EXPERT REVIEWS

Ofatumumab for newly diagnosed and relapsed/refractory chronic lymphocytic leukemia

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Monoclonal antibodies have become an increasingly utilized treatment option for many hematological malignancies, including chronic lymphocytic leukemia (CLL). Ofatumumab is a second-generation fully human anti-CD20 monoclonal antibody that binds to the small extracellular loop of CD20, thereby producing complement-dependent cell lysis and antibody-mediated cell cytotoxicity in cells expressing CD20. Ofatumumab has shown efficacy in the treatment for relapsed or refractory CLL. This success has resulted in the recent US FDA approval of ofatumumab for the treatment of CLL in patients who are refractory to fludarabine and alemtuzumab-based regimens. Major side effects of ofatumumab include infusion reactions, neutropenia and increased risk for infection. This article provides an overview of the current data supporting the use of ofatumumab for CLL and projects the future role of ofatumumab as monotherapy and combination therapy.

Keywords: CD20 • chronic lymphocytic leukemia • CLL • monoclonal antibody • ofatumumab

Chronic lymphocytic leukemia (CLL) is a malignant lymphoproliferative disorder that arises from clonally proliferating B lymphocytes, and remains one of the most common hematological malignancies in developed countries. In recent years, advances in therapy have allowed practitioners to treat CLL patients with the goal of obtaining responses and hopefully prolonging survival. However, CLL remains incurable and more effective therapies are needed as patients survive longer.

Ofatumumab is a novel second-generation anti-CD20 monoclonal antibody recently approved in the USA and Europe for the treatment of refractory CLL. The purpose of this article is to review in a comprehensive manner the preclinical and clinical data available on ofatumumab in CLL, with special emphasis on the clinical development of the drug and a 5-year view of the future.

Current status of CLL

In 2010, an estimated 14,990 new cases and 4390 deaths will be associated with CLL in the USA alone [101]. Overall, there is a slight male predominance with a median age at presentation of 72 years. Since incidence increases with age, one could expect a rise in the overall number of CLL cases in the coming years. The diagnosis of CLL is based on the presence of at least 5000 B lymphocytes/μl in the peripheral blood for more than 3 months. Confirmation of the diagnosis relies on flow cytometry. The classic CLL immunophenotype shows coexpression of CD5 and CD19, and also a dim expression of CD20 [1]. Further testing is not warranted for diagnostic purposes but can be useful for staging and prognosis. The clinical presentation of CLL is the most relevant prognostic factor. Early-stage disease has an estimated life expectancy of over 10 years, while advanced-stage disease has an estimated 1.5–3-year life expectancy [2]. In addition, CLL prognosis is linked to immunoglobulin variable region heavy-chain (IgV_H) mutational status, cytogenetic abnormalities (chromosome 17p deletion), CD38 and ZAP-70 expression, and levels of β-2 microglobulin.

Treatment varies from expectant observation in the early asymptomatic phase of the disease to immunochemotherapeutic regimens once symptoms require control. Response and survival data from selected regimens used for frontline

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Table 1. Selected regimens used as first-line therapy in chronic lymphocytic leukemia.

