A Phase II trial of Ofatumumab and Complement Replacement in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia

Joseph M Tuscano

University of California Davis

Christina Poh (✉ cpoh@ucdavis.edu)

University of California Davis <https://orcid.org/0000-0003-3120-712X>

Aaron S Rosenberg

University of California Davis

Brian A. Jonas

University of California Davis

Gustavo Barisone

University of California Davis

Kathleen Lundeberg

University of California Davis

Emily Schwab

University of California Davis

Paul Kaesberg

University of California Davis

Research article

Keywords: Ofatumumab, chronic lymphocytic leukemia, treatment, fresh frozen plasma

Posted Date: December 6th, 2019

DOI: <https://doi.org/10.21203/rs.2.18338/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: While many humanized monoclonal antibodies utilize complement dependent cytotoxicity, the complement depleting effects of these antibodies and the effect of complement replacement are not well-described. This study sought to examine complement levels and the effect of complement repletion after treatment with ofatumumab in patients with chronic lymphocytic leukemia (CLL).

Methods: Twelve patients with relapsed or refractory CLL were treated with ofatumumab in combination with fresh frozen plasma used as complement replacement. The primary endpoint was objective response rate. Correlative endpoints included complement levels C3 and C4 and complement activity.

Results: Adverse events were minimal, and efficacy was encouraging with an overall response rate of 83% and 2 patients (17%) achieving a complete response. While only 2 (17%) of patients had low complement activity at baseline, 8 (67%) developed low levels of complement activity. At a median follow-up time of 37 months the median progression-free survival was 12.5 months.

Conclusions: While a minority of patients had low complement activity at baseline, a majority developed low levels of complement with ofatumumab treatment. The magnitude of complement depletion did not correlate with response. Future trials are needed to further explore complement replacement as a less toxic strategy to improve efficacy of monoclonal antibody-based regimens in CLL.

Background

Despite recent advances in treatment, chronic lymphocytic leukemia (CLL) remains incurable and relapse is common. Moreover, the median age at diagnosis is 71, thus treatments that are both efficacious and tolerable in older adults are needed. Monoclonal antibodies (mAb), including rituximab, ofatumumab, and obinutuzumab, have become a standard treatment approach both as a single agent and in combination with chemotherapy or targeted agents.

Ofatumumab is a fully human IgG1κ mAb targeting a unique epitope on the CD20 molecule expressed on human B-cells; ofatumumab binds with high affinity, has a prolonged dissociation rate, and results in increased cell killing. Similar to rituximab, ofatumumab enhances complement dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC) [1]. However, previous studies have shown that ofatumumab is more effective than rituximab at activating complement and inducing CDC [2]. Patients with CLL are complement deficient, it has been demonstrated that complement levels drop even lower after treatment with large doses of humanized antibodies including ofatumumab [3, 4] and antibody-mediated therapy may be limited to the exhaustive effects of complement [5, 6]. It has been hypothesized by us and others that replacement with fresh frozen plasma (FFP) may enhance efficacy in these patients [4–6]. (FFP) is a rich source of complement, and a previous report demonstrated a favorable response to rituximab combined with FFP in a patient that had previously failed rituximab as a single agent [7]. Based on this, we hypothesized that treating relapsed/refractory CLL patients that had

failed prior rituximab treatment with ofatumumab in addition to FFP (for complement replacement) would improve efficacy without adding appreciable toxicity.

Methods

Patients and Treatment

This is an open-label phase II clinical trial of ofatumumab administered on a standard schedule (300 mg on day 1, followed by weekly infusions of 2000 mg to complete 8 doses, followed by monthly doses of 2000 mg to complete a total of 12 doses in 24 weeks) in combination with FFP (2 units administered prior to every dose of ofatumumab starting on week 2) (Suppl. Figure 1). Patients were required to have relapsed after at least one prior rituximab-containing therapy. Rituximab exposure must have been > 2 months prior to study enrollment. An Eastern Cooperative Oncology Group (ECOG) performance status of adequate liver, kidney and marrow function were required. Inclusion required full recovery from all non-hematologic and treatment-related toxicities.

