Recent Advances in Therapeutics for B-Cell Lymphoma

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Abstract: Objectives: The molecular targeting drugs for the treatment of B-cell lymphoma have been dramatically developed. Recently, novel drugs of monoclonal antibodies and small molecules are approved by US FDA (Food and Drug Administration). Key Findings: This review summarizes characteristics, mechanisms, and results of the trials in the novel molecular targeting drugs for B-cell lymphoma such as obinutuzumab, polatuzumab vedotin, ibrutinib, idelalisib, and venetoclax. Summary: As a novel anti-CD20 antibody, obinutuzumab has been clinically developed on going. ADC (antibody drug conjugate) against CD79b molecules is also developed for B-cell lymphoma. BCR pathway is one of the most crucial pathways, and ibrutinib is a BTK (Bruton's tyrosine kinase) inhibitor that is under development for the treatment of B-cell malignancies, including CLL (chronic lymphocytic leukemia), MCL (mantle cell lymphoma), and DLBCL (diffuse large B-cell lymphoma), as well as FL (follicular lymphoma). BCL-2 family dysfunction and impairment of apoptosis are common in most B-cell lymphoid malignancies. Venetoclax, which is a highly selective BCL-2 inhibitor, a mimic for its BCL2 homolog 3-domain to induce apoptosis, is also reported to be active against B-cell malignancies. Conclusions: Mechanism-based combination regimens including these drugs may be required in the future.

Key words: obinutuzumab, polatuzumab vedotin, ibrutinib, idelalisib, venetoclax.

1. Introduction

In the past decade, the treatment for B-cell lymphoma has been developed largely. Rituximab, a chimeric monoclonal antibody that targets against CD20 molecule, is the first monoclonal antibody approved for the treatment of B-cell lymphoma 20 years ago [1]. It has been shown that rituximab exerts cytotoxic activities through CDC (complement-dependent cytotoxicity) and ADCC (antibody-dependent cell-mediated cytotoxicity), and that it directly induces apoptosis. The proven clinical efficacy and success of rituximab has led to development of the other anti-CD20 antibodies such as ofatumumab [2] and obinutuzumab [3] in recent years. Moreover, ADCs (antibody-drug conjugates) against CD22 and CD79b molecules are also developed for B-cell lymphoma [4]. On the other hands, the small molecule inhibitors targeting apoptosis pathways, proteasome, and other pathways of B-cell lymphoma are being developed as novel drugs for B-cell lymphoma. Especially, BCR (B-cell receptor) pathway

is one of the most crucial pathways for cell growth, anti-apoptosis of B-cell malignant cells [5]. Ibrutinib is a small molecule, once-daily, orally available, BTK (Bruton's tyrosine kinase) inhibitor [6] that is under development for the treatment of B-cell malignancies, including chronic lymphocytic leukemia, mantle cell lymphoma, and diffuse large B cell lymphoma, as well as follicular lymphoma. Here, I will discuss about development of novel drugs for B-cell lymphoma in the present and the future.

2. Novel Drugs for B-Cell Lymphoma

2.1 Obinutuzumab

Obinutuzumab is a glycoengineered type II anti-CD20 monoclonal antibody (mAb) currently approved for use in previously untreated CLL (chronic lymphocytic leukemia) in combination with chlorambucil, as well as for treatment of rituximab-refractory FL (follicular lymphoma) [7, 8]. Obinutuzumab is distinguished from rituximab by two molecular features. Absence of fucosylation at Fc portion in obinutuzumab results in enhanced ADCC activity [9], and type II-mediated mechanism of action

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of obinutuzumab is characterized by enhanced direct cell death induction [10].

Since preclinical studies and early phase studies of obinutuzumab monotherapy and combination therapy in B-cell malignancies have succeeded, obinutuzumab plus chemotherapy has been investigated in four phase 3 trials (Table 1).

The GALLIUM study was designed as a comparison of the efficacy and safety of obinutuzumab or rituximab plus chemotherapy followed by maintenance immunotherapy in previously untreated indolent NHL [11]. Obinutuzumab plus chemotherapy demonstrated a significantly reduced risk of progression or death relative to rituximab plus chemotherapy in FL (hazard ratio [HR] 0.66, 95% CI [confidence interval] 0.51-0.85 ($p = 0.001$)).

In the GADOLIN study, patients with rituximab-refractory indolent NHL were randomized to bendamustine monotherapy (120 mg/m² for six cycles) or obinutuzumab plus bendamustine (90 mg/m² for six cycles) followed by obinutuzumab maintenance

[12]. Updated results confirmed the PFS benefit and showed OS benefit in favor of obinutuzumab arm.

