

Original Articles

Phase I Study of Ofatumumab, a Human Anti-CD20 Antibody, in Japanese Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

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Objectives: Ofatumumab is a human IgG1 κ monoclonal antibody that targets a membrane proximal epitope encompassing the small and large loops of CD20. This Phase I study evaluated the safety, tolerability, efficacy and pharmacokinetics of ofatumumab monotherapy in Japanese patients with relapsed/refractory B-cell chronic lymphocytic leukemia and small lymphocytic lymphoma.

Methods: Ofatumumab was administered intravenously weekly for a total of eight doses (dose escalation: 500 and 1000 mg). Six patients (two chronic lymphocytic leukemia and four small lymphocytic lymphoma) were enrolled into two dose cohorts (500 mg, three patients; 1000 mg, three patients). All six patients received 300 mg ofatumumab at the first infusion and either 500 or 1000 mg at seven subsequent weekly infusions.

Results: No dose-limiting toxicities or serious adverse events were observed. Grade 3–4 adverse events observed were grade 3 lymphocytopenia ($n = 1$) and neutropenia ($n = 1$). Grade 1–2 infusion-related adverse events leading to temporary interruption of ofatumumab infusion were observed in all six patients on the first infusion day, and all patients completed the planned eight infusions. The overall response rate was 50% (3/6).

Conclusions: Ofatumumab was well tolerated at doses up to 1000 mg and showed preliminary evidence of activity in relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma, warranting further investigations. This study was registered at ClinicalTrials.gov (NCT00742144).

Key words: ofatumumab – chronic lymphocytic leukemia – small lymphocytic lymphoma – CD20 – monoclonal antibody

INTRODUCTION

Ofatumumab (Arzerra™; GlaxoSmithKline, USA; Genmab A/S, Denmark) is a human CD20 monoclonal antibody (mAb) that binds to a unique, membrane-proximal epitope composed of both the large and small loops of CD20, distinct from the epitope recognized by rituximab, which is a chimeric anti-CD20 mAb (1,2). Ofatumumab showed a more rapid and effective *in vitro* complement-dependent cytotoxicity (CDC) than rituximab, including in primary chronic lymphocytic leukemia (CLL) cells and cells with low CD20 expression (1–3).

Ofatumumab is being clinically developed for B-cell malignancies, including follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL) (4–6). CLL is also considered to be an appropriate disease target of ofatumumab due to its superior ability to efficiently lyse B-cells with a relatively low expression of CD20 molecules *in vitro* (7). The safety and efficacy of ofatumumab have been reported in Western CLL patients (8–10). The interim results of a Phase II study (10) showed the efficacy of ofatumumab in CLL patients who were refractory to both fludarabine and alemtuzumab (FA-ref) and who were refractory to fludarabine and considered inappropriate for alemtuzumab due to bulky (>5 cm) lymphadenopathy (BF-ref). The overall response rates were 58 and 47% in the FA-ref and BF-ref groups, respectively. The median progression-free survival (PFS) was 13.7 and 15.4 months in the FA-ref and BF-ref groups, respectively. Based on the favorable safety and efficacy results, ofatumumab has been approved in the USA, European Union, Australia, Switzerland and Croatia for the treatment of CLL in patients who are refractory to fludarabine and alemtuzumab.

Pharmacokinetic/pharmacodynamic analyses have indicated that increased exposure to the antibody correlated with improved clinical outcomes, including the overall response rate (ORR) and PFS, in CLL (9,11).

mAb therapies such as rituximab, alemtuzumab and ofatumumab are currently not approved for clinical use in CLL patients in Japan. Data on the safety and efficacy of ofatumumab in East Asian, including Japanese, patients are lacking. This Phase I study evaluated the tolerability, safety, efficacy and pharmacokinetics of ofatumumab monotherapy in Japanese patients with CD20-positive, relapsed or refractory CLL/SLL and FL.

PATIENTS AND METHODS

PATIENTS

Patients with relapsed or refractory CLL/SLL or FL meeting the following criteria were enrolled into this study. Patients with CLL or SLL, as defined by the World Health Organization (WHO) classification (2001) (12), who had CD5, CD19, CD20 and CD23-positive leukemia that relapsed or was refractory to prior therapies were eligible for

enrollment. Patients with FL who had histologically confirmed FL of grade 1–3a, as defined by the WHO classification (2001) (12), with one or more clearly demarcated lesions with a largest diameter ≥ 1.5 cm on the baseline computed tomography (CT) scan and that were CD20 positive in a lymph node pathological assessment, were eligible for enrollment. Other eligibility criteria included age between 20 and 79 years, Eastern Cooperative Oncology Group (ECOG) performance status (13) of 0–2, life expectancy of 24 weeks or more at screening, time from the most recent rituximab therapy or radioimmunotherapy of at least 12 weeks and time from the most recent anti-tumor therapy of at least 4 weeks.