Author (year)	Regimen	Patients (n)	Average age (years)	ORR/CR (%)	Median PFS	Median OS	Ref.
Rai *et al.* (2000)	Fludarabine	170	64	63/20	20 months	66 months	[3]
	Chlorambucil	181	62	37/4	14 months	56 months	
	Fludarabine + chlorambucil	123	63	61/20	NR	55 months	
Eichhorst *et al.* (2009)	Fludarabine	93	71	72/7	19 months	46 months	[4]
	Chlorambucil	100	70	51/0	18 months	64 months	
Flinn *et al.* (2007)	Fludarabine + cyclophosphamide	137	61	74.3/23.4	31.6 months	24-month OS: 79%	[29]
	Fludarabine	132	61	59.5/4.6	19.2 months	24-month OS: 80%	
Robak *et al.* (2010)	Cyclophosphamide + cladribine	211	58	88/47	2.3 years	4-year OS: 62%	[30]
	Cyclophosphamide + fludarabine	212	59	82/46	2.3 years	4-year OS: 61%	
Robak *et al.* (2006)	Cyclophosphamide + mitoxantrone + cladribine	151	59	80/36	24 months	Not reached	[31]
	Cyclophosphamide + cladribine	162	62	83/29	22 months	Not reached	
	Cladribine	166	61	78/21	24 months	51 months	
Knauf *et al.* (2009)	Bendamustine	162	64	68/31	21.6 months	NS	[5]
	Chlorambucil	157	64	31/2	8.3 months	NS	
Hainesworth *et al.* (2003)	Rituximab	44	66	58/9	18.6 months	NR	[11]
Hillmen *et al.* (2007)	Alemtuzumab	149	59	83/24	14.6 months	24-month OS: 84%	[7]
	Chlorambucil	148	60	55/2	11.7 months	24-month OS: 84%	
Frankfurt *et al.* (2008)	Alemtuzumab + rituximab	20	54	90/75	NR	NR	[32]
Kay *et al.* (2010)	Pentostatin + rituximab	33	65	76/27	11 months	NR	[33]
Kay *et al.* (2007)	Pentostatin + cyclophosphamide + rituximab	64	63	91/41	33 months	NR	[34]
Hallek *et al.* (2010)	Fludarabine + cyclophosphamide + rituximab	408	61	90/44	3-year PFS: 65%	3-year OS: 87%	[12]
	Fludarabine + cyclophosphamide	409	61	80/22	3-year PFS: 45%	3-year OS: 83%	
Parikh *et al.* (2009)	Cyclophosphamide + fludarabine + alemtuzumab + rituximab	60	59	92/70	38 months	NR	[35]
Fischer *et al.* (2009)	Bendamustine + rituximab	117	64	91/33	18-month PFS: 76%	NR	[36]
Wierda *et al.* (2009)	Fludarabine + cyclophosphamide + ofatumumab	61	NR	73–77/32–50	Not reached	NR	[26]

CR: Complete response; NR: Not reported; NS: Not statistically significant; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival.
Data taken from [2].

treatment and relapsed/refractory CLL are shown in Tables 1 & 2, respectively. For several years, the mainstay treatment for CLL was chlorambucil (Leukeran®, GlaxoSmithKline, NC, USA). More recently, fludarabine (Fludara®, Ben Venue Laboratories, OH, USA), a purine analog, and bendamustine (Treanda®, Cephalon, Inc., PA, USA), a nitrogen mustard with alkylating properties, have been shown to have better response rates compared with chlorambucil in randomized controlled trials [3–5]. Currently, chlorambucil, fludarabine and bendamustine are approved by the US FDA for the treatment of CLL. Recently, new promise has arrived in the form of monoclonal antibody (mAb) therapy. The first mAb to receive FDA approval for the treatment of CLL was alemtuzumab (Campath®, Genzyme Corporation, MA, USA), an anti-CD52 mAb that induces responses in one-third of patients with relapsed or refractory CLL [6], and over 80% of patients when used as a first-line treatment [7]. Furthermore, it induces responses in patients with 17p deletion that have historically responded poorly to chemotherapy.

A B-cell marker that has gained considerable attention in CLL is CD20, which is expressed on B cells from the pre-B-cell phase up to prior to differentiation into plasma cells, with the advantage that it remains omnipresent on the B-cell surface as it is neither shed nor internalized [8,9]. These characteristics provide an ample target for mAb therapy. Rituximab (Rituxan®, Genentech, CA, USA) is a chimeric anti-CD20 mAb approved by the FDA for previously untreated or treated CD20-positive CLL in combination with FC chemotherapy. The initial use of rituximab in CLL as monotherapy in relapsed or refractory cases produced only modest results with partial responses (PRs) of 25% [10]. Monotherapy with rituximab as initial treatment of CLL saw these results increase to response rates of 58% [11]. Further trials examining the use of rituximab with chemotherapy, especially fludarabine and cyclophosphamide, have revealed improved overall response rates (ORRs) and prolonged progression-free survival (PFS) [12,13]. The main toxicity associated with rituximab is infusion-related reactions, which although frequent (~90% of patients) tend to be mild to moderate in severity.