In the GOYA trial, previously untreated patients with DLBCL were randomized to obinutuzumab or rituximab every 21 days for eight cycles in combination with 6-8 cycles of CHOP-based chemotherapy [13]. Final analysis showed no significant difference in PFS between obinutuzumab and rituximab treatment arms. However, a trend toward benefit with obinutuzumab compared to rituximab was observed in the germinal center B-cell-like, but not the activated B-cell-like, patients.

In the CLL11 trial, patients previously untreated CLL were randomized to chlorambucil plus obinutuzumab or chlorambucil plus rituximab or chlorambucil alone for six cycles [14, 15]. Both combination therapies significantly improved PFS compared to chlorambucil alone. On the other hands, obinutuzumab arm, but not rituximab arm, significantly prolonged OS.

Table 1 Phase 3 trials of obinutuzumab in patients with B-cell NHL or CLL.

Trials	Number of patients	Regimens	Responses
Gallium (FL, first-line)	601 601	CHOP x6 or CVP x 8 or BEN x 6 + G, G maintenance (2 years) CHOP x6 or CVP x 8 or BEN x 6 + R, R maintenance (2 years)	PFS: G>R, HR 0.66 ($p = 0.001$) OS: G>R, HR 0.75 ($p = 0.21$) TTNT: G>R, HR 0.68 ($p = 0.01$) CR 12% ORR 63% Median PFS 15 mo
GADOLIN (Rituximab-refractory indolent NHL)	202 (198 treated) 194	BEN (120 mg/ m ²) x 6 BEN (90mg/m ²) x 6 + G G maintenance (2 years)	CR 11% ORR 69% Median PFS not reached ($p = 0.0001$) PFS: HR 0.92 ($p = 0.3868$) No differences in OS, TTNT, and other endpoints
GOYA (DLBCL, first-line)	706 712	CHOP x 6-8 + G CHOP x 6-8 + R	Chlorambucil + G vs. Chlorambucil Median PFS: 31 vs. 11 mo (HR 0.20, $p < 0.0001$) Median OS: NR vs. 59 mo (HR 0.62, $p < 0.0167$)
CLL11 (CLL, first-line)	781	Chlorambucil Chlorambucil + G Chlorambucil + R	Median TTNT: 51.1 vs. 15.1 mo (HR 0.24, $p < 0.0001$) Chlorambucil + G vs. Chlorambucil + R Median PFS: 29 vs. 16 mo (HR 0.46, $p < 0.0001$) Median OS: trends (HR 0.77, $p = 0.0932$) Median TTNT: 51.1 vs. 38.1 mo (HR 0.57, $p < 0.0001$)

In the GALLIUM, GOYA, and CLL11, the risk of infusion-related reaction in cycle 1 seems to be higher with obinutuzumab than with rituximab, but the infusion-related reaction occurred with low and similar frequency in subsequent cycles

2.2 Polatuzumab Vedotin

A novel therapeutic approach is the introduction of ADCs (antibody drug conjugates) in which cytotoxic drugs are conjugated to antibodies against antigens expressed on tumor cells [16]. Recently, ADC has been shown to be effective in the treatment of malignant lymphoma. Brentuximab vedotin against CD30 achieved high response rates in patients with relapsed/refractory CD30-positive Hodgkin's lymphoma and anaplastic large-cell lymphoma [17, 18].

CD22 and CD79b are expressed in the vast majority of B cells and therefore represent promising targets for ADCs. Preclinical data for an anti-CD79b antibody conjugated to the microtubule-disrupting agent MMAE (monomethyl auristatin E) showed the efficacy in several B-cell lymphomas including DLBCL and FL [19-21].

Polatuzumab vedotin is an anti-CD79b monoclonal antibody conjugated to MMAE. In a phase I study, this drug was administrated at escalating dose from 0.1 to 2.4 mg/kg for 34 NHL and 18 CLL patients [22]. The recommended dose for phase 2 trial was 2.4 mg/kg as a single agent and in combination with rituximab. On the other hands, MTD in CLL was 1.0 mg/kg due to DLT. In the phase 2 of the study, 34 NHL patients to the single agent arm and nine NHL patients to the rituximab combination arm were enrolled. The most common Grade 3-4 AEs (adverse events) in the single-agent arm were neutropenia (40%), anemia (11%), and sensory neuropathy (9%). In the combination therapy, 77% of patients showed grade 3-4 AEs including neutropenia, febrile neutropenia, and anemia. Objective and durable responses were observed in 23 of 42 patients (54.8%) with NHL in the

