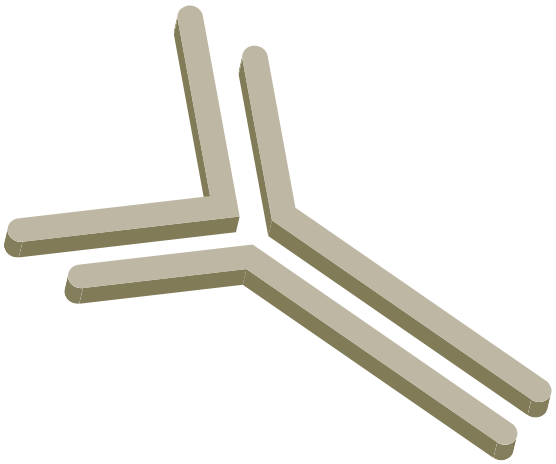
# Ofatumumab

CHRISTOPHER CAMPEN, PHARMD, BCPS



From the University of Arizona College of Pharmacy and Arizona Cancer Center, Tucson, Arizona.

The author has no conflicts of interest to disclose.

Correspondence to: Christopher Campen, PharmD, BCPS, Pharmacy-Pulido Center, 1295 N. Martin Avenue, P.O. Box 210202, Tucson, AZ 85721.
E-mail: chriscampen@gmail.com



The image at top is an illustration of a human monoclonal antibody.

J Adv Pract Oncol 2010;1:125–128

Ofatumumab (Arzerra) is a fully human monoclonal antibody targeting CD20. In October 2009, ofatumumab was approved as monotherapy for the management of chronic lymphocytic leukemia (CLL).

## Pharmacology

Ofatumumab is an anti-CD20 monoclonal antibody with distinct properties that make it a potentially superior monoclonal antibody over rituximab (Rituxan), a chimeric anti-CD20 monoclonal antibody. Ofatumumab is fully human, and therefore there is no risk of the development of human anti-mouse antibodies and a very low risk of the development of human anti-human antibodies (Wierda et al., 2010). Clinical consequences of these attributes include a decreased risk of immunogenic reactions and improved safety of administration.

Another benefit of ofatumumab is seen through its binding with CD20. Ofatumumab binds to a different epitope than rituximab on CD20 that is closer to the cell membrane, resulting in increased activation of the complement and subsequent complement-dependent cytotoxicity (Du, Yang, Guo, & Ding, 2009; Pawluczkowycz et al., 2009).

Ofatumumab may have increased efficacy over rituximab in addition to activity in rituximab-refractory patients. Finally, pharmacokinetic analysis showed a half-life of approximately 410 hours after the fourth infusion, which is in contrast to rituximab at 209 hours (Hagenbeek et al., 2008). This property—likely the result of more stable binding and a slower off rate with the CD20 molecule—allows for extended administration durations and monthly dosing once levels reach steady state.

## Clinical Efficacy

The efficacy of ofatumumab for hematologic disorders has been primarily studied in diseases refractory to multiple agents where there are limited therapeutic options. An initial phase I/II study in CLL was performed to assess the dosing requirements and potential efficacy in a relapsed or refractory disease state. There appeared to be a dose-response relationship, although the maximum tolerated dose was never obtained.

In a follow-up single-arm, multicenter, phase II study, ofatumumab was tested as a single agent in patients with either fludarabine-refractory CLL with bulky disease (BF-ref) or fludarabine- and alemtuzumab (Campath)-refractory (FA-ref). A planned interim anal-

ysis of 138 patients was recently reported (Wierda et al., 2010). This study used weekly treatments of ofatumumab for 8 weeks followed by monthly infusions for 4 more months. A total of 59 FA-ref and 79 BF-ref patients were treated. Overall response rates were similar at 57% and 48%, respectively. Progression-free survival and overall survival were also similar at 5.7 and 13.7 months (FA-ref), and 5.9 and 15.4 months (BF-ref). The overall response rates and survival appear to be superior to those associated with alternative salvage regimens, but further testing is needed to confirm these findings (Tam et al., 2007). Based on the impressive results when compared to historical data with CLL, ofatumumab was approved by the U. S. Food and Drug Administration in October 2009.