Despite the improved responses and prolonged PFS seen in combination therapy with mAbs and conventional chemotherapy, CLL remains an incurable disease with treatment geared toward prevention of progression. Important future areas of improvement include patients with high-risk disease based on unfavorable cytogenetic or molecular profiles, as well as patients who have relapsed or are refractory to current first-line treatment options [14,15]. Those patients resistant to fludarabine and alemtuzumab-based regimens, as well as those with bulky fludarabine-resistant disease, have particularly poor prognoses and therefore would benefit the most from new treatment regimens [16]. Recently, the FDA approved ofatumumab, a second-generation anti-CD20 mAb, for the treatment of CLL refractory to fludarabine and alemtuzumab.

Mechanism of action

Ofatumumab (Arzerra®, Genmab A/S, Copenhagen, Denmark and GlaxoSmithKline), previously known as Humax-CD20, is an IgG1 fully human anti-CD20 mAb with a molecular weight of 149 kDa that functions as a type I (rituximab-like) antibody, which operates via both complement-dependent cytotoxicity (CDC) and antibody-dependent cytotoxicity (ADCC), but does not induce apoptosis directly. It was created by immunizing HCO7 and KM mice with CD20-transfected NS/O cells. The CD20-specific IgG1 mAb-producing hybridomas were subcloned to produce ofatumumab, as well as two additional fully human mAbs (7B8 and 11B8). The production of these three antibodies came about through a desire to create a more potent version of rituximab [17].

Early preclinical studies have determined that ofatumumab is a more potent inducer of CDC compared with rituximab. Work by Teeling and colleagues found increased cell lysis in the presence of plasma or whole blood in cells incubated with ofatumumab compared with those incubated with rituximab [17]. To further elucidate the action of ofatumumab as an inducer of CDC, researchers took plasma with heat-inactivated complement and coincubated this with ofatumumab. This experiment resulted in no cells being killed. However, later studies have shown that complement must be completely inactivated rather than simply inhibited. This is evident when ofatumumab and rituximab are incubated in media containing Raji cells, which contain low levels of CD20 but high levels of the complement defense molecules CD55 and CD59. In this experiment, ofatumumab was still able to induce cell killing while rituximab was not. This work has since confirmed by separate investigations the superior *in vitro* CDC of ofatumumab over rituximab [18].

Like rituximab, ofatumumab redistributes CD20 into Triton X-100 insoluble lipid rafts. The formation of these detergent-insoluble lipid rafts is thought to be the mechanism by which type I anti-CD20 mAbs initiate complement activation. Rituximab and ofatumumab have similar times to initial antibody binding. However, ofatumumab has a much slower off-rate once bound to CD20. The longer off-rate leads to increased C1q binding and with it, the subsequent activation of the complement cascade [17]. The other factor contributing to ofatumumab's enhanced complement-activating function is the drug's binding site on CD20. An additional study determined through epitope mapping that ofatumumab binds to the small loop of CD20 as well as the large loop of CD20 to which rituximab binds (Figure 1) [19]. This different binding site is thought to result in more effective coating of the cell with complement for later cell lysis.

Ofatumumab has also been shown to bind more avidly to C1q, further facilitating the activation of complement [18]. Type I anti-CD20 mAbs also work further along the complement cascade. Initially, the antibody (either rituximab or ofatumumab) induces C3b deposition. This leads to activation of the membrane attack complex and subsequent cell lysis. Beum and colleagues utilized spinning disc conformational microscopy to show that activation of the membrane attack complex leads to 'blebbing' and 'streamer' formation within mAb-opsonized Daudi B cells just prior to cell death. They go on to show that ofatumumab leads to more 'blebbing' and 'streamer' formation than rituximab, in addition to more C3b deposition and overall cell killing [20].

Ofatumumab also works via ADCC. Recent work in mouse models has elucidated that ofatumumab induces cell killing via Fc receptor (FcR) activation and the subsequent mediation of

Table 2. Selected regimens used in relapsed or refractory chronic lymphocytic leukemia.

