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REVIEW

Clinical application of obinutuzumab for treating chronic lymphocytic leukemia

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Abstract: Alkylators and nucleoside analogs were the main drugs for treatingchronic lymphoblastic leukemia (CLL), which have been replaced by monoclonal antibodies, such as rituximab in the past 10 years for refractory or relapsed CLL. The first-line immunochemotherapy regimen, rituximab combined with nucleoside analogs, significantly increased CLL patients' first-reaction rate and improved progression-free survival. Despite the long-lasting remissions by the use of chemoimmunotherapy, most CLL patients will relapse eventually. The obinutuzumab (GA101), an updated CD20 antibody, that is thought to achieve a more durable response with unique molecular and functional characteristics. Obinutuzumab is a humanized, monoclonal type II CD20 antibody modified by glycoengineering. The glycoengineered Fc portion enhances the binding affinity to the FcγRIII receptor on immune effector cells, resulting in increased antibody-dependent cellular cytotoxicity and phagocytosis. In addition, the type II antibody binding characteristics of obinutuzumab to CD20 lead to an efficient induction of direct non-apoptotic cell death. This review summarizes the results of clinical studies using obinutuzumab and looks forward to its further application in treating CLL clinically.

Keywords: CD20 antibody, GA101, obinutuzumab, chronic lymphocytic leukemia

Introduction

For the treatment of chronic lymphocytic leukemia (CLL), current research has found that a combination of chemotherapy and monoclonal antibodies targeting the CD20 antigen can significantly improve the prognosis. In 2010, the CLL8 trial of the German CLL study group (GCLLSG) found that treatment with rituximab plus fludarabine and cyclophosphamide (FCR) increased progression-free survival (PFS) and overall survival (OS).[1,2]

Afterward, chemoimmunotherapy with rituximab has become the standard treatment for most patients with CLL. The disease has long-lasting remissions after chemoimmunotherapy. In some subgroups,[3] the median PFS is more than 6 years, but there is a greater likelihood that the disease will recur after treatment and may develop chemotherapy- or rituximab-refractory disease.

Recently, the study found a novel CD20 antibody with significantly improved efficacy compared to rituximab. Obinutuzumab is a new generation of type II glycoengineered CD20 monoclonal antibody that has been approved for the treatment of CLL.[4] Research reports have identified key advances in the development of this antibody.[5–7]

Meanwhile, new as well as updated data for obinutuzumab have emerged with regard to the treatment of not only CLL but also other B-cell lymphomas. This paper mainly discusses the structure, mechanism of action and development prospect of obinutuzumab, as well as its clinical application in combination with other drugs.

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Structural characteristics and mode of action

Obinutuzumab is a glycoengineered CD20 antibody

Obinutuzumab is a novel humanized, glycoengineered Type II anti-CD20 monoclonal antibody of the immunoglobulin G1 (IgG1) isotype. Obinutuzumab was derived by humanization and elbow-hinge optimization of the parental B Ly1 mouse antibody. It is designed to mediate enhanced direct and immune effector cell-mediated killing compared to the type I CD20 antibody rituximab.[8]

The affinity of the antibody for the FcγRIII fragment is very important, which is influenced by the structure of the oligosaccharide attached to the specific Fc fragment in the antibody. A decent affinity is needed to mediate the interaction (of what) with immune effector cells, and thus induces stronger interaction with neutrophils and NK cells. In the glycoengineering experiment, obinutuzumab was originally designed by removing a molecule of fucose out of the glycan tree linked to asparagine at site 297,[9,10] which resulted in an increase of the affinity between FcγRIIIa and FcγIIIb. Subsequently, the recruitment of FcγRIII expression effector cells also increased, like neutrophils, natural killer cells and macrophages, where stronger signals are observed.[11] Obinutuzumab is the first glycosylated type II anti-CD20 monoclonal antibody, and such modification resembles using the patient's own immune system to eliminate the cancer cells (Figure 1).

The enhanced binding of obinutuzumab to FcγRIII promotes the ADCC, where the obinutuzumab can induce the ADCC activity in vitro to the extent 35 to 100 times greater than rituximab and ofatumumab.[8,11] In contrast to rituximab, ADCC of obinutuzumab is not blocked by either non-specific IgG[8] of physiological concentration or complement.[12] Notably, obinutuzumab has been reported to eliminate inhibitory signals through inhibitory killer cell Ig-like receptor (KIR) or human leukocyte antigen (HLA) interactions. This leads to the recruitment of additional natural killer cells for ADCC, which is not adversely affected by KIR/HLA interactions (Figure 2).[13]

Besides enhancing the ADCC, the glycosyl modified structure of obinutuzumab also promotes recruitments of phagocytes, including neutrophils, monocytes and dendritic cells, through Fc-FcγR interaction and increases the cytotoxic activity of them[14] through FcγRIIIa.