Ofatumumab has also been studied in relapsed and refractory follicular lymphoma. In a phase I/II study, ofatumumab was administered at doses of up to 1,000 mg (Hagenbeek et al., 2008). A promising duration of response among responders (29.9 months) was observed, suggesting potential efficacy and warranting further study. A phase II study testing ofatumumab in rituximab-refractory follicular lymphoma was recently presented at the 2009 American Society of Hematology Annual Meeting (Hagenbeek et al., 2009). The overall response rate was 11% among 116 patients, showing minimal activity and low potential for benefit in this tumor type.

## Role in Therapy for Chronic Lymphocytic Leukemia

In 2009, an estimated 15,490 people were diagnosed with CLL, making it the most commonly diagnosed form of leukemia (National Cancer Institute, 2010). The median age at diagnosis is 72 years old, with less than one third of patients diagnosed under age 65. Many patients are diagnosed on routine laboratory screening tests and show no initial symptoms. Chronic lymphocytic leukemia is often an indolent disease that requires no initial treatment, but a minority of patients develop rapid disease involvement. Many therapeutic options exist for patients once treatment is indicated. Currently available first-line regimens include alkylating agents such as chlorambucil (Leukeran) and bendamustine (Treanda), purine analogs such as fludarabine, and the anti-CD52 monoclonal antibody alemtuzumab. Combination regimens such as rituximab/fludarabine/cyclophosphamide have shown improved response rates and a prolonged progression-free survival, but administration is often too aggressive for the majority of patients. The only modality that can provide a potential cure is allogeneic stem cell transplantation, but this strategy is only recommended for younger patients with limited comorbidities, given the significant associated morbidity and mortality (Gribben, 2010).

Patients with refractory disease are at very high risk for serious infections because of the nature of the disease and the common use of previous immunosuppressive regimens containing fludarabine and alemtuzumab. Current treatment options for refractory disease are limited, with many patients unable to tolerate alternative combination chemotherapy regimens (Motta, Wierda, & Ferrajoli, 2009). Alemtuzumab is an option in patients who are refractory to front-line therapy, with a reported overall response rate of 34% and a progression-free survival of 7.7 months (Stilgenbauer et al., 2009). Unfortunately, the natural course of patients with FA-ref and BF-ref disease suggests a very high rate of infections (60% and 45%, respectively) and early mortality with previously used salvage regimens (Tam et al., 2007).

Ofatumumab has been shown to provide promising clinical outcomes compared to historical data among a refractory and heavily pretreated population. Ofatumumab has not been studied head-to-head with alternative regimens or treatments, but most patients on the approval study were already refractory to currently available therapies. The median age of the patients on study was below the median age at diagnosis (63 vs. 72 years), but there did not appear to be differences in efficacy across age ranges (Wierda et al., 2010). Overall, ofatumumab is an active drug in a group of patients with refractory disease, and it has a relatively positive safety profile.

## Dosage and Administration

Dosing is initiated at 300 mg intravenously for the first dose, followed by weekly doses of 2,000 mg for a total of 8 weekly doses. Subsequent doses are administered monthly at 2,000 mg intravenously. All doses are prepared in 1,000 mL of normal saline, which allows for a standard infusion rate titration. Infusion titration rates are listed in

the package insert (GlaxoSmithKline, 2009). Premedication for infusion reactions is necessary in light of the high incidence of such events seen in early phase I/II studies (Coiffier et al., 2008; Hagenbeek et al., 2008). Table 1 describes the premedications that should be administered prior to infusion of ofatumumab. With doses 1, 2, and 9, the full 100 mg of prednisolone (or its equivalent) should be given. Steroid doses can be titrated down if the patient did not have a grade 3 or greater infusion reaction (GlaxoSmithKline, 2009).