Author (year)	Regimen	Patients (n)	Average age (years)	ORR/CR (%)	Median PFS (months)	Median OS	Ref.
Robak *et al.* (2010)	Fludarabine + cyclophosphamide + rituximab	271	63	70/24	30.6	Not reached	[13]
	Fludarabine + cyclophosphamide	273	62	58/13	21.6	52 months	
O'Brien *et al.* (2009)	Fludarabine + cyclophosphamide + oblimersen	120	63	NR/9	31	5-year OS: 25%	[37]
	Fludarabine + cyclophosphamide	121	63	NR/2	20	5-year OS: 15%	
Byrd *et al.* (2010)	Fludarabine + cyclophosphamide + rituximab + lumiliximab	31	58	65/52	19.3	NR	[38]
Koppler *et al.* (2004)	Bendamustine + mitoxantrone	22	71	86/27	10	39 months	[39]
Stilgenbauer *et al.* (2009)	Alemtuzumab	109	63	33/4	7.7	19.1 months	[6]
Engert *et al.* (2005)	Fludarabine + alemtuzumab	37	61	83/31	13	35.6 months	[40]
Elter *et al.* (2009)	Cyclophosphamide + alemtuzumab + fludarabine	56	63	68/22	NR	NR	[41]
Huhn *et al.* (2001)	Rituximab	30	60	25/0	4.7	NR	[10]
Lamanna *et al.* (2007)	Pentostatin + cyclophosphamide + rituximab	32	62	75/25	NR	44 months	[42]
Zent *et al.* (2007)	Alemtuzumab + rituximab	27	62	93/44	NR	NR	[43]
Fischer *et al.* (2008)	Bendamustine + rituximab	81	67	77/15	NR	NR	[44]
Coiffier *et al.* (2008)	Ofatumumab	33	61	44/0	3.5	NR	[27]
Wierda *et al.* (2010)	Ofatumumab FA refractory	59	64	58/0	5.7	13.7 months	[28]
	BF refractory	79	62	47/1	5.9	15.4 months	
Chanan-Khan *et al.* (2006)	Lenalidomide	45	64	47/9	Not reached	NR	[15]
Lin *et al.* (2009)	Flavopiridol	64	60	53/2	8.6	NR	[14]

BF: Bulky lymphadenopathy; CR: Complete response; FA: Fludarabine and alemtuzumab; NR: Not reported; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival.
Data taken from [2].

ADCC that comes with it, but does not induce apoptosis through FcR crosslinking [21]. An additional study revealed that ofatumumab is a more potent inducer of ADCC compared with rituximab when tumor cell lysis by donor natural killer cells was measured [22]. This was seen regardless of FcR polymorphism. Like CDC, the increase in ADCC is once again thought to be secondary to ofatumumab's binding site on the small loop of CD20.

Pharmacokinetic/pharmacodynamic profile

Through a series of experiments, Bleeker and colleagues determined the ofatumumab dose required for *in vitro* and *in vivo* activity. They note that first and foremost, the ADCC activity of ofatumumab was seen at a lower concentration than CDC activity *in vitro*, and that a dose of 5 µg/ml was required for target saturation *in vitro*. Using a mouse xenograft, they found that a plasma antibody concentration of 5 µg/ml led to full target saturation and inhibited further B-cell tumor development. Tumor regrowth was seen when levels fell to less than half of this value. They then evaluated *Cynomolgus* monkeys to establish pharmacokinetic profiles as their CD20 is similar to humans. They concluded that a relatively high initial dose (>12.5 mg/kg daily for 4 days or 50 µg/ml) was required for sustained initial B-cell depletion while the minimally effective dose for maintaining B-cell depletion is five to tenfold lower at 5–10 µg/ml. Pharmacokinetics were influenced by tumor burden, as mice with greater tumor loads had more rapid antibody clearance [23].

The effect of tumor burden on ofatumumab serum concentrations has been seen in clinical trials as well. A Phase I/II trial showed that higher initial tumor burdens correlate with lower initial serum concentration of ofatumumab, as well as more rapid clearance [24]. They go on to state that high initial serum concentration of ofatumumab coupled with low elimination rates are important not only for the initial response but also correlate with response duration as measured by PFS and time to next CLL treatment. Other investigators also report the relationship between high initial tumor burden and low serum concentrations, and echo the fact that a higher serum concentrations

coupled with lower drug clearance correlate with longer PFS [25]. Higher ofatumumab concentrations throughout treatment also correlated with response when ofatumumab was used in combination with fludarabine and cyclophosphamide [26].