Mode of action of type II CD20 antibody

The antibodies against CD20 have two major classes, namely the type I and II CD20 antibodies (see Table 1). There are some difference between type I and type II CD20 antibodies.

Direct induction of apoptosis

Type II antibodies can more potently induce the homotypic aggregation and direct cell death than its counterpart, the type I antibodies.[8] The action of obinutuzumab to cause cell death is by inducing the homotypic aggregation, which remarks a novel type of actin-dependent and lysosome-induced cell death,[8,14,15] and is associated with actin rearrangement, lysosome cathepsin release. Due to the lack of characteristic markers of apoptosis, such as caspase-dependent or BCL2 expression, this type of cell death can bypass the mechanism of apoptosis resistance.[13] Furthermore, induction of direct cell death is not associated with Fc-FcγR interaction. Therefore, obinutuzumab can also be an improved treatment option for patients with impaired Fc function. Patients with

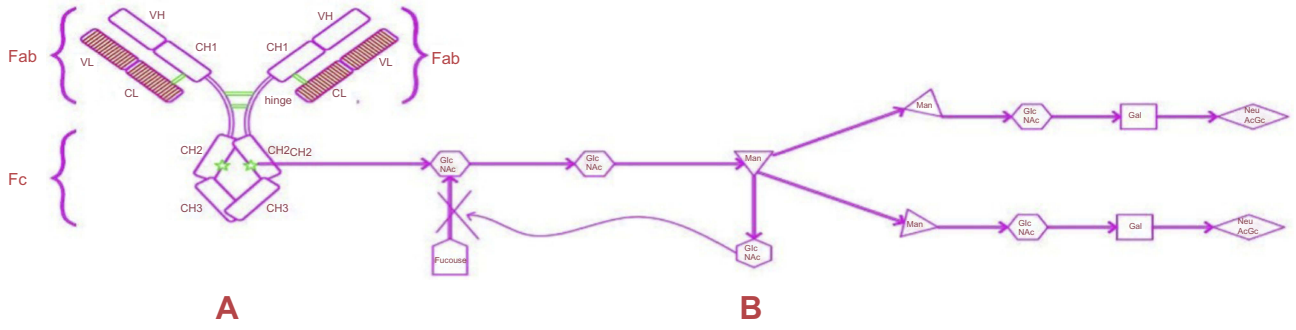

Figure 1 Structure of human IgG1 antibody and carbohydrate of glycoengineered antibody. (**A**) The mAbs of human IgG1 isotype consist of two immunoglobulin light chains and two immunoglobulin heavy chains. Heavy chains are covalently paired by disulfide bonds in hinge regions, and each heavy chain is connected to a light chain by a disulfide bond between CH1 and CL. A pair of VH and VL in Fab regions makes an antigen-binding site. In the CH2 domains of Fc regions, an oligosaccharide is covalently attached to the both domains at asparagine 297 (Asn-297). (**B**) Scheme of the glycoengineered bisected carbohydrate chain of a glycoengineered antibody.

