenalidomide, or bortezomib significantly improved the median overall survival (30.9 *vs.* 14.8 months for patients who did not receive these agents; $P<0.001$).[6] Nevertheless, MM remains an incurable disease.

Several B-cell malignancies, including MM, express CD40, making it an attractive potential target for antibody-based cancer therapy.[7] Dacetuzumab (Seattle Genetics, Inc., Bothell, WA, USA) is a humanized anti-CD40 monoclonal antibody with multiple mechanisms of action. Dacetuzumab kills tumor cells via immune effector functions (antibody-dependent cellular cytotoxicity and phagocytosis [ADCC/ADCP]) and induction of apoptosis through direct signal transduction.[8-10]

Design and Methods

This open-label, phase I study used a traditional 3+3 dose escalation scheme. The maximum tolerated dose (MTD) was the highest dacetuzumab dose at which fewer than one third of patients in a cohort experienced a dose-limiting toxicity (DLT).

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Patients were treated at 6 study centers in the United States. The protocol was approved by all Institutional Ethics Committees and patients provided written informed consent before study-specific procedures began. Data were collected from March 2004 to November 2007.

Eligible patients were adults with recurrent or refractory MM who had failed at least 2 different systemic therapies for MM and had Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less, a life expectancy greater than three months, and adequate organ function. Patients were excluded if they had a history of migraines or severe headaches (Group B only), had received an allogeneic transplant, or had uncontrolled hypercalcemia.

Eleven cohorts of patients received intravenous infusions of dacetuzumab (Table 1). Patients in Group A received 4 uniform weekly doses. The protocol was amended to treat patients in Group B using a 5-week intrapatient dose escalation schema in an effort to reduce the incidence and severity of cytokine release syndrome (CRS) symptoms. Patients in Group B who responded after Cycle 1 were eligible for 4 additional weekly doses (Cycle 2) at the highest cohort-specific dose.

Table 1. Dacetuzumab dose schedule[1] by treatment cohort (doses in mg/kg).

Cohort (n. patients)	Week 1 Day 1	Week 1 Day 4	Week 2 Day 8	Week 3 Day 15	Week 4 Day 22	Week 5 Day 29
Group A						
0.5 mg/kg (n=3)	0.5	–	0.5	0.5	0.5	–
1 mg/kg (n=4)	1	–	1	1	1	–
2 mg/kg (n=6)	2	–	2	2	2	–
4 mg/kg (n=3)	4	–	4	4	4	–
Group B						
I (n=3)	1	1	2	3	3	3
II (n=4)	1	1	2	4	4	4
III (n=4)	1	1	2	4	6	6
IV (n=5)	1	1	2	4	6	8
V[2] (n=3)	2	4	8	8	8	8
VI[2] (n=4)	4	8	12	12	12	12
VII[2] (n=5)	8	8	16	16	16	16

[1]Schedule represents treatment Cycle 1. Patients in Group B could be eligible for 4 additional weekly doses (Cycle 2) at the highest cohort-specific dose; [2]Steroid pre-medication for the first 3 infusions (Days 1, 4, and 8) was required for Cohorts V through VII.

Table 2. Patients with symptoms of cytokine release syndrome[1] within one day of dacetuzumab dose.

	Group A[2] N=16 n/N (%)	Group B[2] (Cohorts I – IV) N=16 n/N (%)	Group B[2] (Cohorts V – VII) N=12 n/N (%)	All patients N=44 n/N (%)
Dosing Day 1	7/16 (44)	9/16 (56)	2/12 (17)	18/44 (41)
Dosing Day 8	5/14 (36)	4/15 (27)	1/12 (8)	10/41 (24)
Dosing Day 15	4/14 (29)	5/15 (33)	3/10 (30)	12/39 (31)
Dosing Day 22	3/11 (27)	0/15 (0)	1/9 (11)	4/35 (11)

[1]Symptoms included in this analysis (e.g. headache, fatigue, fever, chills) were based on medical review, taking into consideration the CTCAE criteria for CRS; [2]A uniform weekly dosing schedule was used for patients in Group A and an intrapatient dose escalation schedule was used for patients in Group B. Steroid pre-medication for the first 3 infusions was required for Cohorts V through VII.

All patients were pre-medicated with acetaminophen (up to 650 mg orally) and diphenhydramine (up to 50 mg intravenously or orally) 30 to 60 minutes prior to dacetuzumab infusion. In addition, steroid pre-medication (methylprednisolone, 50 mg intravenously immediately prior to infusion) was required for the first 3 infusions in the 3 highest dose cohorts of Group B.

Study evaluations were conducted at baseline and on all infusion days. After the final dose, patients were monitored for an additional six weeks. Monitoring was to continue every six weeks until disease progression. Patients were evaluated for adverse events, standard laboratory tests, human anti-human antibodies (HAHA), and serum concentrations of dacetuzumab. Antitumor response evaluations included best clinical response (criteria adapted from Blade *et al.* [11]), serum and 24-hour urine M protein concentrations, and ECOG status.

