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Obinutuzumab: A Novel Anti-CD20 Monoclonal Antibody for Previously Untreated Chronic Lymphocytic Leukemia

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Abstract

Objective: To review and summarize data on obinutuzumab, which was approved by the Food and Drug Administration (FDA) in November 2013 for use in combination with chlorambucil for previously untreated chronic lymphocytic leukemia (CLL). **Data Sources:** A PubMed literature search (August 2002 to March 2014) was conducted using the terms *obinutuzumab, GA101, anti-CD*20 *antibody*, and *CLL*. Data were also obtained through the FDA briefing documents and American Society of Hematology abstracts. **Study Selection and Data Extraction:** The literature search was limited to human studies published in English. Priority was placed on trials of obinutuzumab in previously untreated CLL. **Data Synthesis:** Obinutuzumab is a novel glycoengineered type II anti-CD20 monoclonal antibody, with a higher affinity for CD20 epitope, leading to superior cytotoxicity compared with rituximab. The FDA approval was based on a phase III, randomized trial of chlorambucil monotherapy (n = 118), chlorambucil plus obinutuzumab (n = 333), or rituximab (n =330) in previously untreated elderly CLL patients. Obinutuzumab was administered intravenously as 1000 mg on days 1, 8, and 15 of cycle 1 and day 1 for subsequent cycles. Median progression-free survival was 26.7 months in the chlorambucil plus obinutuzumab arm. The incidence of grade 3 or higher adverse events in the obinutuzumab plus chlorambucil arm was as follows: neutropenia (33%), infusion-related reactions (20%), thrombocytopenia (10%), and infections (7%). **Conclusion:** Obinutuzumab in combination with chlorambucil is a safe and effective new treatment option for previously untreated elderly CLL patients. It should become the new preferred therapy for these patients with significant comorbidities who are not candidates for fludarabine-based therapy.

Keywords

obinutuzumab, untreated chronic lymphocytic leukemia, GA101, and chlorambucil

The American Cancer Society estimates that 15 720 new cases of chronic lymphocytic leukemia (CLL) will be diagnosed in the United States in 2014, with an estimated 4600 deaths.[1,2] CLL is mainly a disease of the elderly population with a median age at diagnosis of 72 years.[3] Prognosis is based on several factors such as genomic aberrations and cytogenetic abnormalities. Unmutated immunoglobulin heavy-chain variable (IGHV), CD38, and ZAP-70 expression and elevated levels of serum β2-microglobulin, del (17p), and del (11q) are clearly associated with shorter progression-free survival (PFS) and overall survival (OS).[3-7]

Treatment of CLL is usually reserved for patients with advanced (Rai III-IV, Binet C) or active, symptomatic disease.[2,3] The choice of treatment depends on clinical stage of the disease, fitness of the patient, cytogenetic abnormalities, and treatment situation (front line vs second line; response to prior therapies).[2,8] The combination of fludarabine, cyclophosphamide, and rituximab (FCR) is currently recommended as first-line therapy for patients <70 years of age without comorbidities.[3] However, based on combined direct and indirect data in a multiple treatment meta-analysis, no single treatment showed significant survival benefit over another.[9] Until recently, the preferred therapy for elderly patients (age ≥ 70 years) or those with significant comorbidities, including renal impairment, was rituximab in combination with chlorambucil.[3,9-12] Other options include bendamustine, fludarabine, or cyclophosphamide/prednisone with or without rituximab, and rituximab, cladribine, or chlorambucil monotherapy.[3] The elderly population remains underrepresented in most CLL studies, and available data have not shown superiority of one regimen over another until recently.[13] In addition, patients with del (17p) do not benefit from FCR, and alemtuzumab-containing regimens remain the only effective option for these patients.[2-3,8] Rituximab, the first monoclonal antibody directed against