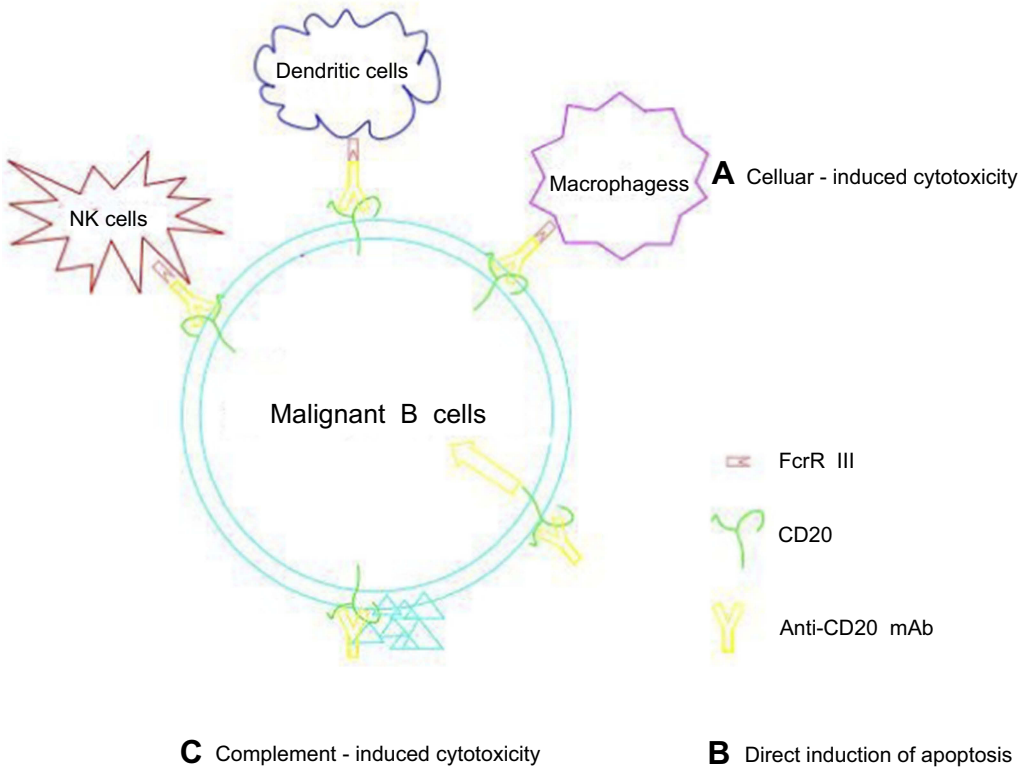

Figure 2 Putative mechanism of action of obinutuzumab.
Abbreviations: ADCC, antibody-dependent cell mediated cytoxicity; ADCP, antibody-dependent cellular phagocytosis; CDC, complement-dependent cytotoxicity.

Table 1 Comparison between Type I CD20 mAb and Type II CD20 mAb

	Type I CD antibodies	**Type II CD antibodies**
ADCC	moderate	strong
ADCP	moderate	strong
CDC	strong	weak
DCC	weak	strong
Homotypic cell aggregation	weak/no	strong
CD20 accumulation in lipid rafts	Yes	No
CD20 binding capacity	Full	Half maximal
Glyco-engineered	No	Yes

Abbreviations: ADCC, antibody-dependent cellar cytotoxicity; ADCP, antibody-dependent cellar phagocytosis; CDC, complement-dependent cytotoxicity; DCC, direct cell death.

low-affinity FcγRIIIa variants, as well as patients with effector cell saturation or failure (Figure 2).[16]

CD20 binding capacity

The type I CD20 antibodies and type II CD20 antibodies differ significantly, where the number of B cells accommodate of type I CD20 antibodies is twice that of Type II CD20 antibodies.[8] It has been hypothesized that Type I antibodies bind between two CD20 tetramers (inter-tetramer binding), whereas Type II antibodies may bind within a tetramer (intra-tetramer binding). Presumably, the different binding topologies of type II antibodies cause the two Fab arms to bind within a single CD20 tetramer, while type I antibodies are assumed to bind different CD20 tetramers with each Fab arm (Figure 3).[17]

Complement-dependent cytotoxicity (CDC)

After binding of the type I CD20 antibody, the CD20 antibody complex is internalized and degraded, thus effector cell recruitment and antibody half-life reduction,[8] which appears to be dependent on binding to the inhibitory FcγRIIb receptor expressed on B-cells in cis mode.[18] In contrast, type II CD20 antibodies showed only minimal CD20 internalization.[19] This specific binding property of the type II antibody prevents its interaction with FcγRIIb, thereby preventing the accumulation