The primary endpoint was objective response rate (ORR), defined as the number of complete responses (CR) and partial responses (PR). Correlative endpoints were evaluation of changes in complement levels (C3 and C4) and complement activity (CH50) measured before and after the infusion of the initial 2 doses of ofatumumab and 2 units of FFP.

Response assessment

Response was evaluated based on the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) [8]. Staging CT/PET was performed at baseline and after completion of therapy. Response was recorded after completion of 24 weeks of treatment with ofatumumab and FFP or when the patient withdrew from the study for any reason.

Statistical analysis

The primary endpoint of this study was ORR, which was analyzed using Simon's optimal 2-stage minimax design. Secondary end-points included monitoring overall and progression-free survival (OS & PFS), determining toxicity and safety of administration of combination ofatumumab and FFP, and evaluating absolute lymphocyte counts (ALC) and complement levels and activity before and after treatment. Baseline complement levels (C3 and C4) and activity (CH50) were reported, as were levels drawn after 2 weeks. Wilcoxon signed-rank tests were used to compare complement and complement activity levels pre-and post-ofatumumab and FFP administration. Progression free survival was estimated by the Kaplan Meier method. A total enrollment of 42 patients was planned but the study was terminated early by the sponsor after 12 patients were accrued.

Results

Patient Characteristics

Twelve patients with relapsed or refractory B-cell CLL that had failed rituximab or a rituximab-containing regimen were enrolled between June 2013 and March 2017 (Suppl. Table 1). Patients had a median age of 63 (range = 49–76). The median time to study from prior treatment was 1 year (range = 0.25–8 years) and the patients received a median of 3 prior regimens. Seven of 12 patients (58%) were considered high risk based on standard FISH analysis (del 17p or 11q/ATM).

Safety

The treatment was generally well tolerated with the most common adverse event being infusion reactions in 7 patients (58%), 2 (17%) being grade 3. All infusion reactions were limited to the first 2 infusions. Other adverse events were $\leq$ grade 2 and included hypertension (16%), fatigue (8%), neutropenia (24%) and anemia (8%). None of the adverse events led to dose reductions, treatment delays or discontinuation.

Efficacy and Complement Activity

As summarized in Table I, the ORR rate of 83% ($n = 12$) included two patients (16.6%) with a CR, 8 patients (66.7%) with a PR and 2 with progressive disease (PD).

At week 24 all 12 patients had reduced white blood cell (WBC) counts, with a median reduction of 31.5%; 11 of 12 patients experienced a decrease in ALC with a median decrease of 32% (Fig. 1). Of the 10 patients who achieved an objective response, 6 relapsed with a median PFS of 12.5 months (Suppl. Figure 2). At a median follow-up time of 37 months, 9 of the 10 patients who achieved an OR were alive and one patient remains in remission for > 25 months.

Assessment of complement levels and activity at baseline and after 2 initial doses of ofatumumab and 2 units of FFP revealed that C3, C4 and CH50 levels were low at baseline in only 17%, 17% and 8% of the patients, respectively. After two weeks of treatment with ofatumumab and FFP 30%, 75% and 67% of patients had decreased levels, respectively (Table 1). This correlated with statistically significant decreases in C3, C4 and CH50 levels compared to baseline despite the addition of FFP to ofatumumab. The mean reduction for C3, C4 and CH50 was 14%, 58% and 54% ($p < 0.001$, $p < 0.004$ and $p = 0.005$) respectively (Table 1). The magnitude of complement reduction did not correlate with response.