This study was performed in accordance with Good Clinical Practice. The protocol was approved by the Institutional Review Board of each participating institution, and it conformed to the provisions of the Declaration of Helsinki of 1995 (as revised in Tokyo 2004). All patients gave their written, informed consent.

STUDY DESIGN

This study was planned as an open-label, non-randomized, multi-center, Phase I study to evaluate the tolerability of ofatumumab as monotherapy by assessing dose-limiting toxicity (DLT) in Japanese patients with CD20-positive CLL or FL. Ofatumumab was administered by intravenous infusion weekly for a total of eight doses. Each patient received 300 mg ofatumumab at the first infusion and either 500 or 1000 mg at seven subsequent weekly infusions. The follow-up period was 7 months after study treatment.

All patients received oral acetaminophen 400 mg and oral or intravenous administration of an antihistamine drug (cetirizine hydrochloride 10 mg or its equivalent) between 30 min and 2 h prior to each ofatumumab infusion. Before the first and second infusions, patients also received intravenous prednisolone 100 mg or its equivalent between 30 min and 2 h prior to the infusion.

DLT AND DOSE-ESCALATION CRITERIA

DLTs were categorized and graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 (Bethesda, MD). DLTs were defined as grades 3 and 4 drug-related non-hematological toxicity excluding grade 3 nausea or vomiting and grade 4 drug-related hematological toxicity, including neutropenia lasting 7 days or more, febrile neutropenia and thrombocytopenia with a platelet count of $2.5 \times 10^9/l$ or less.

DLT was evaluated in the initial three patients at each dose level of ofatumumab (500 and 1000 mg). If all three initial patients in the 500-mg group did not develop DLT, the next three patients were to be enrolled in the 1000-mg group. If one or two of the initial three patients in the 500-mg group developed DLT, an additional three patients were to be enrolled in the 500-mg group. If the total number of patients who developed DLT was no more than two of six

patients in the 500-mg group, the next three patients were to be enrolled in the 1000-mg group. If all of the initial three patients, or if three or more of six patients in the 500-mg group developed DLT, no further patients would be enrolled into the study. Dose escalation to more than 1000 mg was not planned as part of this study.

ASSESSMENT OF SAFETY AND EFFICACY

AEs were categorized and graded according to the NCI CTCAE, version 3.0. The generation of human anti-human antibodies (HAHA) against ofatumumab was assessed at baseline and at 6 and 9 months after the first ofatumumab administration using a Meso-Scale Discovery (MSD) bridging assay format for the detection of anti-ofatumumab antibodies in the human serum samples. The HAHA assay was developed and validated at Clinical Immunology, Biopharmaceutical R&D, GlaxoSmithKline.

Tumor response was evaluated according to the NCI-Sponsored Working Group Guidelines for Chronic Lymphocytic Leukemia, Revised Guidelines for Diagnosis and Treatment (14) for CLL and SLL, and the Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas (15) for FL.

PFS was defined as the time from the start of treatment until the first documented sign of progressive disease (PD) or death due to any cause. Duration of response was defined as the time from the first documented evidence of complete remission (CR) or partial remission (PR) to the first documented sign of PD or death due to disease in patients with CR or PR.

The CD5⁺CD19⁺ B-cell count in peripheral blood was measured by flow cytometry as a surrogate for the malignant CD5⁺CD20⁺ B-cell count.

PHARMACOKINETICS

Blood samples for pharmacokinetic analyses were collected immediately before the first and eighth infusions and for 120 h after the infusions. At the fourth infusion, a blood sample was collected immediately before and 2 h after the infusion. On the second, third, fifth, sixth and seventh infusions, blood samples were collected only immediately before the infusion. In addition, blood samples for pharmacokinetic analyses were also collected at each follow-up visit.

The concentrations of ofatumumab in the human plasma were determined by an antibody capture sandwich ELISA developed and validated at GlaxoSmithKline. The method used a mouse monoclonal anti-idiotypic antibody to capture ofatumumab, a mouse Fc-specific anti-human IgG1 antibody coupled to horseradish peroxidase to detect ofatumumab, and the Super Signal FEMTO substrate to generate a chemiluminescent endpoint. The analytical method was selective, sensitive, precise and accurate for the determination of ofatumumab in the human plasma, with an analytical range of 100–2500 ng/ml. Dilution linearity was validated up to a 1:8032 dilution.