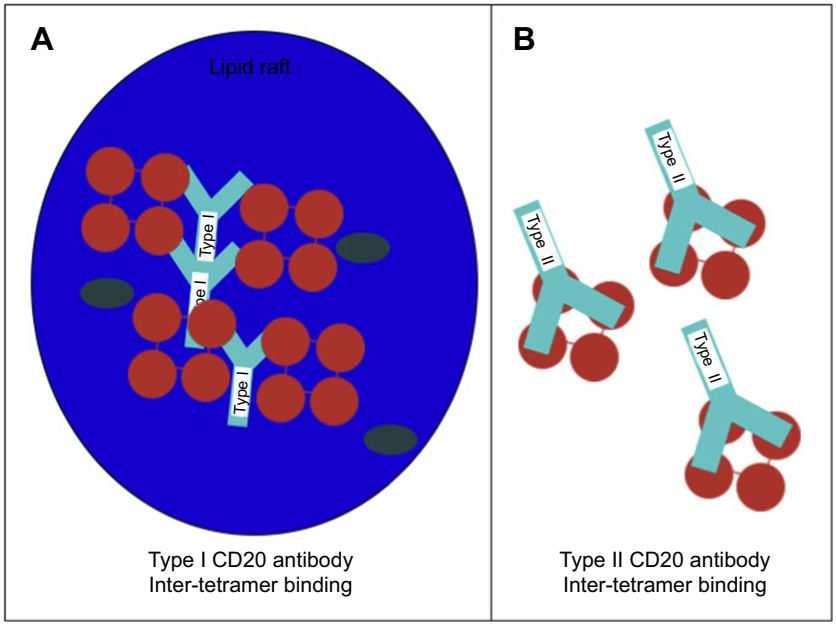

Figure 3 Hypothetical model for the 2:1 binding ratio of type I and type II CD20 antibodies binding to CD20 (tetramers, depicted in red). An explanation to explain the 2:1 binding stoichiometry between type I and type II CD20 antibodies is to assume that (**A**) type I antibodies binding between CD20 tetramer (inter-tetramer, depicted in red) resulting in accumulation in lipid rafts together with FcγRIIb. In contrast, type II (**B**) antibodies may bind within one tetramer (intra-tetramer).

of CD20 in lipid rafts and downregulation of CD20 surface expression. CD20 molecules are not collected by obinutuzumab in lipid rafts, and Fc aggregation does not occur in lipid rafts, which leads to a decrease in CDC activation by C1Q, which is not considered to be a double betuzumab activity relevant clinical mechanisms (Figures 2 and 4).[16]

Clinical data

Efficacy

In the Gauguin I/II trial, obinutuzumab was first tested, including 33 patients with relapsed or refractory CLL. Such an experiment is divided into two phases, the dose escalation and the fixed dose phase. The patient accepted a total amount of 400 to 1200 mg of the first stage of obinutuzumab and a fixed dose of 1000 mg during stage II.[20]

The overall response rate (ORR) for the first phase was 62%, while the second phase was only 30%. Tumor burden imbalance in the two groups of patients was a significant difference in response rates in clinical trials. Median PFS is 10.7 months (Phase 2). In conclusion, obinutuzumab monotherapy is effective in patients who have been pre-treated with relapsed/refractory CLL for a long time.

In another randomized phase II clinical trial (gage), the efficacy of single-agent obinutuzumab for treating the CLL and dose optimization was investigated. A total of 80 previously untreated CLL patients were randomly allocated into 2 groups: (1) taking a low dose of 100 mg on the first day, a low dose of 900 mg on the second day, and taking 1000 mg on the first day and the fifteenth day; or (2) the high-dose group of 100 mg on the first day and the high-dose group of 900 mg on the second day, The high-dose group of 1000 mg was taken for 3 days, and 2000 mg was taken on the 8th and 15th day of the 1st cycle, and 2000 mg was taken on the first day of the 2nd-8th cycle. For the primary endpoint, the 2000 mg group had higher ORR (67% vs 49%) and CR (20% vs 5%). Although this dose plan had an effect on the response, no significant difference in PFS was observed.[21]

The Galton trial examined 41 patients with nonalcoholic CLL who underwent a combination of obinutuzumab and central chemotherapy selected by the investigator.[22] The objective response rate (ORR) of obinutuzumab-bendamustine (G-B) was 90% (18/20) and the complete response rate (CRR) was 20%. Obinutuzumab plus FC (G-FC) has an ORR of 62% (13/21) and a CRR of 10%. In the G-B group, the median follow-up period was 23.5 months while that of the G-FC group is 20.7 months, with no patients relapsed or died, which indicates that obinutuzumab with either B or FC has promising activity.

CLL11 is a large randomized clinical trial. The final analysis results of CLL11 study reported by German researcher Goede et al show that obinutuzumab-based regimen can

