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REVIEW

Role of ofatumumab in treatment of chronic lymphocytic leukemia

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Abstract: The management of chronic lymphocytic leukemia (CLL) has dramatically improved in the past decade with the addition of anti-CD20 monoclonal antibodies to the treatment armamentarium. Ofatumumab is a novel anti-CD20 monoclonal antibody recently approved in the US and Europe for the treatment of CLL refractory to alemtuzumab and fludarabine. Preclinical data showed improved complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity compared with rituximab. Clinical studies have shown single-agent activity for ofatumumab in CLL and in other low-grade non-Hodgkin's lymphomas. Combination studies are being conducted to enhance the therapeutic efficacy of ofatumumab. This paper reviews some of the key clinical studies that led to approval of ofatumumab, and future directions.

Keywords: ofatumumab, chronic lymphocytic leukemia, efficacy, safety

Introduction

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is the most common leukemia in the Western hemisphere, with an age-adjusted incidence rate of 4.2 per 100,000 men and women per year.[1] It is a monoclonal B cell malignancy that affects mainly older individuals, with a median age at diagnosis of 72 years. The spectrum of this disease varies from a simple lymphocytosis to splenomegaly and/or cytopenias. Some patients have an indolent course, while others have a more accelerated course. In either case, the disease relapses frequently, and there is considerable morbidity from the disease and the treatments themselves.[2]

Several predictive factors have been identified in CLL. In addition to clinical staging, traditional prognostic factors for identifying high risk of disease progression have included elevated serum levels of beta-2 microglobulin, soluble CD23, diffuse bone marrow infiltration, short lymphocyte doubling time, and high levels of zeta-associated protein on the surface of malignant cells.[3,4] More recently, the presence of certain cytogenetic abnormalities identified by fluorescence in situ hybridization analysis and mutational status of immunoglobulin heavy chain have become a more meaningful predictor of disease progression and duration of response to therapy.[5]

The median survival is highly variable, with some patients following an indolent course with a survival of over 20 years, whereas others exhibit an aggressive behavior with survival less than three years. The management of patients with CLL/SLL is currently undergoing profound changes. Historically, the approach to management of CLL focused on reducing tumor bulk and controlling symptoms, while maintaining a good quality of life. Treatment options for decades included alkylating

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agents, purine analogs, or a combination of the two. More effective combination regimens, such as fludarabine, cyclophosphamide, and rituximab, have recently been shown to prolong progression-free survival and overall survival, thereby changing the treatment paradigm to one with a goal of complete elimination of the disease in patients who are younger or older but physically fit. Because there is no proven survival benefit of early treatment of asymptomatic patients, most patients are followed by watchful waiting until symptoms develop. Although most patients with CLL respond to first-line therapy, all patients eventually relapse, after which the therapeutic options are limited and the prognosis is particularly poor after development of fludarabine-refractory disease.

Preclinical data

Addition of the CD20 monoclonal antibody, rituximab, to chemotherapy for CLL has improved outcomes, particularly in early lines of therapy. Typically CLL cells have low CD20 expression, which helps explain why the efficacy of rituximab monotherapy in CLL is limited, potentially in part because of reduced cell lysis via complement-dependent cytotoxicity, which is dependent on CD20 expression.

Ofatumumab is an IgG1κ, fully humanized CD20 monoclonal antibody that targets an epitope distinct from the epitope recognized by rituximab. The antibody is generated via transgenic mouse and hybridoma technology and produced in a recombinant murine cell line (NS0) using standard mammalian cell cultivation and purification technologies.[6] The mechanism of action of ofatumumab was studied indepth, and compared with that of the marketed chimeric anti-CD20 monoclonal antibody, rituximab. Ofatumumab binds specifically to epitopes which encompass the amino acid residues 163 and 166 in the second extracellular loop of the CD20 molecule. Ofatumumab induces crosslinking of CD20 molecules and relocation of these CD20 molecules to the so-called lipid rafts.[7] The translocation of CD20 into lipid rafts is considered important for induction of cell signaling and more effective complement activation.[8] Differences in antibody function between various anti-CD20 antibodies might be explained by their distinct ability to induce relocation of the CD20 molecules within the lipid rafts. The binding of ofatumumab induces cell death, primarily through complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity and not by apoptosis. Ofatumumab has similar antibody-dependent cellular cytotoxicity when compared with rituximab, but delivers stronger complement-dependent cytotoxicity in in vitro models, even in malignant B cells with low CD20 expression levels.[6,9] Laboratory studies have shown ofatumumab to be effective at inducing lysis of several B cell lines, as well as being able to kill fresh CLL B cells resistant to rituximab.[6,9,10]