**Table 1. Premedications to be administered 30 minutes to 2 hours prior to infusion of ofatumumab**

| Class | Drug | Dose |
|---|---|---|
| Antipyretic | Acetaminophen | 1,000 mg |
| Antihistamine | Cetirizine[a] | 10 mg |
| Corticosteroid | Prednisolone[b] | 100 mg |

*Note:* Derived from Arzerra® package insert (GlaxoSmithKline, 2009).
[a]Or equivalent (e.g., loratadine, diphenhydramine)
[b]Or equivalent (e.g., methylprednisolone, 80 mg).

## Adverse Effects

Infusion reactions were seen in approximately 60% of patients in the approval study (Wierda et al., 2010). The majority of reactions were grade 1 or 2 and occurred during the first or second infusion. Nearly 40% of patients had an infusion reaction occur with the first dose. Table 2 describes the adverse effects that are commonly observed. It is important to note that the adverse effects reported were determined by the investigators to be drug-related. Many patients with CLL are immunocompromised and at high risk of infection; therefore, the overall rate of adverse effects is much higher than reported in the study. In 9% of patients, the cause of death was infection, with sepsis or pneumonia accounting for the majority of cases. Reactivation of hepatitis B can lead to fulminant liver failure and has been observed in patients treated with CD20-targeting monoclonal antibodies. One patient died of progressive multifocal leukoencephalopathy, which has been seen clinically with both rituximab and alemtuzumab (Piccinni et al., 2010). Overall, it is important to note that the rates of infection and early death among those treated with ofatumumab were significantly lower than those seen in the natural course of this FA- or BF-refractory disease state (Tam et al., 2007).

## Nursing Implications

Ofatumumab is associated with a very high frequency of infusion-related reactions with the first and second doses. For this reason, the clinician should pay careful attention to the patient and use standard titration rates based on the package insert. Based on titration rates, the minimum duration of infusion for the first and second dose is approximately 6.5 hours, excluding time for premedication. The duration can be much longer if infusion reactions occur. In the initial phase I/II study in follicular lymphoma, two patients required the infusion to be run over 13 hours because of infusion reactions (Hagenbeek et al., 2008).

The average wholesale price (AWP) of 300 mg of ofatumumab is $1,584, and for 2,000 mg, the AWP is $10,560 (Murry, 2009). Because the infusion must be completed within 24 hours of mixing, infusions may run beyond normal clinic hours. For these reasons, careful planning, patient scheduling, and evening coverage is required to manage infusion reactions and prevent waste and loss of revenue. Acetaminophen, an antihistamine, and a steroid must be administered at least

**Table 2. Reported incidence of adverse effects determined by investigators to be ofatumumab-related**

| Adverse event | Incidence (grade 3/4) |
|---|---|
| Infection | 21% (9%) |
| Neutropenia | 12% (9%) |
| Fatigue | 7% (0%) |
| Cough | 7% (0%) |
| Anemia | 7% (3%) |
| Diarrhea | 6% (0%) |
| Dyspnea | 6% (1%) |
| Nausea | 6% (0%) |
| Rash | 7% (0%) |
| Fever | 4% (1%) |

*Note:* Based on information from Wierda et al., 2010.

30 minutes prior to each dose of ofatumumab to prevent and/or decrease the intensity of infusion reactions. Protocols addressing the management of infusion reactions should be developed within the institution.

## Conclusion

Chronic lymphocytic leukemia is for most patients an incurable but slowly progressing disease. Many patients are diagnosed with CLL but die before symptoms present. Unfortunately, a subgroup of patients will be diagnosed with the disease at a young age or have rapidly progressive disease. Many patients will become refractory to first-line therapies, where there are limited therapeutic options. Ofatumumab appears to be an effective therapy for patients with CLL, but risks to the patient include infusion reactions and infections. Additional issues that need to be addressed in patient management include costs of therapy, administration times, and infusion reaction management.