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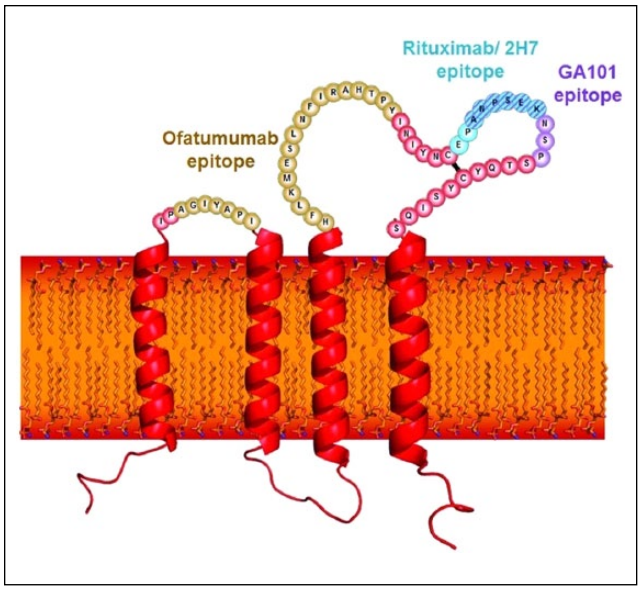

Figure 1. The structure and topology of CD20 and the epitopes recognized by rituximab, ofatumumab, and GA101 (adapted from Klein et al).[25]

CD20 antigen expressed on the surface of the human B cells, was initially approved in 2010 for previously untreated CLL.[14] Rituximab is less active when used as a single agent in CLL when compared with its use in combination with chemotherapy. CLL8 was the first trial to show that adding rituximab to chemotherapy (fludarabine and cyclo-phosphamide) resulted in significantly improved OS.[8,15]

Ofatumumab, a second-generation anti-CD20 monoclonal antibody, was approved in October 2009 for refractory CLL.[16] On November 1, 2013, obinutuzumab, a third-generation typeII anti-CD20 monoclonal antibody, became the first treatment approved with the Food and Drug Administration's (FDA's) breakthrough therapy designation for use in combination with chlorambucil as a first-line therapy for CLL.[17,18]

Data Selection

A PubMed literature search (August 2002 to March 2014) was conducted for English-language publications using the terms *obinutuzumab, GA101, anti-CD20*, and *CLL*. Data from ongoing studies were obtained through clinicaltrials.gov and American Society of Hematology abstracts. Additional references were obtained from cross-referencing bibliographies. Priority was placed on clinical trials of obinutuzumab in CLL.

Pharmacology

CD20 is a cell surface molecule expressed at high levels on the majority of the normal and malignant B cells. Although the precise molecular function of CD20 remains obscure, in vitro studies have shown that it plays a central role in the generation of T-cell-independent antibody response. It is also implicated in regulating early steps in B lymphocyte activation by acting as a calcium ion channel. Interestingly, the CD20 antigen is neither shed nor internalized in resting B cells; hence it serves as an ideal target for monoclonal antibodies in B cell mali-gnancies.[19,20]

Rituximab is a type I chimeric IgG1 monoclonal antibody against CD20 that causes cell death via complement-dependent cytotoxicity, antibody-dependent cell cytotoxicity, and direct apoptosis via cross-linking of several molecules of rituximab and CD20.[4,14] Obinutuzumab is a glycoengineered type II humanized CD20 IgG1 monoclonal antibody with an increased affinity to an activating F_c receptor expressed by immune effector cells. It recognizes the same CD20 epitope as rituximab but binds to it in a different orientation (Figure 1) and over a larger surface area, allowing a superior induction of direct cell death, enhanced natural killer cell activation, and antibody-dependent cell cytotoxicity (5-100 times greater than rituximab). It is, however, 10- to 1000-fold less potent in inducing complement-dependent cytotoxicity.[17,21-25]

Pharmacokinetics

Obinutuzumab elimination consists of a linear clearance and a time-dependent, saturable, nonlinear clearance pathway. Based on the population pharmacokinetics, the mean volume of distribution, terminal clearance, and half-life are approximately 3.8 L, 0.09 L/d, and 28 days, respectively. Obinutuzumab elimination is likely a result of target-mediated drug disposition. Obinutuzumab has not been tested in renal (creatinine clearance [CrCl] ≤ 30 mL/min) and hepatic impairment.[17]

Efficacy

Four phase I studies have demonstrated clinical activity of obinutuzumab in CLL. In a phase 1 study of 22 heavily pretreated patients with relapsed non-Hodgkin's lymphoma or CLL (n = 5), obinutuzumab (200-2000 mg) administered weekly for 4 weeks yielded a partial response of 23%.[26] In another phase Ib study of 41 previously untreated CLL patients, obinutuzumab, fludarabine, and cyclophosphamide (n = 21) yielded an overall response rate (ORR) of 62% (complete response = 10%) compared with an ORR of 90% (complete response = 20%) in patients receiving obinutuzumab plus bendamustine (n = 20).[27]