Further studies have demonstrated that although ofatumumab and rituximab bind the same antigen, ofatumumab dissociates from its target at a slower rate compared with rituximab,[6] and binds a novel, membrane-proximal epitope. In experiments using radiolabeled antibodies, more than 70% of ofatumumab, but only 30% of rituximab, remained bound to deoxyhypusine hydroxylase cells after three hours. Epitope mapping has indicated that ofatumumab binds an epitope located closer to the N-terminus of CD20 compared with the location targeted by rituximab, and includes an extracellular loop of the antigen. It is hypothesized that the complement-dependent potent cytotoxicity of ofatumumab may be due to both the slow off-rate and the precise location of binding on CD20 compared with rituximab.[10]

To evaluate the in vivo efficacy of ofatumumab, its effect was tested in a mouse xenograft model.[11] Severe combined immunodeficiency mice were first injected with Daudi B cells transfected with luciferase, and then treated with either 0.5 mg/kg of ofatumumab or anti- keyhole limpet hemocyanin monoclonal antibody as a control. Tumor growth was assessed by bioluminescence. A single dose, resulting in an initial plasma antibody concentration of 5 μg/mL, expected to result in full target saturation, effectively inhibited human B cell tumor development. Tumor growth resumed when plasma concentrations dropped below levels that are expected to result in half-maximal saturation. Compared with the control group, the ofatumumab cohort showed delayed tumor induction (3–4 weeks) and lower tumor growth rate. In cynomolgus monkeys, initial depletion of circulating and tissue-residing B cells required a relatively high dose level. A 1.25 mg/kg intravenous (IV) dose administered daily for four days effectively depleted B cells. Initial plasma concentrations were approximately 50 μg/mL, and repopulation of B cell compartments only became detectable when ofatumumab levels dropped below 10 μg/mL. The cell count did not return to a normal level until 96 days later, but the animals developed primate antihuman antibodies. The results of these animal studies suggested that high initial dosing would be necessary to saturate CD20, but maintenance of a plasma concentration at 5–10 μg/mL maintains target saturation on circulating cells and is probably sufficient for sustained biological activity.[11] These observations may provide a rationale for establishing dosing schedules for maintenance

immunotherapy following initial depletion of CD20-positive tumor cells. These data suggest that ofatumumab may deplete B cells for a longer period of time than rituximab, which may lead to a longer duration of treatment response and could potentially result in a smaller dose being needed. Ofatumumab is a human monoclonal antibody with very low anticipated immunogenicity. Therefore, subjects are not expected to produce human antihuman antibodies to the same degree as the human antichimeric antibodies seen in some subjects following treatment with rituximab. Based on these in vivo studies, clinical studies of ofatumumab were initiated in different diseases, including B cell malignancies, such as CLL. The following section reviews the current clinical data on ofatumumab in CLL, as well as future therapeutic directions.

Clinical studies of ofatumumab in CLL

The Table 1 summarizes completed and ongoing clinical studies of ofatumumab in CLL/SLL. A Phase I/II dose-escalating study evaluating ofatumumab in patients with relapsed and refractory CLL was initiated at 12 sites in the US and Europe. This study evaluated 33 patients in three different dosing cohorts.[12] The majority of patients (27/33) received a total of four doses administered once weekly. The response rate for the cohort receiving an initial dose of 500 mg followed by three 2000 mg doses was 50%, with partial remission observed in 13/26 patients. The drug was well tolerated, with the majority of adverse events being related to infusion reactions and Grade 1 and 2 infections.