Clinical findings

Phase I/II study

Coiffier and colleagues performed the first clinical study of ofatumumab in CLL in 2008 [27]. A total of 33 patients with relapsed or refractory disease were included in the study, with 66% having Binet stage B disease. Furthermore, the population was heavily pretreated with a median number of previous treatments of three. Three cohorts were created, all of which received four total weekly doses of ofatumumab. In cohort A, three patients received one 100-mg followed by three 500-mg doses, cohort B had three patients who received one 300-mg followed by three 1000-mg doses, and cohort C received one 500-mg dose followed by three 2000-mg doses. The response rate in cohort C was 50%. All responses were partial and the median PFS was 106 days.

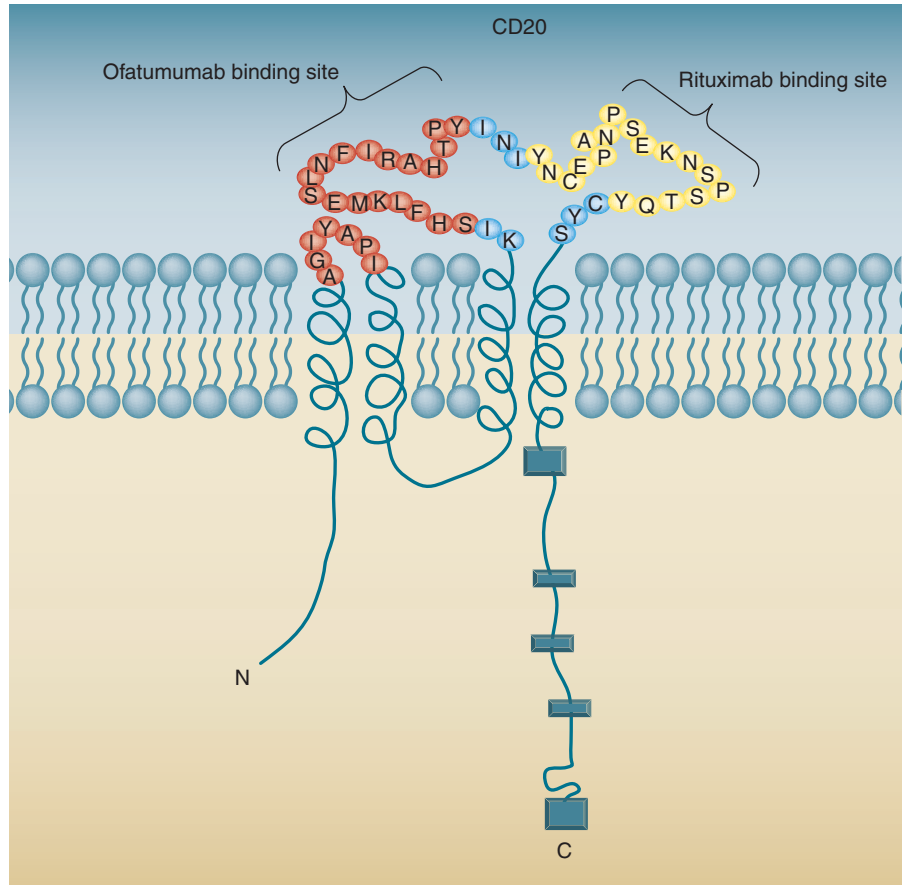

Figure 1. Ofatumumab and rituximab have distinct binding sites on the CD20 molecule.
Redrawn with permission from [45].

Phase II studies

A Phase II trial of ofatumumab as single-agent therapy in relapsed or refractory CLL was completed recently [28]. All patients were heavily pretreated with at least one fludarabine-containing regimen in addition to either one alemtuzumab-containing regimen (FA-ref) or were considered less suitable for alemtuzumab secondary to bulky lymphadenopathy (BF-ref). A total of 138 patients were analyzed for response. The trial was an international single-arm study that consisted of 8-weekly infusions (dose 1 of 300 mg followed by doses 2–8 of 2000 mg) followed by 4-monthly infusions (doses 9–12 of 2000 mg). The ORR for FA-ref was 58% while that for BF-ref was 47%, with one complete response (CR). Patients previously treated with rituximab had ORRs of 54 and 44% in the FA-ref and BF-ref groups, respectively. Median PFS and median overall survival (OS) were 5.7 and 13.7 months, respectively, in FA-ref patients while BF-ref patients had 5.9 months for median PFS and 15.4 months for median OS.