Values of the following pharmacokinetic parameters were calculated for each patient by the non-compartmental method using WinNonlinTM software version 4.1. The parameters were the maximum plasma concentration (C_{max}), time to observed maximum drug concentration (t_{max}), plasma half-life at a terminal phase ($t_{1/2}$), area under the concentration–time curve (AUC), clearance (CL), volume of distribution at steady state (V_{ss}) and mean residence time (MRT).

RESULTS

PATIENTS

Between September 2008 and November 2009, six patients were enrolled into this study and received all eight infusions of ofatumumab; three patients each were enrolled to the 500- and 1000-mg groups (Table 1). Three male and three female patients were enrolled and treated. All six patients had CLL/SLL. Two patients had Rai stage II CLL, and four patients had Ann Arbor stage III ($n = 1$) or IV ($n = 3$) SLL. The median age was 47.5 (range, 41–61) years. The median number of prior therapeutic regimens was two (range, 1–5). All six patients completed the treatment period without any dose delay. Two patients in the 500-mg group were withdrawn from the study at 4.2 and 7.0 months after study initiation during the follow-up period due to PD.

SAFETY

AEs in the study are summarized in Table 2. All six patients had AEs during this study. None of the patients developed DLT. No deaths or serious AEs (SAEs) were reported during the study. None of the patients in the study developed an AE leading to withdrawal or permanent discontinuation of ofatumumab.

Urticaria ($n = 5$) and neutropenia ($n = 4$) were the most common AEs in both treatment groups. Most of the AEs were grade 1 or 2. Grade 3 lymphocytopenia was reported in one patient in the 500-mg group; this patient also had grade 2 lymphocytopenia at baseline. Grade 3 neutropenia was reported in one patient in the 1000-mg group; this patient had grade 2 neutropenia at baseline. No grade 4 AEs were reported during the study.

All six patients developed an infusion-related AE during the 300-mg dose infusion on the first infusion day, which was resolved by temporary infusion interruption and supportive care (Fig. 1), but they received all subsequent infusions. One CLL patient in the 1000-mg group also developed an infusion-related AE on the second and sixth infusion days, which led to temporary infusion interruption, but the patient received all subsequent doses. The remaining five CLL/SLL patients did not develop an infusion-related AE leading to temporary infusion interruption on the subsequent infusion days. All infusion-related AEs were grades 1 and 2 and resolved by temporary infusion interruption and appropriate supportive care. The most common infusion-related AE leading to an infusion

Table 1. Patients' characteristics

Characteristics	Ofatumumab treatment group		
	500 mg (<i>n</i> = 3)	1000 mg (<i>n</i> = 3)	Total (<i>n</i> = 6)
Age, years			
Median [range]	52 [43–57]	41 [41–61]	48 [41–61]
Sex, no. (%)			
Female	2 (67)	1 (33)	3 (50)
Male	1 (33)	2 (67)	3 (50)
Diagnosis, no. (%)			
CLL	1 (33)	1 (33)	2 (33)
SLL	2 (67)	2 (67)	4 (67)
FL	0	0	0
Number of prior therapies			
Median [range]	2 [1–3]	2 [1–5]	2 [1–5]
Prior therapies, no. (%)			
Rituximab and fludarabine combination	2 (67)	1 (33)	3 (50)
Rituximab-containing regimen	0	1 (33)	1 (17)
Fludarabine-containing regimen	0	1 (33)	1 (17)
Others	1 (33)	0	1 (17)
Time from end of most recent therapy, weeks			
Median [range]	17 [8–21]	66 [26–106]	24 [8–106]
Time from diagnosis, years			
Median [range]	1.9 [1.3–3.7]	5.8 [1.8–8.4]	2.8 [1.3–8.4]
Modified Rai stage in CLL patients (<i>n</i> = 2), no. (%)			
II	1 (100)	1 (100)	2 (100)
Binet stage in CLL patients (<i>n</i> = 2), no. (%)			
B	1 (100)	1 (100)	2 (100)
Ann Arbor stage in SLL patients (<i>n</i> = 4), no. (%)			
III	0	1 (50)	1 (25)
IV	2 (100)	1 (50)	3 (75)
Constitutional symptoms, no. (%)			
Present	0	0	0
Absent	3 (100)	3 (100)	6 (100)

CLL, chronic lymphocytic leukemia; FL, follicular lymphoma; SLL, small lymphocytic lymphoma.

interruption was urticaria (*n* = 5), which was observed only with the first infusion. Other infusion-related AEs leading to temporary infusion interruption included throat irritation (*n* = 1), pruritus (*n* = 1), cytokine release syndrome (*n* = 1) and infusion-related reaction (*n* = 1).