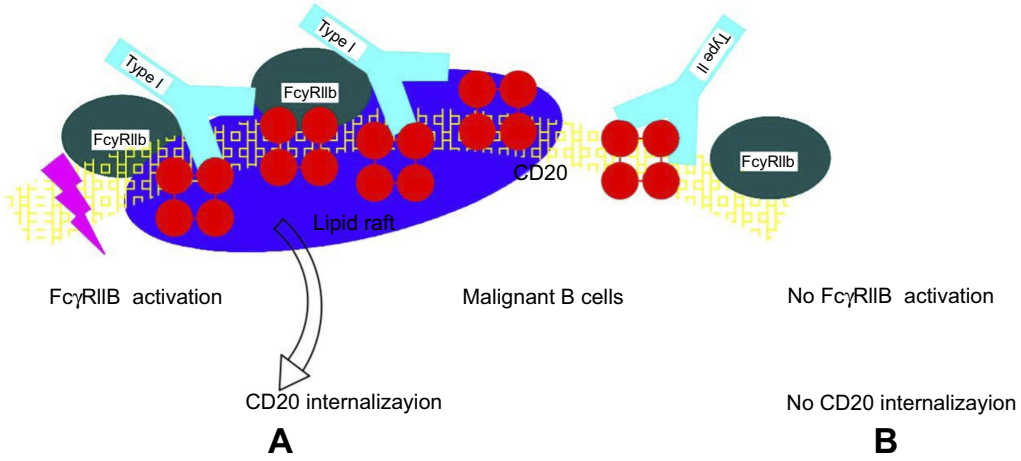

Figure 4 Hypothetical model for CD20 binding of type I and type II CD20 antibodies explaining the impact of FcγRIIb on internalization. (**A**) Type I antibodies, such as rituximab, may bind to CD20 in a conformation that allows simultaneous binding to FcγRIIb and subsequent cross-linking and activation followed by internalization in lipid rafts. (**B**) Type II antibodies, such as obinutuzumab, may bind in a conformation that does not allow simultaneous binding to FcγRIIb, thus resulting in low/no internalization.

significantly improve PFS and overall survival (OS) compared with rituximab-based regimen for patients with CLL and can reduce the risk of death by 24%. The multicenter open-label phase III randomized study included patients with CD20 positive CLL (median 73 years old), who were given obinutuzumab combined with chlorambucil (Chl) regimen (333 cases), rituximab combined with Chl regimen (330 cases) and Chl monotherapy regimen (238 cases). The results showed that the median follow-up was 59.4 months (nearly 5 years). Obinutuzumab combined with Chl regimen can reduce the risk of disease progression by 51% compared with rituximab combined with Chl regimen. The median PFS is 28.9 months and 15.7 months, respectively (HR=0.49, P<0.0001), which can reduce the risk of death by 24%, and the median OS is 73.1 months (HR=0.76, P<0.0245). The median time to start follow-up treatment was 56.4 months and 34.9 months, respectively (HR=0.58, P<0.0001), and the negative conversion rate of minimal residual disease was 24% and 2%, respectively. The 2-year survival rate was 91% and 84%, the 5-year survival rate was 66% and 57%, and the total mortality rate was 37% and 45%, respectively. And there is no new or unexpected security event.

Compared with Chl monotherapy group, median PFS of obinutuzumab combined with Chl group was significantly prolonged (31.1 months vs 11.1 months; HR=0.21, P<0.0001), median OS was not reached and 66.7 months, respectively (HR=0.68, P=0.0196), and median time to start subsequent treatment was 55.7 months and 15.1 months, respectively (HR=0.25, P<0.0001).

Researchers pointed out that obinutuzumab combined with Chl group has better curative effect, and these newly treated patients are older, accompanied by typical senile diseases, such as hypertension, diabetes, heart failure, chronic obstructive pulmonary disease or renal damage. In addition, the combined scheme is also effective for patients with IGHV mutation and non-mutation.[23]

The clinical trials of obinutuzumab as monotherapy or in combination with chemotherapy focusing on CLL are summarized in Table 2.

Safety and tolerability

The severe toxicity most commonly seen associated with obinutuzumab was infusion-related reactions (IRRs). There are several mechanisms for the increased incidence of IRRs. Due to the high affinity of obinutuzumab for FcγRIII, thus the firm binding to CD20 and the subsequent FcγR triggering would leads to effector cell recruitment. The cytokine releases potently subsequently and the clinical symptoms then appear, especially in severe CLL patients. Cytokine profiling manifested that with the first obinutuzumab infusion, the levels of TNF-α and IFN-γ, together with the IL-6 and IL-8 increased significantly, while that of circulating B-lymphocytes drop instead, often showing cytopenias, especially neutropenia. Preclinical models presumed the mechanism underlying the more pronounced neutropenia is that the obinutuzumab-mediated ADCP can strengthen the recruitment and consumption of neutrophils.[24]

So far, the IRRs and the more pronounced cytopenias were well managed in clinical trials and the therapeutic efficacy was not influenced.