Ofatumumab has also been shown to be effective in combination regimens for initial treatment of CLL. A separate study has added ofatumumab to fludarabine and cyclophosphamide for frontline treatment of CLL [26]. Preliminary results from this randomized study include 31 patients treated with ofatumumab at 500 mg (group A) and 30 patients with ofatumumab at 1000 mg (group B) every 4 weeks for six total courses. The initial ofatumumab dose in each arm is 300 mg, with ofatumumab given on day 1 followed by fludarabine 25 mg/m^2 and cyclophosphamide 250 mg/m^2 on days 2–4 for cycle 1, and days 1–3 for cycles 2–6. This study has thus far been reported only in abstract format with a median follow-up of 8 months. Nevertheless, initial complete response and ORRs are encouraging. For groups A and B the CR/ORR is 32/77% and 50/73%, respectively.

Current Phase II trials further examining the role of ofatumumab alone and in combination in patients with CLL in the frontline and relapsed settings are shown in Tables 3 & 4, respectively.

Phase III studies

A Phase III study is looking at the efficacy of ofatumumab added to chlorambucil versus chlorambucil monotherapy in newly diagnosed patients with CLL. Yet another Phase III study examined fludarabine and cyclophosphamide with and without ofatumumab as a treatment for patients with relapsed CLL. Details of all current enrolling Phase III trials utilizing ofatumumab in CLL are outlined in Tables 3 & 4 [102].

Safety & tolerability

Overall, ofatumumab is generally well tolerated. In a Phase I/II trial, ofatumumab did not reach a maximum tolerated dose. Most adverse events (AEs) occurred after the first infusion, with the

Table 3. Current clinical trials for first-line treatment of chronic lymphocytic leukemia.

Trial number	Phase	Treatment	Expected completion date	Estimated enrollment (n)	Sponsoring site
NCT01024010	II	Ofatumumab + pentostatin + cyclophosphamide	December 2015	33	Mayo Clinic
NCT01125787	II	Ofatumumab + bendamustine	Not specified	39	Nevada Cancer Institute
NCT01145209	II	Ofatumumab induction + maintenance	December 2014	46	University of Virginia
NCT01113632	II	Ofatumumab monotherapy	July 2012	47	Sarah Cannon Research Institute
EudraCT 2010-022332-37	II	Ofatumumab + pentostatin + cyclophosphamide in elderly patients	June 2014	45	Niguarda Hospital
NCT00748189	III	Chlorambucil ± ofatumumab	May 2013	444	GlaxoSmithKline
NCT00824265	III	Fludarabine + cyclophosphamide ± ofatumumab	August 2011	352	GlaxoSmithKline

Data taken from [102].

percentage of AEs declining with subsequent treatments. All but one patient completed all four planned infusions. The one patient who withdrew from treatment developed grade 3 cytolytic hepatitis that resolved after 3 days. In total, 27 patients developed 246 AEs and only 19 of these were grade 3 or 4. A total of 61% of AEs were considered to be related to treatment. The most common AEs were infusion-related reactions with symptoms including transient rigors, pyrexia, fatigue, rash and diaphoresis. Infusion reactions made up 56% of all AEs, with 61% of these reactions occurring on the first infusion. In total, 17 patients (51%) reported infections, most commonly nasopharyngitis. However, only four infectious events were considered grade 3 or worse, with one of these resulting in fatality from infectious interstitial lung disease. Hematological toxicities were also seen in 15% of patients. A total of 9% developed grades 3–4 thrombocytopenia and 6% exhibited grades 3–4 neutropenia. In total, there were ten serious AEs in nine out of 33 patients. Five serious AEs were considered treatment related: one patient with herpes zoster, two patients with neutropenia, as well as the previously noted cases of infectious interstitial lung disease and hepatitis. Serum IgA and IgG levels remained unchanged throughout the study while mean IgM levels trended lower than normal with ofatumumab [27].

In another Phase II trial using ofatumumab monotherapy in refractory CLL, a similar AE profile was observed. A total of 90% of patients were able to complete at least eight out of 12 planned treatments. Infusion reactions occurred in 64% of FA-ref patients and 61% of BF-ref patients. These reactions were most common during the first and second infusion, and diminished significantly during later treatments. The most common AE during the course of treatment was infection, seen in 67% of patients. Of these, 74% were grade 1 or 2 in severity. The most common grade 3/4 infections were pneumonia and other respiratory tract infections. Eight infections led to death within 30 days from last ofatumumab administration. One patient also developed progressive multifocal leukoencephalopathy during treatment. Other common AEs (seen in >10% of patients) include cough, diarrhea, anemia, fatigue, fever, neutropenia, nausea and rash [28].