Grade 1 infections occurred in four patients, two each in the 500- and 1000-mg groups. One patient each in the 500- and 1000-mg groups developed nasopharyngitis. One patient in the 500-mg group developed pharyngitis. One patient in the 1000-mg group developed an upper respiratory tract infection. All infectious AEs were considered to be related to ofatumumab, except nasopharyngitis in one patient in the

500-mg group. All of these AEs were manageable and resolved between 1 and 18 days after onset.

One patient in the study had a positive result for HAHA at baseline, prior to any ofatumumab administration. However, all post-ofatumumab samples tested negative in this patient. There were no other positive HAHA results in the study.

EFFICACY

The ORR of all 6 patients was 50% (3/6). All three patients in the 1000-mg group achieved PR. The prior therapies of the responders were a rituximab and fludarabine combination

Table 2. All adverse events

Adverse event, <i>n</i> (%)	Ofatumumab treatment group					
	500 mg (<i>n</i> = 3)		1000 mg (<i>n</i> = 3)		Total (<i>n</i> = 6)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Hematological						
Neutropenia	2 (67)	0	2 (67)	1 (33)	4 (67)	1 (17)
Lymphocytopenia	2 (67)	1 (33)	1 (33)	0	3 (50)	1 (17)
Thrombocytopenia	0	0	2 (67)	0	2 (33)	0
Leukopenia	0	0	1 (33)	0	1 (17)	0
Non-hematological						
Urticaria	3 (100)	0	2 (67)	0	5 (83)	0
Blood lactate dehydrogenase increased	2 (67)	0	2 (67)	0	4 (67)	0
Nasopharyngitis	1 (33)	0	1 (33)	0	2 (33)	0
Weight increased	0	0	1 (33)	0	1 (17)	0
Pruritus	1 (33)	0	0	0	1 (17)	0
Pharyngitis	1 (33)	0	0	0	1 (17)	0
Upper respiratory tract infection	0	0	1 (33)	0	1 (17)	0
Fatigue	1 (33)	0	0	0	1 (17)	0
Infusion-related reaction	0	0	1 (33)	0	1 (17)	0
Oedema peripheral	1 (33)	0	0	0	1 (17)	0
Hyperbilirubinaemia	1 (33)	0	0	0	1 (17)	0
Cytokine release syndrome	0	0	1 (33)	0	1 (17)	0
Thermal burn	1 (33)	0	0	0	1 (17)	0
Throat irritation	1 (33)	0	0	0	1 (17)	0

therapy regimen (*n* = 1), a rituximab-containing regimen without fludarabine (*n* = 1), and a fludarabine-containing regimen without rituximab (*n* = 1) (Table 1). In the 500-mg group, one patient had SD and two patients had PD. The median PFSs of all 6 patients, of the 500 mg cohort and of the 1000 mg cohort were 32.1, 17.1, and 39.3 weeks, respectively. The median duration of response of all three patients in the 1000-mg group was 30.8 weeks.

CHANGE IN THE CD5⁺CD19⁺ B-CELL COUNTS

The changes in the CD5⁺CD19⁺ B-cell counts in individual patients of the 500- and 1000-mg groups are shown in Fig. 2A and B, respectively. One CLL patient (Patient 1) in the 1000-mg group had a high baseline CD5⁺CD19⁺ B-cell count of 68.00 × 10⁹/l that decreased with each ofatumumab infusion (Fig. 2B).

The other CLL patient in the 500-mg group (Patient 21) had a somewhat high baseline CD5⁺CD19⁺ B-cell count of 7.28 × 10⁹/l but did not show continuous reduction in the CD5⁺CD19⁺ B-cell counts (Fig. 2A). The remaining four SLL patients, who had low peripheral CD5⁺CD19⁺ B-cell

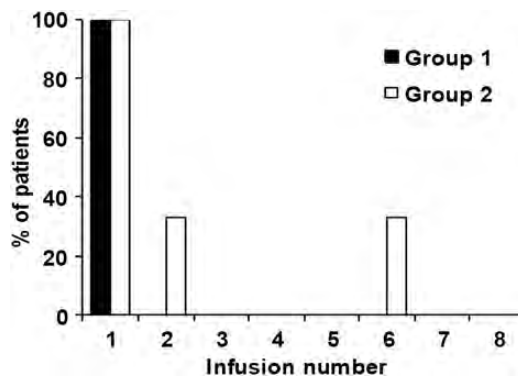


Figure 1. Frequency of temporary infusion interruption due to AEs on each infusion day, Group 1, ofatumumab 500-mg infusion (*n* = 3); Group 2, ofatumumab 1000-mg infusion (*n* = 3). The first infusions were 300 mg for both infusion groups.

counts at baseline, showed relatively small changes after ofatumumab infusion.