Results and Discussion

Forty-four patients were enrolled. Demographics and baseline characteristics were similar in Groups A and B. Overall, the median age was 60 years (range 40 to 80 years), 59% of patients were men, and 41 patients (93%) had an ECOG status of 0 or 1. The median time since diagnosis of MM was 4.3 years (range 1-14 years), and the median number of previous systemic therapies was 5 (range 2-14). Eighteen of 39 patients with data available (46%) had at least 50% bone marrow plasma cells and 13 (33%) had at least 70% plasma cells at baseline.

Treatment was generally well tolerated, although 11 of the 44 patients withdrew from treatment during Cycle 1 (6 due to DLTs and 5 due to disease progression). One patient entered and received all 4 doses in Cycle 2. Forty-three patients (98%) experienced at least one adverse event. The most common adverse events were fatigue (25 patients, 57%), headache (19 patients, 43%), nausea (10 patients, 23%), and anemia (9 patients, 21%). Other adverse events with an incidence greater than 10% were anorexia, back pain, constipation, diarrhea, ocular hyperemia, pyrexia, thrombocytopenia, and vomiting. These events were observed in 5 to 7 patients each (11-16%).

Most adverse events were Grade 1 or 2 in severity. Thirteen patients (30%) had adverse events of at least Grade 3. Seven weeks after the last dose of dacetuzumab, one patient died due to sequelae from a fall. Two Grade 4 adverse events were reported: aseptic meningitis (4 mg/kg cohort) and hyperviscosity syndrome (Cohort I). Adverse events of at least Grade 3 observed in 2 or more patients were thrombocytopenia (3 patients, 7%) and anemia, aseptic meningitis, headache, hypercalcemia, neutropenia, and renal failure (2 patients each, 5%). Serious adverse events were reported for 8 patients (18%).

Adverse events potentially related to dacetuzumab included headache and other symptoms of CRS, non-infectious ocular inflammation, and elevated hepatic enzymes, generally occurring within two weeks of starting treatment.

The overall incidence of CRS symptoms within one day of infusion was 41% following the first dose of dacetuzumab and lower with subsequent doses (Table 2). Intrapatient dose escalation in Group B allowed doses of dacetuzumab greater than 4 mg/kg to be given without CRS-related DLTs; while the incidence was not reduced, the severity of symptoms was (*data not shown*). Addition of steroid pre-medication reduced first-dose CRS symptoms in Group B from 56% to 17%.

Nine patients (21%) experienced non-infectious inflammatory eye disorders: 2/16 patients (13%) in Group A, 5/16 patients (31%) in the first 4 cohorts of Group B, and 2/12 patients (17%) in the last 3 cohorts of Group B. With one exception, these disorders were Grade 1: one patient (Cohort IV) experienced Grade 2 conjunctivitis that resolved with steroid eyedrops.

Elevated hepatic transaminases of at least one toxicity grade were observed for 18 patients (41%), without evident relationship to cohort or steroid pre-medication. With the exception of 4 patients, all reported abnormalities in hepatic transaminases were Grade 1 in severity. For the 4 patients with Grade 2 or 3 elevations, the abnormalities were transient, asymptomatic, and not associated with marked changes in bilirubin.

Six patients were withdrawn from study due to DLTs that were Grade 3 in severity, with one exception (Grade 4 aseptic meningitis). In Group A, one patient in the 2 mg/kg cohort had a DLT of transient neutropenia and 2 of 3 patients in the 4 mg/kg cohort had DLTs following the first dose of dacetuzumab (Grade 3 or 4 aseptic meningitis, both in conjunction with Grade 3 headache). Thus the MTD for uniform weekly dosing (without steroid pre-medication) was 2 mg/kg. Both patients with aseptic meningitis recovered completely, and one required no additional MM therapy until receiving steroids approximately 12 months later. These DLTs were believed to be a manifestation of CRS, and the intrapatient dose escalation schedule was implemented for Group B in an effort to reduce CRS and allow higher doses of dacetuzumab.

In Group B, no DLT was reported for the first 6 cohorts. Three patients in Cohort VII had DLTs but no pattern was evident: one patient each had atrial fibrillation, syncope, and Grade 3 elevation of ALT that did not resolve to Grade 1 within 14 days. Thus the MTD for intrapatient dose escalation (including steroid pre-medication) was 12 mg/kg/week.

Intrapatient dose escalation allowed higher doses of dacetuzumab to be given, suggesting that partial agonistic signaling may result in less inflammation after initial exposure to a lower dose. Steroid pre-medication allowed even higher doses to be given, likely reflecting the ability of steroids to dampen the cytokine response. This dosing strategy (intrapatient dose escalation with steroid pre-medication) appears effective in reducing both the incidence and severity of CRS symptoms and was implemented in other trials of dacetuzumab. In contrast, eye disorders and elevations in hepatic transaminases were not diminished by these changes, likely reflecting that these events are not related to cytokine release.

Mild hematologic toxicity was observed in some patients. Seven patients (16%) and 12 patients (27%) had decreased hemoglobin and platelet counts, respectively, by at least one grade at the end of treatment. Twelve patients (27%) had reduced absolute lymphocyte counts of at least one toxicity grade, an expected consequence of dacetuzumab treatment.