In the phase I part of the GAUGUIN study, obinutuzumab (400-2000 mg) was administered to 13 heavily pretreated patients with relapsed/refractory CLL on days 1, 8, and 22 and subsequently every 3 weeks for a total of 9 infusions. The best ORR was 62%.[28] In the phase II part of the study, obinutuzumab was administered as 1000 mg

Table 1. Efficacy and Safety Outcomes From CLL11.

	Chlorambucil + Rituximab (Safety Analysis: n = 321; Efficacy Analysis: n = 333)	Chlorambucil + Obinutuzumab (Safety Analysis: n = 336; Efficacy Analysis: n = 330)	P Value
Efficacy			
Median PFS, months	15.2	26.7	<0.001
Median OS, months	NR	NR	0.09
ORR (%)	65	78	—
CR rate (%)	7	21	<0.001
MRD negative (%)	Bone marrow: 2.6	19.5	<0.001
	Blood: 3.3	37.7	<0.001
Grade 3-5 adverse events			
Overall (%)	55	70	—
Neutropenia (%)	28	33	—
Anemia (%)	4	4	—
Thrombocytopenia (%)	3	10	—
Leukopenia (%)	1	4	—
Infections (%)	14	12	—
Infusion-related reactions (%)	4	20	—

Abbreviations: CLL, chronic lymphocytic leukemia; CR, complete response; MRD, minimal residual disease; NR, not reported; PFS, progression-free survival; ORR, overall response rate; OS, overall survival

intra-venously on days 1, 8, 15, and 22, then every 21 days for a total of 10 infusions. Among the 16 evaluable patients, the ORR was 25%. Similar to other phase I studies, the dose-response relationship was not identified.[29] Based on all the available clinical data in B-cell malignancies as well as modeling and simulation, a flat dose of 1000 mg was chosen to be administered on days 1, 8, and 15 of the first cycle for phase III studies to rapidly achieve and maintain adequate drug levels.[30]

The CLL11 was a phase III, randomized controlled, open-label, international study that enrolled 781 previously untreated CLL patients with comorbidities in a 3-arm, 2-stage trial. Notable eligibility criteria included a Cumulative Illness Rating Scale total score >6 or an estimated CrCl of 30 to 69 mL/min. Notable exclusion criteria included inadequate liver function, positive hepatitis (hepatitis B and C) serology, or immunization with live vaccine within 28 days prior to randomization. Patients were randomized to receive either obinutuzumab plus chlorambucil (stage 1, n = 238; stage 2, n = 333) or rituximab plus chlorambucil (stage 1, n = 233; stage 2, n = 330) or chlorambucil alone (stage 1, n = 118) in six 28-day cycles. Chlorambucil was administered orally at a dose of 0.5 mg/kg on days 1 and 15 of each cycle. Obinutuzumab was administered intravenously as 1000 mg on days 1, 8, and 15 of cycle 1 and on day 1 of cycle 2 through 6. To ameliorate the infusion-related reactions (IRRs) seen in 89% of the first 53 patients receiving obinutuzumab, the protocol was amended to administer first obinutuzumab infusion over 2 days. The first dose was split between day 1 (100 mg) and day 2 (900 mg) and was administered to 42% of the patients. Rituximab was administered intravenously at 375 mg/m^2 on day 1 of cycle 1 and 500 mg/m^2 on day 1 of cycle 2 through 6. Dose modifications were not permitted. The median age of enrolled patients was 73 years. About 60% of the patients in each group had unmutated IGHV, which indicates a poor prognosis.[31]