Table 2 Clinical trial of obinutuzumab

Trials	Phase	Dose (mg)	No. of pts	Treatment	Best response
GAUGUIN	I	400–1200	13	O	ORR 62%
GAUGUIN	II	1000	20	O	ORR 30%
GALTION	Ib	1000	20	O+B	ORR 90%
GALTION			21	O+FC	ORR 62%
GAGE	II	1000	41	O	ORR 49%
GAGE		2000	39	O	ORR 66%
CLL11	III (stage 1)	1000	238	O+C	ORR 31%
CLL11			233	R+C	ORR 79%
CLL11	(stage 2)		330	R+C	ORR 65%
CLL11			333	O+C	ORR 78.4%

Abbreviations: O, obinutuzumab; B, bendamustine; FC, fludarabine/cyclophosphamide; R, rituximab; C, chlorambucil; ORR, overall response rate.

Elderly patients and patients with complications

The first-line standard treatment for CLL is the FCR therapy, which has been reported to improve PFS in patients with progressive disease. However, elderly patients or patients with complications cannot well tolerate such treatment, whom are usually treated using the Chl. They can tolerate the chlorambucil well tolerated as a single agent, but the treatment efficacy is limited. Moreover, the combination therapy of an anti-CD20 mab with Chl can improve the response rates of the patients and prolong the PFS in these patients, with barely toxicity increased. Therefore, the European Society for Medical Oncology (ESMO) guidelines recommend to combine the Chl and an anti-CD20 antibody, such as rituximab, ofatumumab or obinutuzumab for treating CLL in those untreated patients having relevant complications, but no TP53 deletion/mutation.[25] There is still debate on which anti-CD20 antibody to choose. Nevertheless, obinutuzumab has been found to have a better treatment efficacy, compared with its counterparts.[25] However, the combination of obinutuzumab–Chl can lead to certain toxicity that needs to be addressed throughout the therapy.[26]

A retrospective analysis showed that 86 elderly CLL patients, accompanying with severe complications, with the median age as 74 years old, were treated with obinutuzumab-chlorambucil as a first-line regimen. The cumulative disease assessment scale scores of all patients were greater than 6 and/or creatinine clearance rates were 30 to 69 mL/min. Two months after treatment, the overall remission rate has improved to 95.3%, with the complete remission rate as 43% and the partial remission rate (PR) 52.3%. The stable incidence of disease was 4.7%. No depression was observed after treatment. The median PFS was not achieved until a median of 18-month long follow-ups, and the PFS of 30 months was estimated to be 62%. We observed 6 cases of recurrence (7%), 3 cases (3.5%) and 3 cases (3.5%) of PR after immunochemotherapy, where the most common adverse outcomes were neutropenia and infusion-related response (IRR). The incidence of grade III m,neutropenia was 11.6%, and that of grade III IRR was 2.3%. What's more, no adverse events were observed at level 4 or 5. Their data confirm that the combination of obinutuzumab and nitrogen mustard phenylbutyrate can serve as an effective and well-tolerated treatment for the complications in patients with untreated CLL.[27]

Combination therapy with the obinutuzumab

Many lines of research are now exploring ways in which targeted therapy can improve outcomes in CLL; a number of potential therapeutic targets have been identified. Use of obinutuzumab in combination with agents targeting other cellular pathways or receptors is now being explored (see Table 3).

Apoptosis pathway-targeting agents venetoclax (ABT-199 GDC-0199)

BCL-2 now is one of the heated clinical research targets of CLL. Venetoclax selectively acts on BCL-2, has high affinity for BCL-2, and has low affinity for BCL-XL, MCL-1, etc (other BCL-2 family anti-apoptosis proteins).[28–31]

Combination studies of venetoclax and obinutuzumab have been initiated. In vitro studies have measured direct cell death induction/apoptosis in primary CLL patient samples and the effect of BCL-2 inhibition on ADCC induction.[32] Venetoclax enhanced cell death when combined with obinutuzumab or rituximab in vitro, with more pronounced effects for venetoclax plus obinutuzumab at lower concentrations.