A second larger study was done evaluating patients with CLL refractory to alemtuzumab and fludarabine. The interim analysis of this pivotal international study evaluated a total of 138 patients (59 were refractory to fludarabine and alemtuzumab [FA-ref] and 79 were refractory to fludarabine but did not receive treatment with alemtuzumab due to bulky disease [BF-ref]).[13] Ofatumumab was administered as eight weekly infusions followed by four monthly infusions. The first infusion was given as a 300 mg dose and the subsequent infusions were given at a dose of 2000 mg. The objective response rate was found to be 58% and 47% in the FA-ref and BF-ref groups, respectively. All of these were partial responses, with the exception of one complete response. Complete resolution of constitutional symptoms and improved performance status occurred in 57% and 48% of FA-ref and BF-ref patients, respectively. The response was also significant in those who received prior rituximab therapy (objective response rate 54% in the FA-ref patients and 44% in the BF-ref patients) as well as those who received prior treatment with the combination of fludarabine, cyclophosphamide, and rituximab (objective response rate of 50% and 44% in the FA-ref and BF-ref groups, respectively). Furthermore, ofatumumab was also active in those having a 17p deletion, with a response rate of 41% in the FA-ref group, although the response was lower at 14% in the BF-ref group with 17p deletion. The median time to response was 1.8 months, and the median duration of response was 7.1 months in the FA-ref group and 5.6 months in the BF-ref group. Median progression-free survival and overall survival times were 5.7 and 13.7 months in the FA-ref group, respectively, and 5.9 and 15.4 months in the BF-ref group, respectively. The most common adverse events occurring during treatment were infections (67%) and infusion-related reactions (seen in 64% of patients in the FA-ref group and 61% of patients in the BF-ref group), nearly all of which were Grade 1 or 2. These reactions predominantly occurred during the first and second infusions, subsided during the course of treatment, and included cough (18%), diarrhea (16%), anemia (16%), fatigue (15%), fever (15%), neutropenia (15%), dyspnea (13%), nausea (11%), and rash (10%). No human antihuman antibodies were detected in any of the evaluable patients. This study led to accelerated approval of ofatumumab in patients with CLL refractory to fludarabine and alemtuzumab by the US Food and Drug Administration in October 2009.

The final results for the primary endpoint of this study for 206 enrolled patients were reported at the 2010 American Society of Hematology annual meeting. The objective response rate by independent endpoint review committee evaluation was 51% for the FA-ref group and 44% for the BF-ref group. Two patients in the BF-ref group achieved a complete response. The median duration of response was 5.7 months in the FA-ref group and six months in the BF-ref group. Progression-free survival and overall survival were 5.5 months and 14.2 months for the FA-ref group, and 5.5 months and 17.4 months for the BF-ref group.[14]

Another single-arm Phase II study currently recruiting patients is investigating the effects of ofatumumab retreatment and maintenance in CLL patients who received the monoclonal antibody in a previous study (study number Hx-CD20-406). Patients will receive eight weekly infusions (300 mg, then seven × 2000 mg doses), followed by 2000 mg doses once a month for two years. The study is expected to enroll 25 patients, and primary outcome measures should be reported after January 2012 (clinicaltrials.gov study #NCT00802737).

Table 1 Clinical studies of ofatumumab in chronic lymphocytic leukemia

Phase	Status	Indication	Design	Patients (n)	Results	Reference clinicaltrials.gov
II	Untreated, not open for recruitment yet	Untreated high-risk patients with Stage 0–II	O single agent 300 mg IV day 1 of cycle 1; and full dose 1000 mg over 4 hours one time each week (±3 days)	44	n/a	NCT01243190
II	Ongoing, completed accrual	Untreated	Two-dose, parallel group trial; total of six monthly infusions of O in combination with FC will be administered; the first infusion will be 300 mg, followed by five infusions of 500 mg (Group A) or 1000 mg (Group B)	61	The CR rate was 32% for Group A and 50% for Group B; the ORR was 77% and 73%, respectively	9
II	Ongoing, recruiting	Untreated	Single-arm study of O combined with PC	33	n/a	NCT01024010
II	Ongoing, recruiting	Untreated	O 300 mg on day 1 and 1000 mg on day 8 of cycle 1 only + B IV 90 mg/m^2 on days 1–2; during cycles 2–6 O 1000 mg will be given on day 1 only	39	n/a	NCT01125787
II	Ongoing, recruiting	Untreated	Previously untreated older patients and patients who refuse fludarabine-based regimens; O administered as 300 mg week 1 then 2000 mg weeks 2–8	47	n/a	NCT01113632
III	Ongoing, recruiting	Untreated	Randomized, multicenter study of O + Chl versus Chl monotherapy	444	n/a	NCT00748189
I/II	Completed	Rel/ref	3 doses cohorts of O: 100 mg (Group A), 300 mg (Group B) or 500 mg (Group C) were administered in first of 4 treatment weeks; concentrations were increased to 500 (A), 1000 (B), and 2000 (C) mg in following 3 weeks	33	Remission rate was 50% in high dosage group; all patients experienced B cell depletion, and most patients in Group C had lymph node reduction	6
II	Ongoing, recruiting by invitation only	Relapsed	Single-arm study evaluating O retreatment and maintenance in patients who progressed following response or stable disease after O treatment in a previous study; doses 8 weekly infusions (1 × 300 mg + 7 × 2000 mg), then 2000 mg monthly for two years	25	n/a	NCT00802737
II	Ongoing, recruiting	Rel/ref	3–28-day cycles of HDMP 1 gm/m^2/day for 3 consecutive days every cycle combined with O 300 mg on day 1 of cycle 1 followed by 12 doses of 1000 mg administered based on specific schedule	21	n/a	NCT01191190
II	Ongoing, recruiting	Rel/ref	O 300 mg IV on day 1 of week 1 and then 1000 mg on day 1 of each cycle for 6 cycles plus B 70 mg/m^2 IV on days 1 and 2 of each cycle for 6 cycles	40	n/a	NCT01010568
II	Not open for recruitment yet	Rel/ref	O 300 mg IV day 1 and 1000 mg IV day 8 cycle 1; 1000 mg IV day 1, cycles 2–6 in combination with B 70 mg/m^2 IV on days 1–2 of each cycle	49	n/a	NCT01244451
II	Not open for recruitment yet	Rel/ref	O 300 mg IV day 1 and 1000 mg IV day 8 cycle 1; 1000 mg IV day 1, cycles 2–6 in combination with B 90 mg/m^2 on days 1–2 of all cycles	37	n/a	NCT01131247