Discussion

All CD20-targeted mAbs mediate ADCC and, to a variable degree, have the capability to fix complement and utilize CDC as part of their mechanism of action. While data exists assessing how complement levels or activity are affected by mAb treatment [4–6], there is very little data that examines if repletion would enhance efficacy. Moreover, higher cumulative doses of humanized mAbs are being used and some mAbs are designed for enhanced complement fixation. Ofatumumab has been found to be effective at mediating CDC and recent studies have suggested that it mediates complement depletion which may affect efficacy [3–6]. Our study began to examine the relationship between complement activity, treatment with ofatumumab, FFP-based complement repletion and efficacy. We found that, after the first

2 doses of ofatumumab (2300 mg total), all patients had a reduction in complement activity ranging from 20 to 100% from baseline values (mean 54% reduction). This reduction was despite replacement with 2 units of FFP prior to the second dose of ofatumumab. Given the exploratory nature of this study we do not have enough data on the complement depleting effects of ofatumumab without FFP replacement and thus the magnitude of ofatumumab-mediated complement depletion is likely more significant. Complement replacement using FFP has not been well studied, and although well-defined indications exist for the use of FFP in single or multiple coagulation deficiencies, indications and doses for many of its other uses may be empiric [9]. Interestingly, the minority of our patients were hypocomplementemic at baseline despite prior therapies. While not thoroughly examined, it is hypothesized that complement levels drop even lower after treatment with large doses of humanized antibodies. In our study nearly all patients had some reduction in their ALC and 83% had an objective response. The magnitude of complement depletion did not correlate with response and while the ORR observed here compares favorably with previous studies using single agent ofatumumab (ORR 4–54%) [10], especially considering the majority would be considered high risk, the small sample size precludes a valid assessment of efficacy and comparison to other studies. However, it could be hypothesized that the high ORR in the current study may be related to better baseline complement levels than seen in prior studies, and that if complement levels were more effectively repleted, this might translate into improved efficacy and may be a less toxic strategy to improve efficacy of mAb-based regimens in future trials.

Conclusions

Ofatumumab treatment in patients with CLL was generally well tolerated and efficacious with an ORR rate of 83% (n = 12) which included two patients (16.6%) with a CR, 8 patients (66.7%) with a PR and 2 with progressive disease (PD). While a minority of patients had low complement activity at baseline, a majority developed low levels of complement with ofatumumab treatment. The magnitude of complement depletion did not correlate with response. While the numbers are small, the results demonstrate tolerability and surprising activity in a high-risk group of CLL patients. Future trials are needed to further explore complement replacement as a less toxic strategy to improve efficacy of monoclonal antibody-based regimens in CLL.

Abbreviations

ADCC

antibody-dependent cell-mediated cytotoxicity

ALC

absolute lymphocyte count

CDC

complement dependent cytotoxicity

CLL

chronic lymphocytic leukemia

CR
complete response
ECOG
Eastern Cooperative Oncology Group
FFP
fresh frozen plasma
IWCLL
International Workshop on Chronic Lymphocytic Leukemia
mAb
monoclonal antibodies
ORR
objective response rate
OS
overall survival
PD
progressive disease
PFS
progression-free survival
PR
partial response
WBC
white blood cell

Declarations

Ethics approval and consent to participate

This study was carried out in compliance with the protocol and Good Clinical Practice, as described in the International Council for Harmonisation Harmonized Tripartite Guidelines for Good Clinical Practice 1996 and the Declaration of Helsinki, concerning medical research in humans. This study was reviewed and approved by a properly constituted Institutional Review Board of the University of California, Davis. IRB Number is 333961. Written informed consent was obtained from every study participant

Consent for publication: not applicable

Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests:

BAJ: Consulting or advisory role: AbbVie, Amgen, Jazz, Tolero; Grant/Research support to his institution: AbbVie, Accelerated Medical Diagnostics, AROG, Celgene, Daiichi Sankyo, Esanex, Forma, Genentech/Roche, GlycoMimetics, Incyte, KaloBios, LP Therapeutics, Pharmacyclics.

ASR: Consulting: Celgene, Amgen, Karyopharm; Grant/Research Support to his institution: Amgen; NIH: *"The project described was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through grant number UL1 TR001860. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH, and linked award KL2 TR001859"*

JMT: Research support: Celgene, Amgen, Novartis, Spectrum, Pharmacyclics, Genentech, AbbVie and Takada. Honoraria: Celgene, Amgen, Seattle Genetics

Funding:

This study was supported by research funding from Novartis/GSK Pharmaceutical Company, Basel, Switzerland. Award number GSK 1841157.