The primary end point of the study was PFS, and key secondary end points included response rates, minimal residual disease, and OS. At 3 months after the end of treatment, compared with chlorambucil monotherapy, the median PFS was significantly higher for patients receiving obinutuzumab and chlorambucil (11.1 vs 26.7 months, hazard ratio [HR] = 0.18, $P < 0.001$) and those receiving rituximab and chlorambucil (11.1 vs 16.3 months, HR = 0.44, $P < 0.001$). Similar benefit was seen in all subgroups except in patients with del (17p). Chlorambucil combination with obinutuzumab resulted in significantly longer PFS compared with rituximab (HR = 0.39; 95% CI, 0.31-0.49, $P < 0.001$). OS was also prolonged in patients receiving obinutuzumab and chlorambucil compared with those receiving chlorambucil alone (rates of death, 9% vs 20%, HR = 0.41; 95% CI, 0.23-0.74, $P = 0.002$). In contrast, significant benefit was not seen with rituximab and chlorambucil over chlorambucil monotherapy. Survival benefit with obinutuzumab and chlorambucil over rituximab and chlorambucil was also not observed (HR = 0.66 [0.41-1.06]; $P = 0.08$). Median OS was not reached in either of the combination therapy arms. Obinutuzumab-containing combination therapy yielded higher overall, complete and molecular response rates compared with rituximab combination therapy (Table 1).[31] Results of this trial led to FDA approval of obinutuzumab in November 2013.

Safety

The most frequent grade 3 or higher adverse events (AEs; Table 1) in the obinutuzumab arm included IRRs (20%), infections (12%), and hematological AEs such as neutropenia (33%), thrombocytopenia (10%), anemia (4%), and leukopenia (4%). The incidence of these AEs was similar to that in the rituximab arm except for lower rates of thrombocytopenia (3%) and IRRs (4%). All grade 3 to 4 IRRs occurred during the first infusion of obinutuzumab, which led to discontinuation of therapy in 8% of the patients. Predictors of obinutuzumab-related IRRs were not identified, and prophylactic medications had minimal impact on IRRs. A total of 4% of the patients died in the obinutuzumab arm as a result of AEs compared with 6% in the rituximab arm. The incidence of tumor lysis syndrome was higher with obinutuzumab (4%) compared with rituximab (<1%). Other serious AEs included newly diagnosed neoplasms; however, the rates were comparable with both monoclonal antibodies.[31]

Dosage and Administration

Obinutuzumab is administered as an intravenous infusion of 1000 mg for six 28-day cycles. The first dose of cycle 1 should be administered as 100 mg on day 1 and 900 mg on day 2. The first dose of the first cycle should be administered at 25 mg/h; however, the second dose can be titrated by 50 mg/h every 30 minutes to a maximum rate of 400 mg/h. Subsequent infusions can be started at 100 mg/h and increased by 100 mg/h every 30 minutes up to a maximum rate of 400 mg/h.[31]

All patients should be premedicated with acetaminophen (650-1000 mg), intravenous gluco-corticoids (dexamethasone 20 mg or methylprednisolone 80 mg), and an antihistamine (diphenhydramine 50 mg) at least 30 minutes prior to the first dose. For subsequent infusions, premedication with an antihistamine, for history of grade ≥1 IRR, and intravenous glucocorticoids, for history of grade ≥3 IRRs or lymphocyte count >25 × 10^9/L, is recommended.[31]

Place in Therapy

Previously untreated CLL patients with comorbidities that are not eligible for fludarabine-based therapies are candidates for obinutuzumab. Other treatment options for elderly patients (age ≥70 years) or younger patients with comorbidities include variations of rituximab, chlorambucil, bendamustine, and reduced FCR.[3] No other randomized trial to date, except for CLL11, has shown that targeting CD20 antigen in patients with CLL and coexisting conditions results in improved survival over chlorambucil monotherapy. Results of CLL11 establish that obinutuzumab plus chlorambucil is an effective option for elderly CLL patients, including those with unmutated IGHV.

Because chlorambucil combination with obinutuzumab yielded superior PFS compared with rituximab, obinutuzumab should be investigated in other clinical settings, where targeting the CD20 antigen remains an important therapeutic strategy. As the place in therapy for obinutuzumab expands, comparison with other agents used in frontline therapy and relapsed/refractory settings will become critical. Even though chlorambucil plus obinutuzumab failed to achieve mortality benefit over rituximab, it achieved significant improvement in minimal residual disease, which has predicted longer OS in other studies.[32] In addition, CLL11 data may not be mature enough at this point to see the survival benefit, and with longer patient follow-up, this difference may become apparent. Obinutuzumab is fairly well tolerated, with an AE profile similar to that of rituximab, but is associated with a higher incidence of IRRs.