Regulatory affairs

Ofatumumab was granted accelerated approval by the US FDA on 26 October 2009 for the treatment of patients with CLL who are refractory to fludarabine and alemtuzumab [103]. Ofatumumab has been authorized in Europe since 19 April 2010 by the European Medicines Agency and the Committee for Orphan Medicinal Products in patients with CLL who are refractory to fludarabine and alemtuzumab [104].

Conclusion

Ofatumumab is a novel fully human anti-CD20 mAb that has received FDA approval for the treatment of CLL. It is a type I or rituximab-like antibody that primarily works through CDC and ADCC with enhanced activity when compared with rituximab in preclinical studies. This increased *in vitro* activity of ofatumumab is thought to be secondary to ofatumumab's prolonged binding

to CD20 in addition to its novel binding epitope present on the small loop of CD20. Most importantly, ofatumumab has already shown good clinical activity in patients who are double refractory to fludarabine and alemtuzumab, as well as those who are refractory to fludarabine and are not candidates for alemtuzumab based on bulky disease. This activity led to the accelerated approval of ofatumumab by the FDA and the EMA.

Expert commentary

Chronic lymphocytic leukemia remains a disease with high prevalence for which there is no long-term cure. Therefore, there is a need for new treatment options that should focus on improving OS and quality of life while limiting treatment-related toxicities. Currently, there are a number of options for therapy that we as clinicians must consider for our patients. The time to treat and the drug with which to treat CLL depends heavily on patient characteristics such as symptom presentation, medical comorbidities and age. Thus far, there is no magic bullet that has been developed for CLL.

However, recently the understanding of cancer biology at a molecular level has increased dramatically and there now exist more selective treatments to target the malignant cell population. In order to limit toxicity, these targets would ideally be expressed by malignant cells but not normal cells. The benefit of selectively targeting $CD20^+$ cells in CLL is that it provides selective killing of B lymphocytes. Furthermore, CD20 is never internalized or shed, making it a reliable target for therapy throughout the B-cell life cycle.

Ofatumumab is emerging as a therapeutic option in patients with CLL. Its specific characteristics, some of them distinct from rituximab, make ofatumumab an interesting drug for future clinical development (Table 5). The FDA has recently approved ofatumumab for the treatment of fludarabine and alemtuzumab-refractory CLL based on the rate of PRs obtained with it in heavily pretreated patients. We believe the development of ofatumumab should focus on the development of combination therapy and using ofatumumab at earlier stages of the disease. It is likely that when used in these settings, complete and durable responses will be seen, if not survival benefits.

Recently, the combination of fludarabine, cyclophosphamide and rituximab has shown, for the first time, a survival benefit in patients with newly diagnosed CLL [12]. We think one of the most important trials to position ofatumumab in the treatment of CLL is the current Phase III trial that compares fludarabine, cyclophosphamide and ofatumumab (FCO) with FC. This head-to-head comparison will probably provide information on survival benefits, if any, with FCO. It would also be interesting to see the proportion of patients achieving minimal residual disease (MRD)-negative CRs with FCO. However, owing to the indolent nature of CLL, these answers will not come quickly.

Most of our CLL patients are elderly and are not suitable candidates for intensive regimens such as the fludarabine, cyclophosphamide and rituximab combination or FCO. In this population, the Phase III study comparing chlorambucil with and without ofatumumab in newly diagnosed CLL patients will be of most importance. The goal of this study will not be the induction of MRD-negative responses but rather PFS prolongation. A special point to

Table 4. Current clinical trials for relapsed or refractory chronic lymphocytic leukemia.

Trial number	Phase	Treatment	Expected completion date	Estimated enrollment (n)	Sponsoring site
NCT01010568	II	Ofatumumab + bendamustine	July 2012	40	Georgetown University
NCT01002755	II	Ofatumumab + lenalidomide	November 2013	36	MD Anderson Cancer Center
NCT01191190	II	Ofatumumab + high-dose methylprednisolone	August 2012	21	University of California, San Diego
NCT01039376	III	Ofatumumab maintenance	November 2013	532	GlaxoSmithKline

Data taken from [102].