PHARMACOKINETICS

The plasma concentration profiles of ofatumumab in individual patients of the 500- and 1000-mg groups are shown in

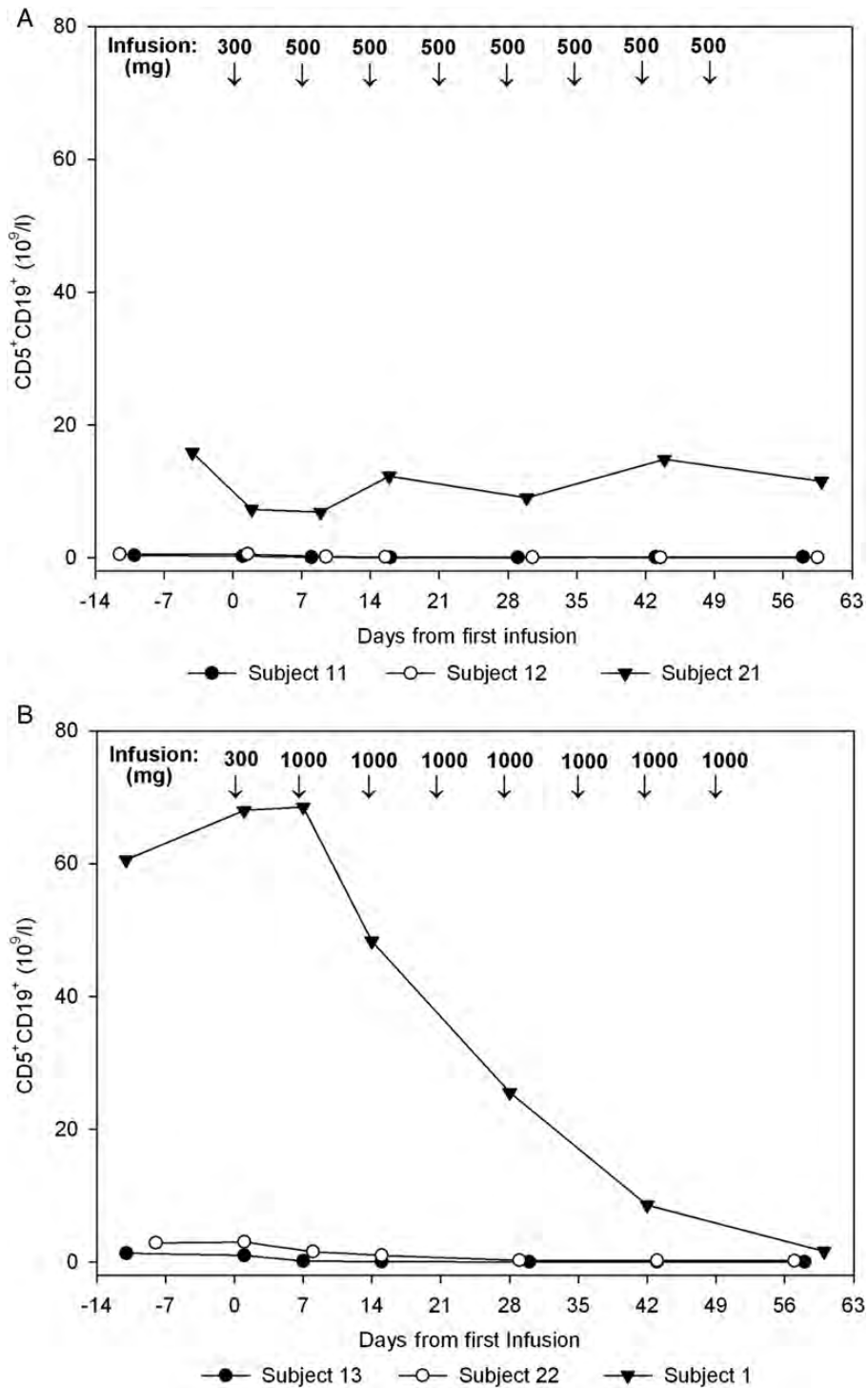


Figure 2. (A) Individual CD19⁺CD5⁺ B-cell counts in the three patients in the 500-mg group; patients received 300 mg ofatumumab at the first infusion and seven subsequent once-weekly infusions of 500 mg. The time of administration of each of the eight ofatumumab doses is indicated by an arrow. (B) Individual CD19⁺CD5⁺ B-cell counts in the three patients in the 1000-mg group; patients received 300 mg ofatumumab at the first infusion and seven subsequent once-weekly infusions of 1000 mg. The time of administration of each of the eight ofatumumab doses is indicated by an arrow.