single-agent arm and seven of nine (77.8%) in the combination arm. In CLL patients, no responses were observed. Moreover, Morschhauser et al. [23] reported the results of a phase 2 randomized trial of polatuzumab vedotin and rituximab for patients with relapsed/refractory NHL. Fifty-nine patients received polatuzumab vedotin (2.4 mg/kg) plus rituximab (375 mg/m²) every 21 days. Patients included 39 with DLBCL and 20 with FL. An additional 20 patients received polatuzumab vedotin (1.8 mg/kg) plus rituximab (375 mg/m²) every 21 days in nonrandomized cohort. The overall response rate (ORR) in DLBCL was 56% with 15% of CR (complete response) rate, and median PFS was 5.4 months. The ORR in FL was 70% with 40% of CR rate, and median PFS was not reached. The patients receiving polatuzumab vedotin at dose of 1.8 mg/kg showed only PR in seven cases (44%). The most common AEs in polatuzumab vedotin arm included fatigue (55%), diarrhea (43%), nausea (37%), peripheral neuropathy (39%), neutropenia (27%), constipation (26%), sensory neuropathy (25%), and decreased appetite (25%). Serious AEs were reported 36% in polatuzumab vedotin arm. Treatment discontinuation was reported in 41% of patients, mostly due to peripheral neuropathy with median time of 5.6 months.

2.3 BCR Pathway-Targeted Drugs (Small Molecules)

The BCR (B-cell receptor) has been recognized as an important pathway in B cell development as well as B-cell lymphomas (Fig. 1) [24]. Various approaches for the treatments have been tried to target this pathway. Regarding these approaches, targeting Syk [25], phosphatidylinositol-3 kinase delta (PI3K delta) [26], and BTK (Bruton's tyrosine kinase) showed preclinical and clinical activities such as the BTK inhibitor ibrutinib and the PI3K inhibitor idelalisib.

2.4 BTK Inhibitor Ibrutinib

Ibrutinib is the first-in-class orally bioactive small molecule inhibitor of BTK and acts by forming a stable

Fig. 1 BCR signaling pathway and their inhibitors.

covalent bond to the amino acid cysteine at position 481 in the BTK active site [27]. Although ibrutinib shows a short half-life, the covalent binding nature and high selectivity allows a once-daily dosing with a complete occupancy of the BTK active site in peripheral mononuclear cells [28]. Moreover, BTK activation plays a major role in other B cell lymphomas as well as CLL.

MCL (mantle cell lymphoma) is a rare subtype of non-Hodgkin's B-cell lymphoma characterized by the translocation [11, 14] with Cyclin D1 activation. MCL often shows an aggressive clinical course with poor prognosis. Younger patients (< 65 years old) are treated with intensive chemotherapy such as R-hyper CVAD/MA regimen followed by autologous stem cell transplantation [29]. Elderly patients were commonly treated with more tolerable immunochemotherapies such as bendamustine plus rituximab [30, 31], VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisolone) with rituximab maintenance as front-line therapy as frontline therapy [32]. In spite of high OOR with these frontline therapies, prognosis of most MCL patients is not improved so far. Therefore, since pathogenesis of MCL

is biologically related to chronic BCR signaling, BTK inhibitor was tested in this lymphoma. Data of a phase 1 study for ibrutinib in relapsed/refractory MCL patients showed high efficacy (28). A phase 2 study in 111 relapsed/refractory MCL patients showed OOR of 68% with 21% CR and median PFS of 13.9 months [33]. Finally, a phase 3 trial compared ibrutinib monotherapy with temsitorimus monotherapy [34]. Ibrutinib showed better tolerability and significant higher response rates in relapsed/refractory MCL patients (ORR 72% versus 40%, $p < 0.001$). Median PFS was significantly prolonged (14.6 vs. 6.2 months, $p < 0.0001$).

Combination with ibrutinib and rituximab showed response in almost all patients with non-blastoid MCL with low Ki67 index, whereas early relapses were frequently seen in patients with aggressive disease [35].

Nodal Marginal zone lymphoma (MZL) is a rare indolent lymphoma. Since Nodal MZL is small population and heterogeneous, clinical study are few and mostly small. Therefore, patients are treated as patients with indolent lymphoma groups. MZL is also associated with chronic inflammation, leading to

continuous B cell stimulation by BCR signaling. A phase 2 trial for single-agent ibrutinib in patients with relapsed/refractory MZL showed high efficacy by disrupting the BCR signaling with ibrutinib [36]. Patients with at least one prior anti-CD20-based therapy showed ORR of 51% with median duration of response of 19 months. FDA approved ibrutinib for MZL by this data in January 2017.