Table 5. Key similarities and differences between ofatumumab and rituximab.

Similarities/differences	Antibody	
	Ofatumumab	*Rituximab*
Overall description	Fully human anti-CD20 mAb	Chimeric anti-CD20 mAb
Mechanism of action	CDC and ADCC	CDC and ADCC
Binding site	Small and large loop of CD20	Large Loop of CD20
ORR/CR as monotherapy in relapsed/refractory CLL	44–58/0–1% [27,28]	25/0% [10]
Most common adverse event	Infusion reactions (64% of the time)	Infusion reactions (90% of the time)
US FDA-approved indication in CLL	Treatment of patients refractory to alemtuzumab and fludarabine	First-line and refractory treatment of CLL in combination with FC chemotherapy

ADCC: Antibody-dependent cytotoxicity; CDC: Complement-dependent cytotoxicity; CLL: Chronic lymphocytic leukemia; CR: Complete response; FC: Fludarabine and cyclophosphamide; mAb: Monoclonal antibody; ORR: Overall response rate.
Data taken from [9,10,27,28,103].

bear in mind in this frail population is the toxicity profile of the combination of chlorambucil and ofatumumab. From this perspective, an important point favoring ofatumumab combinations over rituximab is that the rate of infectious complications will probably be lower than that reported in heavily pretreated CLL patients.

Unfortunately, given there will not be a direct comparison between rituximab and ofatumumab, the potential biological differences between these two anti-CD20 mAbs will remain unanswered. However, a Phase II study on newly diagnosed patients with CLL treated with ofatumumab monotherapy is underway and it would be of great importance to see the response rates obtained by ofatumumab single-agent therapy in the frontline setting. Historically, single-agent rituximab administered at standard doses demonstrated ORR and CR rates of 58 and 9%, respectively, in previously untreated CLL [11].

Finally, there are several combinations using ofatumumab in patients with relapsed or refractory CLL being evaluated in prospective Phase II studies. Some of these combinations use novel agents such as lenalidomide or bendamustine, looking for a synergistic effect against CLL. Once a patient has developed relapsed or refractory disease, the goal of therapy should be mainly directed at symptom control, prolonging PFS and decrease toxicity. It is likely that the results of these studies will be seen earlier than the Phase III studies, and will probably give way to the use of ofatumumab in combination not only in patients who are refractory but also unsuitable for fludarabine or alemtuzumab.

Five-year view

In 5 years from the publication of this article, the results of several Phase II studies and preliminary data from Phase III studies will probably be available. These data will probably show that ofatumumab in combination with chemotherapy or other biological agents do not carry excessive toxicity, besides the classic reactions seen during the first infusions, occasional hepatitis B reactivation and rare progressive multifocal leukoencephalopathy, and is very effective inducing CRs and PRs in the relapsed setting. Furthermore, the preliminary data from Phase III studies will show the induction of MRD-negative CRs and early signs of benefit on PFS and OS. Ofatumumab will be under evaluation for approval in the frontline setting and its use in the relapsed or refractory setting will be more generalized, and will not be limited to fludarabine or alemtuzumab-refractory patients only.

Information resource

National Comprehensive Cancer Network (NCCN) guidelines for non-Hodgkin's lymphomas: www.nccn.org/professionals/physician_gls/PDF/nhl.pdf

Key issues

- Ofatumumab is a second-generation, fully human anti-CD20 monoclonal antibody directed against CD20, an antigen present in the membrane of normal and malignant B lymphocytes.
- Ofatumumab binds to a distinct epitope in the CD20 molecule, has slower off-rates and requires less CD20 expression to effectively bind than rituximab.
- The US FDA has recently approved ofatumumab for the treatment of patients with chronic lymphocytic leukemia who are refractory to fludarabine and alemtuzumab.
- The most common adverse events seen with ofatumumab are infusion reactions, which require the use of acetaminophen, diphenhydramine and steroids prior to administration.
- The initial dose of ofatumumab is 300 mg followed by 11 doses of 2000 mg; ofatumumab is administered intravenously and a dose calculation per meter squared is not needed.
- Several Phase II studies in patients with relapsed chronic lymphocytic leukemia (CLL) and few Phase III studies in patients with newly diagnosed CLL are ongoing.

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