Fig. 3A and B, respectively. Following the first infusion, the maximum ofatumumab concentrations were observed shortly after the end of the infusion. The concentrations decreased over the following 7 days until the next ofatumumab dose was administered. Trough concentrations were increased by

each infusion up to the eighth infusion. Although the profiles showed no clear difference among the three patients in the 500-mg group (Fig. 3A) and in two of the three patients (Patients 13 and 22) in the 1000-mg group (Fig. 3B), the patient with a high baseline CD5⁺CD19⁺ B-cell count

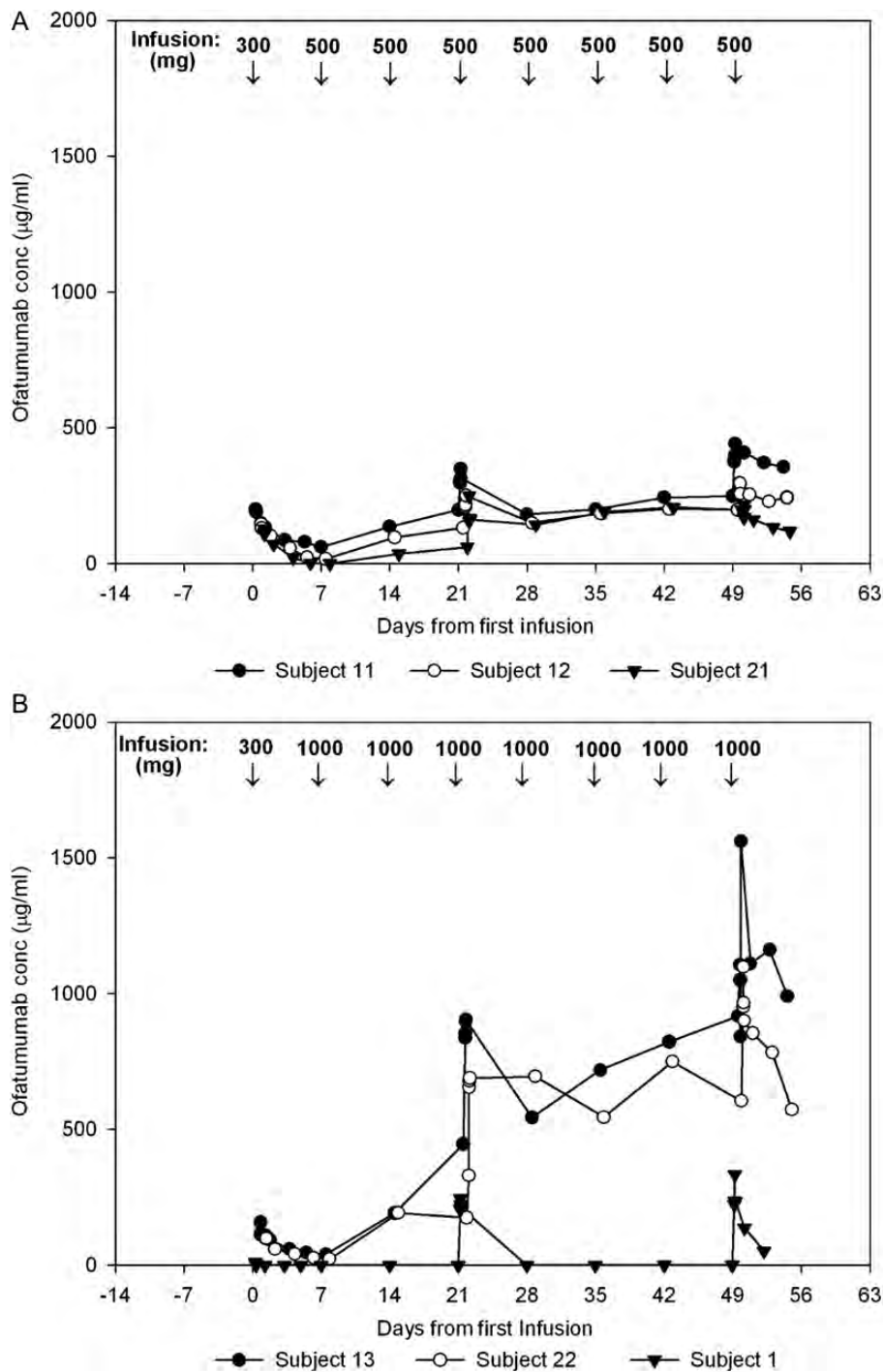


Figure 3. (A) Individual plasma concentration of ofatumumab in the three patients in the 500-mg group; patients received 300 mg ofatumumab at the first infusion and seven subsequent once-weekly infusions of 500 mg. The time of administration of each of the eight ofatumumab doses is indicated by an arrow. (B) Individual plasma concentrations of ofatumumab in the three patients in the 1000-mg group; patients received 300-mg ofatumumab at the first infusion and seven subsequent once-weekly infusions of 1000 mg. The time of administration of each of the eight ofatumumab doses is indicated by an arrow.