Immunogenicity (HAHA) results were available at Day 29 or later for 37 patients. One patient (0.5 mg/kg cohort) had a low-titer seropositive result on Day 63 that was not associated with any adverse event. Thus immunogenicity of dacetuzumab does not appear to be a significant problem in this patient population.

Pharmacokinetic data were available for 38 patients. Peak blood levels of dacetuzumab increased with dose (Figure 1). After the final dose of Cycle 1, mean Cmax val-

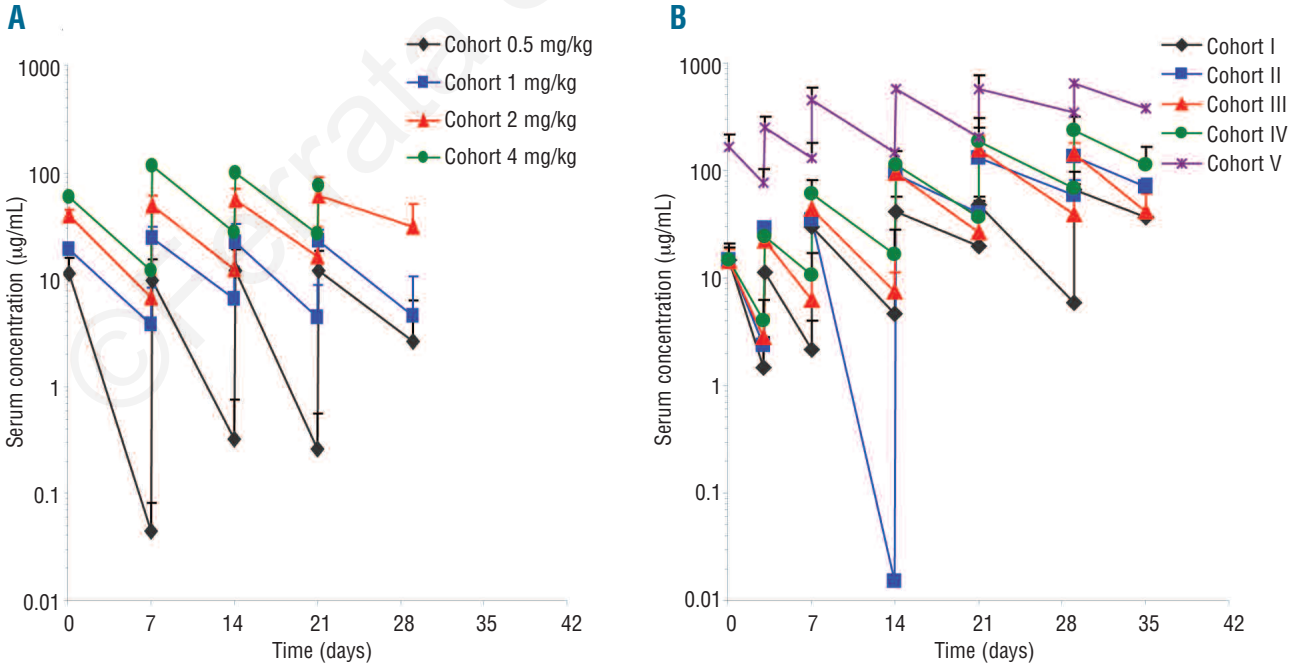

Figure 1. Mean (+SD) serum concentration *vs.* time profiles for dacetuzumab by cohort in cycle 1. (A) Group A patients. (B) Group B patients. Mean Cmax and Cmin could not be summarized for Cohorts V and VI due to missing values.

ues in Group A ranged from 12.1 μg/mL (0.5 mg/kg cohort) to 74.8 μg/mL (4 mg/kg cohort) and those in Group B ranged from 65.5 μg/mL (Cohort I) to 636 μg/mL (Cohort VII). Additional pharmacokinetic parameters could not be determined.

Although transient decreases in serum and 24-hour urine M-protein levels were observed for some patients, no objective responses were reported. Nine patients (20%) had a best clinical response of stable disease; the distribution did not appear to be dose related. Twenty-nine of 42 patients with data available had no change in ECOG status at end of treatment. Five patients (12%) had a one-level improvement, including one patient in Cohort II who received a second cycle of dacetuzumab based on the improvement; her disease remained stable three months after completing Cycle 2.

This first-in-human study showed that multiple dacetuzumab doses up to 12 mg/kg were generally well tolerated, when administered using an intrapatient dose escalation schedule with steroid pre-medication. While single-agent dacetuzumab was not highly active in this study, the observed safety profile suggested that testing dacetuzumab in combination with other MM therapies would be feasible. Preliminary *in vitro* results suggest that combining dacetuzumab with lenalidomide is synergistic,[12] and this combination may produce better response rates. Two trials are underway in patients with relapsed MM to evaluate dacetuzumab in combination with lenalidomide or bortezomib.

Authorship and Disclosures

MH, JRB, RN, NM, and JGD developed the study, concept and design. MH, JRB, RN, NM, JM, and RS provided study patients. All authors collected and/or assembled the data, interpreted the results, and wrote and approved the final manuscript.

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