Authors' contributions:

JT conceived of the study, its design and coordination, analyzed the data, drafted and finalized the manuscript. CP edited the manuscript. AR, BJ and PK enrolled patients and edited the manuscript. GB, KL and ES analyzed data and edited the manuscript. All authors read and approved the final manuscript.

Acknowledgement: None to declare

References

1. Teeling JL, French RR, Cragg MS, et al. Characterization of new human CD20 monoclonal antibodies with potent cytolytic activity against non-Hodgkin lymphomas. *Blood*. 2004;104:1793-800.
2. Pawluczko AW, Beurskens FJ, Beum PV, Lindorfer MA, van de Winkel JG, Preen PW, Taylor RP. Binding of submaximal C1q promotes complement-dependent cytotoxicity (CDC) of B cells opsonized with anti-CD20 mAbs of ofatumumab (OFA) or rituximab (RTX): considerably higher levels of CDC are induced by OFA than by RTX. *J Immunol*. 2009; 183(1):749-758.
3. Tempescul A, Bagacaan C, Riou C et al, Ofatumumab capacity to deplete B cells from chronic lymphocytic leukaemia is affected by C4 complement exhaustion. *Eu J Haem*. 2015;96:229-235.
4. Middleton O, Cosimo E, Dobbin E et al. Complement deficiencies limit CD20 monoclonal antibody treatment efficacy in CLL. *Leukemia* 2015;1: 107-114
5. Kennedy AD, Beum PV, Solga MD, et al. Rituximabinfusion promotes rapid complement depletion and acute CD20 loss in chronic lymphocytic leukemia. *The J of Immunol* 2004;172:3280-3288
6. Beurskens FJ, Lindorfer MA, Farooqui M, et al. Exhaustion of cytotoxic effector systems may limit monoclonal antibody-based immunotherapy in cancer patients. *The J of Immunol*. 2012;188:1-10.

7. Klepfish A, Rachmilewitz, EA, Kotsianidis I. Adding fresh frozen plasma to rituximab for the treatment of patients with refractory advanced CLL. Q J Med 2008; 101:737–740

8. Hallek M, Cheson BD, Catovsky D, et al. Cuidlines for diagnosis, indications for treatment, response assessment and supportive management of chronic lymphocytic leukemia. Blood. 2018;

9. Rudmann SV. Textbook of blood banking and transfusion medicine ISBN 9780721603841. (18 February 2005). Elsevier Health Sciences. pp. 247-52

10. Coiffier B, Safety and efficacy of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with relapsed or refractory B-cell chronic lymphocytic leukemia. A phase I-II study. Blood 2008; 111:1094-1100.

Table

Table 1 Complement Levels and Activity

Patient #	Baseline C3	Baseline C4	Baseline CH50	Week 2 C3 (%Δ)	Week 2 C4 (%Δ)	Week 2 CH50 (%Δ)	Best Response
1	154	42	111	125 (-19)	22 (-48)	105 (-5)	PR
2	113	29	127	87 (-23)	4.9* (-83)	0 * (-127)	PR
3	148	31	136	99 (-33)	4.9 * (-84)	35* (-74)	CR
4	153	45	193	128 (-16)	20 (-56)	110 (-43)	CR
5	133	30	77	114 (-14)	7 * (-77)	58* (-25)	PR
6	89*	4.9*	17*	79 (-11)	4.9* (0)	1* (-94)	PR
7	88*	14*	79	85 (-3)	4.9* (-64)	32* (-59)	PD
8	187	45	145	134 (-22)	9 * (-80)	52* (-64)	PD
9	125	26	95	118 (-6)	17* (-35)	111 (+17)	PR
10	141	31	145	143 (+1)	25 (-19)	114 (-20)	PR
11	128	24	146	107 (-16)	5 * (-79)	15* (-90)	PR
12	100	20	117	84 (-16)	4.9* (-75)	40* (-66)	PR

%Δ-percent change from baseline. * Low complement values (normal range: C3;92-21-, C4; 18-56, CH50; 60-144)

Figures

Figure 1

Percent change in total WBC and ALC in patients treated with ofatumumab and fresh frozen complement

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryTable1.docx](#)