(Patient 1) in the 1000-mg group showed very low concentrations of ofatumumab compared with others and showed no plasma accumulation.

The pharmacokinetic parameter values for ofatumumab are shown in Table 3. The mean C_{max} at the first infusion in all six patients was 94 µg/ml after 300 mg dosing, and at the eighth infusion, it was 304 and 830 µg/ml for the 500 mg

(three patients) and 1000 mg (three patients) groups, respectively. The mean $AUC_{0-\infty}$ at the first infusion was 5116 h µg/ml after 300 mg dosing, and at the eighth infusion, it was 200 109 and 126 217 h µg/ml for the 500- and 1000-mg groups, respectively. Lower clearance and longer half-life values for ofatumumab were observed after the eighth infusion than after the initial infusion.

Table 3. The plasma ofatumumab pharmacokinetic parameter values

Pharmacokinetic parameter	Ofatumumab treatment group		
	First infusion	Eighth infusion	
	300 mg (n = 6)	500 mg (n = 3)	1000 mg (n = 3)
C_{max} ($\mu\text{g/ml}$)			
Geo. mean	94	304	830
% CVb	155	37	96
t_{max} (h)			
Median	7.3	5.2	4.7
Min, max	6.4, 10.2	4.6, 6.1	4.3, 7.2
$t_{1/2}$ (h)			
Geo. mean	34.7	474	93.8
% CVb	1076	58	571
AUC_{0-168} (h $\mu\text{g/ml}$)			
Geo. mean	3766	47 633	65 612
% CVb	1259	40	324
$AUC_{0-\infty}$ (h $\mu\text{g/ml}$)			
Geo. mean	5116	200 109	126 217
% CVb	1939	16	1873
CL (ml/h)			
Geo. mean	58.6	12.9	16.0
% CVb	1938	49	300
V_{ss} (l)			
Geo. mean	3.82	1.73	1.25
% CVb	120	43	122
MRT (h)			
Geo. mean	65.1	694	157
% CVb	354	60	451

AUC, area under the concentration–time curve; CL, clearance; C_{max} , maximum concentration; MRT, mean residence time; t_{max} , maximum drug concentration time; $t_{1/2}$, terminal-phase elimination half-life; V_{ss} , steady-state volume of distribution.

DISCUSSION

There is a need for medical treatment options in patients with relapsed/refractory CLL/SLL or FL, although rituximab has demonstrated an improvement in treatment outcomes. This Phase I study showed the tolerability, safety and preliminary efficacy of ofatumumab at doses up to 1000 mg in Japanese patients with relapsed or refractory CLL/SLL. No patients with FL were enrolled into the study. Six CLL/SLL patients were enrolled, including three in the ofatumumab 500-mg group, and another set of three patients was enrolled in the ofatumumab 1000-mg group after no DLT was observed in the 500-mg group. All six patients completed the protocol-defined infusions. None of the patients

met the DLT criteria in the study. The present Phase I dose-escalation study in Japanese patients with relapsed or refractory CLL/SLL showed that ofatumumab 500- and 1000 mg infusions were well tolerated.

In this study, no SAEs or DLTs were reported. Two grade 3 AEs were observed: one of lymphopenia in the 500-mg group and one of neutropenia in the 1000-mg group in a patient with baseline grade 2 neutropenia. Neutropenia was one of the most common grade 3 or 4 AEs, occurring in 9.4% of CLL patients treated with ofatumumab in a previous study, though those patients had refractory CLL (10). Although four of six Japanese CLL/SLL patients developed grade 1 to 3 neutropenia, none required granulocyte colony-stimulating factor or developed serious neutropenic infections. Patients with relapsed or refractory CLL have a high risk of infectious complications (16), and infection was also a common AE in the previous study (10). Infections occurred in four of six Japanese CLL/SLL patients in the present study. All of the infections were grade 1 and clinically manageable.