2.5 PI3K Inhibitor Idelalisib

Another critical molecule for BCR pathway is PI3K in survival of CLL and FL cells. Idelalisib is a first-in-class, reversible, potent, selective PI3K δ inhibitor [37], and induces cell cycle arrest in G0/G1 phase inhibiting proliferation and apoptosis in B-cell by caspase activation.

A phase 1 study of single-agent idelalisib in 54 patients with relapsed/refractory CLL showed ORR of 75% and median PFS of 15.8 months [38]. From this result, a phase 3 study was conducted as a randomized, double-blind, placebo-controlled trial on 220 patients with previously treated CLL. The patients, including high-risk patients with del17p, TP53 mutation, or IGHV lack, were randomized to receive rituximab plus idelalisib (150 mg BID) or placebo twice daily. The PFS in idelalisib versus placebo at 24 weeks was 93% versus 46% ($p < 0.001$), and OS at 12 months was 92% versus 80% ($p = 0.02$), respectively [26].

The role of single-agent idelalisib in relapsed indolent NHL was investigated in a phase 2 trial with 125 patients including FL ($n = 72$), SLL ($n = 28$), MZL ($n = 15$), and lymphoplasmacytic lymphoma ($n = 10$). The ORR was 57%, and the median duration of response was 12.5 months. The median PFS and OS

were 11 months and 20.3 months, respectively (Table 2) [39].

The AEs related to idelalisib combining three most recent clinical studies are listed in Table 3 [26, 39, 40]. In the relapsed CLL study, the most common AEs in the idelalisib plus rituximab arm were fatigue (24%), nausea (24%), diarrhea (19%), fever (29%), and chills (22%). SAEs (Serious AEs) included pneumonia (6%), febrile neutropenia (5%), diarrhea (3%), pyrexia (6%), and dyspnea (1%). Laboratory abnormalities included elevation in alanine transaminase/aspartate transaminase, mostly occurring within the first 12 weeks of the treatment. Others were anemia, neutropenia, thrombocytopenia, and lymphocytosis.

In relapsed/refractory indolent NHL study, the most common AEs with single-agent idelalisib included diarrhea (13%) and pneumonia (7%). Dose reduction from 150 mg BID to 100 mg BID was required in 34% of indolent NHL patients due to AEs such as hepatotoxicity, colitis, and pneumonia [40].

2.6 Anti-apoptosis Molecule Mimetic Drug

Apoptosis is an evolutionarily conserved process of cell death which plays a critical role in homeostasis [41]. There are two different apoptosis pathways: the “extrinsic pathway” and the “intrinsic pathway”. The intrinsic pathway is triggered by a range of signals, such as DNA damage, growth factor-deprivation, and the release of apoptogenic proteins, including cytochrome *c*. BCL-2 gene product was the first anti-apoptosis protein discovered as fusion gene of t [14, 18] chromosomal translocation, which is the hallmark of FL [42]. Thereafter, more than 20 of BCL-2 family members have been identified so far.

Table 2 Efficacy of idelalisib in patients with previously treated indolent NHL.

Outcomes	Indolent NHL (previously treated, $n = 125$)
Median PFS (months)	11
Overall response rate	57%
Complete response	6%
Partial response	50%
Lymph node response	90%
OS (12 months)	80%

Table 3 Adverse events and laboratory abnormalities of idelalisib.