II	Ongoing, recruiting	Relapsed	Len 10 mg daily up to 24 cycles (cycle = 28 day); O IV infusions 300 mg week 1; 1000 mg weeks 2, 3, and 4, then monthly during months 2–6, and once every two months during months 7–24	40	n/a	14
II	Ongoing, recruiting	Relapsed previously exposed to rituximab	O 2000 mg (300 mg on first cycle) IV on day 1 in combination with Len 10 mg (5 mg on first cycle) orally days 8–28 × 6 cycles	21	n/a	NCT01123356
III	Ongoing, recruiting	Refractory	O 300 mg × 1 followed by 2000 mg × 7 weekly, then 2000 mg × 4 monthly	225	ORR was 51% for the fludarabine- and alemtuzumab-refractory group and 44% for the bulky fludarabine-refractory group	7, 8
III	Ongoing, recruiting	Relapsed	Randomized, multicenter study of O maintenance versus observation in patients who have responded to second- or third-line treatment	532	n/a	NCT01039376
III	Ongoing, recruiting	Relapsed	Randomized trial of OFC versus FC	352	n/a	NCT00824265
Single center	Completed	Refractory	HDMP 1 g/m^2 IV daily × 3 every 28 days for 3 consecutive cycles, plus O 300 mg dose × 1 followed by 11 doses of 2000 mg over a 6-month period	8	ORR 50% (4 PR), 25% had stable disease	15

Abbreviations: Rel/ref, relapsed/refractory; O, ofatumumab; F, fludarabine; C, cyclophosphamide; HDMP, high-dose methylprednisolone sodium succinate; P, pentostatin; B, bendamustine; Chl, chlorambucil; Len, lenalidomide; n/a, not available yet; ORR, objective response rate; PR, partial response; IV, intravenous.

Following on from the single-agent results, studies evaluating ofatumumab combined with other chemotherapeutic agents have recently been undertaken. One of these studies was a two-dose parallel group, international, randomized, multicenter Phase II study looking at ofatumumab combined with fludarabine and cyclophosphamide (O-FC) in patients with previously untreated CLL.[15] A total of 61 patients were randomized to receive ofatumumab 500 mg (Group A) or 1000 mg (Group B) on day 1, combined with fludarabine (25 mg/m^2 IV daily on days 1–3) and cyclophosphamide (250 mg/m^2 IV daily on days 1–3) every four weeks for a total of six courses. In both groups, the first dose of ofatumumab was 300 mg. The complete response rate was 32% for Group A and 50% for Group B, and the objective response rate was 77% and 73%, respectively. After a median follow-up duration of eight months, the median progression-free survival has not been reached. This study demonstrates the activity of ofatumumab combined with fludarabine and cyclophosphamide in previously untreated patients with CLL, and although the objective response rate of O-FC was lower when compared with historical controls, the rate of complete response was higher when compared with patients having similar prognostic risk. Overall, the patients in the O-FC trial were reportedly of high risk, which was primarily determined by an elevated β_2-microglobulin. Furthermore, a study evaluating 224 patients treated with fludarabine, cyclophosphamide, and rituximab in the frontline setting showed a complete response rate of 72% and an objective response rate of 95%. However, this study had a lower number of patients with Rai Stage III–IV disease of 36% compared with 45% in the O-FC trial.[16]