Therapeutic infusions of mAbs are associated with a characteristic infusion-related syndrome (8,10,17–19). Infusion reactions, predominantly occurring on the first or second administration of ofatumumab, were common, and the pattern was similar to what has been observed in other ofatumumab studies. Cytokine release may be responsible for the infusion-related reactions (20). In the present study, all six patients developed an infusion-related AE on the first infusion day, which was resolved by temporary infusion interruption and supportive care (Fig. 1). However, all but one patient developed no further infusion-related AEs leading to temporary infusion interruption on the subsequent infusion days, resulting in the administration of the fully scheduled dose for all patients. All infusion-related AEs were grade 1 or 2. In the present study, all patients received prophylactic acetaminophen, antihistamine and glucocorticoid before the first and second infusions. All infusion-related AEs were manageable by these premedications, temporary infusion interruption and supportive care. The premedications administered in this study appear to have been effective in reducing the severity of ofatumumab-induced infusion reactions in CLL/SLL patients.

Three of six patients (50%) were assessed as responders in this study. All of these three patients, who were assessed as PR, were in the ofatumumab 1000-mg group. There were no patients assessed as responders in the ofatumumab 500-mg group. The median PFSs were 17.1 and 39.3 weeks in the ofatumumab 500- and 1000-mg groups, respectively. These results suggest that there is a dose–response relationship for ofatumumab monotherapy in Japanese CLL/SLL patients. In previous Phase I/II studies involving Western CLL patients (8,9), monotherapy with an ofatumumab dose of 2000 mg was studied, and responses were observed.

Ofatumumab is eliminated via two mechanisms: target-mediated and non-target-mediated clearance (21,22). Ofatumumab specifically binds to CD20 molecules expressed

on the surface of B-cells, reducing quantifiable ofatumumab concentrations in the plasma. Following binding to the CD20 molecule on malignant B-cells, the bound ofatumumab is eliminated when the target cell is destroyed by antibody-dependent cellular cytotoxicity or CDC. The second mechanism of ofatumumab elimination is non-specific catabolism in cells of the reticuloendothelial system, termed non-target-mediated elimination. Previous studies showed a close relationship between anti-CD20 mAb clearance and baseline B-cell counts, suggesting the large contribution of target-mediated clearance in patients with high levels of circulating malignant B-cells (9,18). In the 1000-mg ofatumumab group in the present study, pharmacokinetic data from Patients 13 and 22 showed gradual accumulation of ofatumumab in the plasma (Fig. 3B). In contrast, the plasma ofatumumab concentrations during the study period were low in Patient 1 who had higher CD5⁺CD19⁺ B-cell counts, consistent with the results of the previous studies.

The ofatumumab concentrations in Japanese CLL/SLL patients were generally higher after the eighth ofatumumab infusion of 1000 mg than after 500 mg. AUC_{0-∞}, C_{max} and C_{trough} values were higher, and CL values were lower in patients with than those without a clinical response to ofatumumab. All of these pharmacokinetic parameters were significantly associated with PFS. Previous pharmacokinetic/pharmacodynamic analyses showed that ofatumumab exposure was correlated with clinical outcomes such as ORR and PFS in CLL patients (9,11). A similar exposure–response relationship was also reported for rituximab (18,19). The observed correlations between anti-CD20 mAb exposure and clinical outcomes in CLL should be interpreted with caution with respect to causality. Higher anti-CD20 mAb concentrations may cause a greater depletion of CD20⁺ B-cells and, therefore, a longer period of time before the B-cell population recovers to an appreciable level. Alternatively, patients who have a greater response will subsequently have a lower ‘target-mediated’ clearance because of reduced CD20⁺ B-cell mass, resulting in higher drug concentrations with continued dosing.

Ofatumumab as monotherapy administered at 300 mg for the first dose, followed by seven once-weekly infusions and four subsequent once-monthly infusions of 2000 mg has been approved for FA-ref CLL patients (10). Currently, a Phase I/II study (OMB112758) is evaluating efficacy and safety with the same 2000 mg ofatumumab dosing regimen in Japanese and Korean patients with relapsed or refractory B-CLL, which will enable us to compare the study results between Western and East Asian B-CLL patients. Furthermore, a Phase III study (OMB113676) evaluating the PFS of single-agent ofatumumab 1000 mg compared with single-agent rituximab 375 mg/m² is ongoing in patients, including Japanese patients, with relapsed FL.

In conclusion, this Phase I study provides important information for ongoing and future clinical development of ofatumumab, not only for CLL/SLL, but also for FL and DLBCL patients in Japan.

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Conflict of interest statement

The authors, M.O. and K.T., have received research grants from GlaxoSmithKline K.K. and other pharmaceutical companies and are consultants for pharmaceutical company. R.C.J. is an employee of and owns stock in GlaxoSmithKline. K.K. is an employee of and owns stock in GlaxoSmithKline K.K. The remaining authors have no conflict of interest.

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