Formulary Considerations

Obinutuzumab is supplied as a 1000-mg single-use vial, which is recommended to be diluted in adequate amount of 0.9% sodium chloride to yield a final concentration of 0.4 to 4 mg/mL. Diluted solution for infusion should be used immediately; however, it can be stored up to 24 hours at 2°C to 8°C followed by 48 hours at room temperature.[14] The current average wholesale prices for 1000 mg of obinutuzumab (single vial) and rituximab (two 500-mg vials) are $6192 and $8233, respectively.[33] For a person with a body surface area of 2.0 m^2, the cost of obinutuzumab for the first cycle will be about 56% higher than that of rituximab; however, the overall cost is fairly similar for 6 cycles of treatment duration.

Future Directions

Obinutuzumab-based combination therapies are being studied as frontline and salvage therapy for relapsed and refractory CLL (Table 2) as well as for other subtypes of non-Hodgkin's lymphoma. Fludarabine remains an important backbone of chemoimmunotherapy for fit CLL patients without significant comorbidities.[3,34] Whether the substitution of obinutuzumab for rituximab in the FCR regimen results in better outcomes is currently under investigation (NCT01300247). Compared with chlorambucil monotherapy, bendamustine and alemtuzumab in combination with rituximab have yielded superior response rates and PFS in previously untreated elderly CLL patients. It is important to note that alemtuzumab has also shown superior outcomes in patients with del (17p) compared with chlorambucil monotherapy.[10,35-38] Several combinations of obinutuzumab and bendamustine are currently under evaluation in various stages of clinical trials; however, there are currently no trials evaluating the efficacy and safety of alemtuzumab plus obinutuzumab, which would be an important area of investigation in the future.

Increasing evidence shows that antigen-dependent and antigen-independent B-cell receptor (BCR) signaling and

Table 2. Ongoing or Planned Studies of Obinutuzumab in CLL.

Clinicaltrials.gov NCT Identifier	Study Type	Regimen	Study Population	Status
NCT01905943	Phase IIIb, multicenter, open label	Obinutuzumab versus obinutuzumab plus fludarabine, cyclophosphamide, and bendamustine or obinutuzumab plus chlorambucil	Previously untreated or relapsed/refractory CLL	Accruing
NCT02071225	Phase II	Obinutuzumab and bendamustine	Refractory or relapsed CLL	Accruing
NCT01685892	Phase Ib, multicenter, open label	Obinutuzumab and GDC-1099 (ABT-199)	Previously untreated or relapsed/refractory CLL	Accruing
NCT01414205	Phase II, open label, multicenter, randomized	Obinutuzumab 1000 mg versus 2000 mg	Previously untreated CLL	Ongoing, but not recruiting
NCT02100852	Phase I/Ib, multicenter	Obinutuzumab plus TGR-1202 plus chlorambucil	CLL (exact population not defined)	Accruing
NCT01300247	Phase Ib, open label, multicenter	Obinutuzumab plus bendamustine or fludarabine and cyclophosphamide	Previously untreated	Ongoing but not recruiting

Abbreviation: CLL, chronic lymphocytic leukemia.

proteins in the B-cell CLL/lymphoma 2 (Bcl-2) family play a central role in the pathogenesis of CLL. Recently, it was found that kinases immediately downstream of BCR, such as phosphatidylinositol 3-kinase (PI3K), play an essential role in the pathogenesis of CLL. Several small molecules have been developed to inhibit a variety of kinases in the BCR pathway as well as Bcl-2 family proteins.[39] Obinutuzumab combination therapy is under investigation with 2 such molecules: ABT-199, a Bcl-2 inhibitor, and TGR-1202, a PI3K inhibitor (Table 2).

Summary

Obinutuzumab is a safe and effective third-generation anti-CD20 monoclonal antibody for elderly CLL patients with comorbidities who are not candidates for fludarabine-based therapy. The role of obinutuzumab is also currently being investigated in relapsed/refractory CLL as well as various other B-cell malignancies. As the results from various ongoing studies become available, the role of obinutuzumab may expand, and it may begin to be used as a first-line treatment option over rituximab, hence changing the way we have been managing CLL for the past two decades.

Declaration of Conflicting Interests

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