Another study, recently reported at the 2010 American Society of Clinical Oncology meeting, showed a historic objective response rate of 92% and complete response rate of 66% for fludarabine, cyclophosphamide, and rituximab in previously untreated CLL patients.[17] On the other hand, updated results of the German CLL Study Group for fludarabine and cyclophosphamide versus fludarabine, cyclophosphamide, and rituximab in the frontline setting revealed an objective response rate of 95.1% for the fludarabine, cyclophosphamide, and rituximab arm, but only a complete response rate of 44.1%.[18] Another study evaluated bendamustine combined with rituximab in the frontline setting and showed an objective response rate of 90% with only a complete response rate of 32%.[19] Due to patient differences, it is hard to make comparisons using historical data. O-FC seems to be a promising and active regimen in the upfront setting, but Phase III data would likely be necessary to determine further its definite role.

The initial results of a Phase II study evaluating the efficacy and tolerability of the combination of lenalidomide and ofatumumab in patients with relapsed CLL was recently presented at the 2010 American Society of Hematology meeting.[20] In this trial, ofatumumab was administered IV weekly for four weeks (300 mg week 1, 1000 mg week 2, and all subsequent doses), then monthly for months 2–6 and once every two months for months 7–24. Lenalidomide was given orally at a dose of 10 mg daily, starting on day 9 and continued daily. The treatment duration was 24 months. Results for the first 16 of 40 planned patients who have been on study for at least three months were presented. Four patients (25%) were refractory to fludarabine and all patients had received prior rituximab. Ten of the 16 evaluable patients achieved a response (two complete responses [13%], eight partial responses [50%]) for an objective response rate of 63%. Four patients with stable disease were continuing on treatment. The most common Grade 3–4 treatment-related adverse events observed were neutropenia (eight patients, 50%) and anemia (two patients, 13%). Lenalidomide-associated tumor flare reaction was limited to Grade 1 in two patients (13%). The authors concluded that the combination was therapeutically active in patients with relapsed CLL and was well tolerated.

The combination of high-dose methylprednisolone and ofatumumab was recently reported in patients with CLL not considered to be good candidates for chemotherapy due to comorbidities, poor performance status, profound cytopenia, or refractory status to fludarabine and/or alemtuzumab.[21] Eight patients with progressive, symptomatic CLL were treated with high-dose methylprednisolone 1 g/m^2 IV daily every 28 days for three consecutive cycles, and a single dose of ofatumumab 300 mg, followed by 11 doses of 2000 mg over a six-month period. The median patient age was 69 years, and the median number of prior treatments was 4.5, including four patients who had previously received high-dose methylprednisolone and rituximab and two patients who had undergone matched unrelated donor stem cell transplantation. All patients had been previously treated with rituximab, 75% had failed or were intolerant to fludarabine and/or alemtuzumab, and 75% had high-risk prognostic markers, including unfavorable cytogenetics, unmutated IgV_H region genes, or high expression levels of zeta-associated protein. Most of the patients had bulky disease and splenomegaly. All patients completed the planned therapy with no major side effects or toxicities. There was no evidence of marrow suppression, and even patients with pancytopenia improved their peripheral blood counts with this salvage regimen. The objective response rate was 50% (four partial remissions), 25% of patients had stable disease, and the remainder showed progressive disease. These data suggest that the combination of high-dose methylprednisolone and ofatumumab is a safe and effective salvage regimen for high-risk CLL patients who otherwise would not be candidates for additional treatment. Further clinical studies of this combination are warranted.

Conclusion

Ofatumumab has significant antileukemic activity, and offers another effective agent with which to improve the outcome of patients with CLL/SLL. Further studies will clarify the optimal dose and time to use this drug. CLL refractory to fludarabine is a high-risk disease that has very few treatment options. In this regard, ofatumumab seems to be an effective agent. However, in the previously untreated CLL setting, we do not believe any of the current studies can justify using this therapy over one of the other more established and cost-effective regimens, such as fludarabine, cyclophosphamide, and rituximab. Ongoing clinical trials will determine the role of ofatumumab in CLL in both the upfront and the relapsed setting. Furthermore, randomized Phase III clinical trials will be required to determine if ofatumumab is a clinical advance over rituximab.

Disclosure

The authors report no conflicts of interest in this work.

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