Table 3 Clinical trial of combination obinutuzumab with other new agents

Clinical trial	Phase	Population	Regimen	Status
NCT02242942	3	Untreated CLL	O+ABT-199 vs O+CLB	Active
NCT02950051	2	Untreated CLL	FCR/BR or ABT-199+R or ABT-199+O or ABT-199+R+O	Recruiting
NCT01685892	1b	Relapsed/refractory CLL or untreated CLL	O+ABT-199	Active
NCT02264574	3	Untreated CLL	Ibrutinib reduces obinutuzumab infusion related reactions in patients with chronic lymphocytic leukemia and is associated with changes in plasma cytokine levels+O vs O+Chl	Active
NCT02427451	1b/2	Relapsed/refractory CLL or untreated CLL	ABT-199+O+Ibrutinib	Recruiting
NCT02315768	1/2	Untreated CLL	O+Ibrutinib	Active
NCT02475681	3	Elderly and unfit adult patients with first-line CLL	ACP-196+O or Chl+ACP-196+O	Active
NCT02296918	1	Relapsed/refractory CLL or untreated CLL	ACP-196+O	Active
NCT02968563	2	Relapsed/refractory CLL	Tirabrutinib+Idelalisb+O	Active
NCT01644253	1b	Relapsed/refractory CLL or untreated CLL	TRU-016+R vs TRU-016+O	Active
NCT02100852	1	CLL (no defined)	TGR-1202+Chl+O	Active
NCT01644253	1b	Relapsed/refractory CLL or untreated CLL	TRU-016+R vs TRU-016+O	Active
NCT02225275	2	Relapsed/refractory CLL	O+L	Active
NCT02401503 (CLL2-BAG)	2	First-line/relapsed/ refractory CLL	B→O/ABT-199	Active
NCT02445131 (CLL2-BCG)	2	Relapsed/refractory/ First-line/CLL	B→O+Idelalisb	Active
NCT02758665 (CLL2-Give)	2	Untreated CLL with TP53 deletion (17p-) and/or mutation	ABT-199+Ibrutinib+O	Active
NCT02983617	2	Relapsed or refractory CLL	Tirabrutinib+Entospletinib+O vs Tirabrutinib+Entospletinib	Active
NCT02612311	3	CLL	Ublituximab+TRG-1202 vs O+Chl	Active
NCT02320487	2	Untreated CLL	B+O	Completed
NCT03755947	2	First and second line for patients with CLL	Ibrutinib+O+ABT-199	Recruiting
NCT03529227	–	CLL with certain comorbidities	O+Chl	Active

(*Continued*)

Table 3 (Continued).

Clinical trial	Phase	Population	Regimen	Status
NCT03462719	3	Untreated CLL	Ibrutinib+ABT-199 vs O+Chl	Active
NCT03701282	3	Untreated younger patients with CLL	Ibrutinib+O+ABT-199 vs Ibrutinib+O	Recruiting
NCT03737981	3	Older people with untreated CLL	Ibrutinib+O+ABT-199 vs Ibrutinib+O	Recruiting
NCT03516617	2	Early stage CLL	ACP-196+O	Recruiting

Abbreviations: B, bendamustine; BTKi, Bruton tyrosine kinase inhibitor; Chl, chlorambucil; CLL, chronic lymphocytic leukemia; FC, fludarabine plus cyclophosphamide; L, lenalidomide; PI3Ki, phosphatidylinositol-3 kinase inhibitor; R, rituximab; O, obinutuzumab.

Furthermore, venetoclax did not affect NK cell-mediated ADCC or B-lymphocyte depletion induced by obinutuzumab or rituximab. Similar robust antitumor effects were also seen in primary patient CLL samples.[32]

Phase 1b study (NCT01685892) of venetoclax-obinutuzumab in previously untreated and relapsed/refractory chronic lymphocytic leukemia shows that the regimen has an acceptable safety profile and elicited durable responses and high rates of undetectable MRD.[33]

The CLL14 study (NCT02242942; Table 3) showed that among patients with untreated CLL and coexisting conditions, venetoclax-obinutuzumab was associated with longer PFS than chl-obinutuzumab.[34]

B-cell receptor pathway inhibitors

Ibrutinib

Bruton's tyrosine kinase (BTK) plays a key role in BCR signaling, which regulates the proliferation and survival of B-cell.[35] The small molecule drug ibrutinib was the first BTK inhibitor to be introduced. Ibrutinib is approved for use in patients with pretreated MCL, CLL/SLL whether with 17p deletion or not, and in Waldenström's macroglobulinemia (WM).[36] Consider that BTK is a downstream mediator of BCR signaling, there has been interest in the clinical potential of combining BTK inhibitors with other immunotherapeutic agents.

Results from the phase III iLLUMINATE trial (NCT02264574) showed that ibrutinib plus obinutuzumab was an effective chemotherapy-free treatment regimen compared with the chemoimmunotherapy regimen chlorambucil and obinutuzumab in patients with treatment-naïve CLL.[37]

In January 2019, the FDA approved the combination of ibrutinib plus obinutuzumab for the treatment of patients with CLL/SLL in the first-line setting based on these trial data, making it the first chemotherapy-free regimen that includes an anti-CD20 antibody approved in the United States to treat this patient population.