## REFERENCES


Coiffier, B., Lepretre, S., Pedersen, L. M., Gadeberg, O., Fredriksen, H., van Oers, M. H., . . . Robak, T. (2008). 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 1-2 study. *Blood, 111*(3), 1094–1100. doi: 10.1182/blood-2007-09-111781

Du, J., Yang, H., Guo, Y., & Ding, J. (2009). Structure of the fab fragment of therapeutic antibody ofatumumab provides insights into the recognition mechanism with CD20. *Molecular Immunology, 46*(11–12), 2419-2423. doi:10.1016/j.molimm.2009.04.009

GlaxoSmithKline. (2009). Arzerra® (ofatumumab) prescribing information. Retrieved from http://us.gsk.com/products/assets/us_arzerra.pdf.

Gribben, J. G. (2010). How I treat CLL up front. *Blood, 115*(2), 187-197. doi: 10.1182/blood-2009-08-207126

Hagenbeek, A., Gadeberg, O., Johnson, P., Pedersen, L. M., Walewski, J., Hellmann, A., . . . Radford, J. (2008). First clinical use of ofatumumab, a novel fully human anti-CD20 monoclonal antibody in relapsed or refractory follicular lymphoma: Results of a phase 1/2 trial. *Blood, 111*(12), 5486–5495. doi: 10.1182/blood-2007-10-117671

Hagenbeek, A., Fayad, L., Delwail, V., Rossi, J. F., Jacobsen, E., Kuliczkowski, K., . . . Czuczman, M. S. (2009). Evaluation of ofatumumab, a novel human CD20 monoclonal antibody, as single agent therapy in rituximab-refractory follicular lymphoma. *ASH Annual Meeting Abstracts, 114*(22), 935.

Motta, M., Wierda, W. G., & Ferrajoli, A. (2009). Chronic lymphocytic leukemia: Treatment options for patients with refractory disease. *Cancer, 115*(17), 3830–3841. doi: 10.1002/cncr.24479

Murry L. (Ed.). (2009). *Red book: Pharmacy's fundamental reference*. Montvale, NJ: Thomson PDR.

National Cancer Institute. *SEER stat fact sheets: Chronic lymphocytic leukemia.* Retrieved from http://seer.cancer.gov/statfacts/html/clyl.html

Pawluczkowycz, A. W., Beurskens, F. J., Beum, P. V., Lindorfer, M. A., van de Winkel, J. G., Parren, P. W., & Taylor, R. P. (2009). Binding of submaximal C1q promotes complement-dependent cytotoxicity (CDC) of B cells opsonized with anti-CD20 mAbs ofatumumab (OFA) or rituximab (RTX): Considerably higher levels of CDC are induced by OFA than by RTX. *Journal of Immunology, 183*(1), 749–758. doi:10.4049/jimmunol.0900632

Piccinni, C., Sacripanti, C., Poluzzi, E., Motola, D., Magro, L., Moretti, U., . . . Montanaro, N. (2010). Stronger association of drug-induced progressive multifocal leukoencephalopathy (PML) with biological immunomodulating agents. *European Journal of Clinical Pharmacology, 66*(2), 199–206. doi: 10.1007/s00228-009-0739-z

Stilgenbauer, S., Zenz, T., Winkler, D., Buhler, A., Schlenk, R. F., Groner, S., . . . German Chronic Lymphocytic Leukemia Study,Group. (2009). Subcutaneous alemtuzumab in fludarabine-refractory chronic lymphocytic leukemia: Clinical results and prognostic marker analyses from the CLL2H study of the german chronic lymphocytic leukemia study group. *Journal of Clinical Oncology, 27*(24), 3994–4001. doi: 10.1200/JCO.2008.21.1128

Tam, C. S., O'Brien, S., Lerner, S., Khouri, I., Ferrajoli, A., Faderl, S., . . . Wierda, W. G. (2007). The natural history of fludarabine-refractory chronic lymphocytic leukemia patients who fail alemtuzumab or have bulky lymphadenopathy. *Leukemia & Lymphoma, 48*(10), 1931–1939. doi: 10.1080/10428190701573257

Wierda, W. G., Kipps, T. J., Mayer, J., Stilgenbauer, S., Williams, C. D., Hellmann, A., . . . Hx-CD20-406 Study Investigators. (2010). Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. *Journal of Clinical Oncology, 28*(10), 1749–1755. doi: 10.1200/JCO.2009.25.3187