The clinical trial (NCT02315768) found that the combination of ibrutinib with obinutuzumab reduces the number and severity of IRR in previously untreated patients with CLL and is associated with changes in plasma cytokine levels.[38]

The BIG regimen (NCT02345863) is a sequential treatment with bendamustine, ibrutinib and obinutuzumab in chronic lymphocytic leukemia, which has proved to be a safe and highly effective therapy for CLL.[39]

Second-generation BTK inhibitors

Other second-generation BTK inhibitors like ACP-196 (acalabrutinib) have been developed to improve on the safety profile of ibrutinib and enhance its pharmacodynamic profile by reduced "off-target" inhibition.

PI3K inhibitors

Idelalisib, the earliest commercially available oral selective phosphoinositide 3-kinase delta (PI3K-delta, P110-delta) inhibitor, was authorized by the FDA of America to be applied in the clinic for the treatment of the relapsed/refractory small lymphocytic lymphoma, follicular non-Hodgkin lymphoma and the CLL.[40–42]

Some clinical studies investigating idelalisib combined with other agents in hematologic malignancies were terminated because of reports of toxicity. This included a phase III study comparing obinutuzumab plus idelalisib or chlorambucil in patients with previously untreated CLL (NCT01980875). Other studies are still in progress and include a phase II efficacy and safety trial of idelalisib with and without obinutuzumab in relapsed/refractory CLL (NCT02968563), and a phase Ib trial of otlertuzumab

(TRU-016) and rituximab, obinutuzumab, idelalisib or ibrutinib in previously untreated CLL (NCT01644253).

Other PI3K inhibitors with a potential for combination with obinutuzumab include duvelisib,[42] copanlisib,[43] and TGR-1202.[44]

Novel mAb and antibody–drug conjugates

Under investigation, another B-cell target is CD37 is. Otlertuzumab (TRU-016) contains an anti-CD37 single-chain variable fragment which is connected with the heavy and light chain fused to immunoglobulin G1 via its Fc domain. Compounds of this type to induce apoptosis and are associated with ADCC in B-cell leukemia or lymphoma cell lines and CLL cells.[45]

Immunomodulators

Thalidomide analog lenalidomide is an immunomodulator with direct tumoricidal and immunomodulatory effects. Direct cytotoxicity caused by actin aggregation and membrane protein repositioning can cause cell cycle arrest and cytoskeleton reorganization, further prevent autocrine cytokines and oncogenes, and induce tumor suppressor genes. Moreover, at the molecular level, lenalidomide interacts with brain protein, which is the substrate receptor of the ubiquitin ligase complex of Cullin 4 RING E3, thus degrading IKZF1 and IKZF3. Lenalidomide plus anti-CD20 therapy may have therapeutic potential in recurrent/refractory CLL.[45]

Inhibitory killer cell Ig-like receptors (KIRs) can mediate NK cell-mediated ADCC,[13] which interact with the class I HLA on the target cells. This KIR/HLA interaction selectively inhibits rituximab-induced ADCC in cells expressing homologous HLA KIR ligands and has several other effects on rituximab activity.[13] Conversely, obinutuzumab triggers the activation of NK cells without expressing KIR.[46] Interestingly, stronger FcgRIIa (CD16) activation induced by obinutuzumab may also help abrogate inhibitory signals by inhibitory KIR/HLA interactions.[47] Analysis of the association between KIR/HLA genotype and the outcomes of treatment using data from the CLL11 study[47] showed consistently better outcomes in patients with lower numbers of KIR/HLA interactions. This was particularly notable in the obinutuzumab plus chlorambucil arm. The authors indicated that the combination therapy of KIR blockade and anti-CD20 drugs warrants investigation.

Conclusion

The application of the anti-CD20 mab rituximab has provided new perspectives for the treatment of CLL. Obinutuzumab, the second-generation of anti-CD20 mAb, has been reported to increase the affinity of antibody to FcγRIIIa through glycosylation technology, thus enhancing ADCC and weakening CDC. At present, the drug has also been approved to combine with chlorambucil to treat untreated CLL patients.

The clinical application of obinutuzumab is still being explored. The preliminary data suggest that obinutuzumab, compared with rituximab, can produce a higher objective response rate. But this may also be because that a higher doses obinutuzumab is given than rituximab clinically.

All in all, obinutuzumab is a drug with promising potential that can actively combat against the CLL, which seems to employ a higher potential than other anti-CD20 mAb. Moreover, owing to its moderate toxicity, it can be readily used solely or to keep accompany with the other chemotherapeutic medicine. To better apply obinutuzumab clinically and obtain better prognosis of CLL patients, more clinical trials are needed, particularly those analyzing the effects of obinutuzumab solely or in combination with other novel drugs.

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Disclosure

The authors report no conflicts of interest in this work.

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