AEs	Idelalisib+R (n = 110)		Idelalisib+placebo (n = 107)		CLL front-line (n = 64)		Indolent NHL previously treated (n = 125)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Pyrexia	32 (29)	3 (3)	17 (16)	1 (1)	27 (42)	2 (3)	35 (28)	2 (2)
Fatigue	26 (24)	3 (3)	29 (27)	2 (2)	20 (31)	0	37 (30)	2 (2)
Nausea	26 (24)	0	23 (21)	0	24 (38)	1 (2)	37 (30)	2 (2)
Chills	24 (22)	2 (2)	17 (16)	0	23 (36)	0	-	-
Diarrhea	21 (19)	4 (4)	15 (14)	0	25 (39)	11 (17)	54 (43)	16 (13)
Infusion-related reaction	117 (15)	0	30 (28)	4 (4)	-	-	NA	NA
Cough	16 (15)	0	27 (25)	2 (2)	21 (33)	1 (2)	36 (29)	0
Constipation	13 (12)	0	12 (11)	0	11 (17)	0	-	-
Decreased appetite	13 (12)	0	9 (8)	1 (1)	-	-	22 (18)	1 (1)
Vomiting	13 (12)	0	8 (7)	0	14 (22)	2 (3)	19 (15)	3 (2)
Dyspnea	12 (11)	2(2)	10 (19)	3 (3)	16 (25)	4 (6)	22 (18)	4 (3)
Night sweats	11 (10)	0	8 (7)	0	10 (16)	0	14 (11)	0
Rash	11 (10)	2 (2)	6 (6)	0	37 (58)	8 (13)	16 (13)	2 (2)
AST/ALT elevation	38 (35)	6 (5)	20 (19)	1 (1)	43 (67)	15 (23)	59 (47)/44 (35)	16 (15)/10 (8)
Anemia	28 (25)	6 (5)	32 (30)	15 (14)	15 (23)	2 (3)	35 (28)	2 (2)
Neutropenia	60 (55)	37 (34)	52 (49)	24 (22)	34 (53)	18 (28)	70 (56)	34 (27)
Thrombocytopenia	19 (17)	11 (10)	28 (26)	17 (16)	9 (14)	1 (2)	32 (26)	8 (6)

The anti-apoptotic proteins such as BCL-2, BCL-X_L, BCL-W, BFL-1/A1, and MCL-1 have four BH (BCL-2 homology) domains and interact with other BCL-2 family proteins to prevent mitochondrial outer membrane permeabilization, which is the key point of “no return” in the intrinsic pathway.

2.7. Venetoclax

Venetoclax was developed as a highly BCL-2-selective BH3-mimetic. It has a strong affinity only for BCL-2, with 100-fold less affinity for other BCL-2 family such as BCL-X_L or BCL-W. As well as navitoclax, which is another BH3-mimetic and inhibits not only BCL-2 but also BCL-X_L or BCL-W, *in vitro* cytotoxicity of venetoclax is dependent on the presence of BAX and BAK, which in turn leads to cell death by apoptosis [43].

Venetoclax was first tested in relapsed/refractory CLL patients. It induced lymphocyte reduction in a dose-dependent manner without thrombocytopenia [44]. The first clinical trial of venetoclax was a phase 1 dose escalation study that enrolled 116 patients with

relapsed/refractory CLL or SLL (small lymphocytic lymphoma), of which 92 (79%) had a response and 20% achieved CR, including 5% with MRD negative as assessed by flow cytometry. Objective responses were common among patients with resistance to fludarabine with del17p and unmutated IGHV. PFS estimated for the 400 mg dose groups was 69% (Table 4) [44]. In Phase 2, single-arm, multicenter study of venetoclax conducted exclusively in CLL patients with del17p, 107 patients were enrolled [45]. ORR determined by an independent review was achieved in 85 (79.4%) patients with a median follow-up of 12.1 months. Response rates were similar regardless of refractory to prior fludarabine-based therapy. The clinical responses of CLL patients were also independent of del17p, TP53 mutation, and TP53 function [46]. Recently, a phase 2, open label, two-arm study reported the outcome of single-agent venetoclax in 64 CLL patients who relapsed after, or were refractory to ibrutinib or idelalisib, of whom 43 were on prior ibrutinib (Arm A) and 21 on prior idelalisib (Arm B). ORR by an independent review for Arm A

Table 4 Clinical trials of single-agent venetoclax in CLL and B-cell malignancies.

Diseases	Phase	Number of patients	ORR	CR+CRi
R/R CLL	1	116	79%	20%
R/R CLL with del17p	2	107	79%	12.1%
R/R CLL	2	120	70% (post-ibrutinib) 48% (post-idelalisib)	Not reported
R/R NHL	1	106	18% (DLBCL, 6/34) 35% (FL, 11/29)	Not reported

Fig. 2 Developing rational combination therapies based on biological knowledge in DLBCL.

and Arm B was 70% and 48%, respectively. At the time of analysis, neither the PFS nor the OS has been reached. The estimated 12-month PFS was 72%, and OSI was 90% for the overall group. This study demonstrated that venetoclax had strong activity in CLL patients who progressed during or after treatment with ibrutinib or idelalisib (Table 4) [47].

Single-agent venetoclax was also investigated in a phase 1 study in patients with relapsed/refractory NHL. The ORR varied in the different histologic subgroups, with the highest rates observed in WM (100% including all PR) and MCL (75% including 21% CR). Responses were less frequent in FL (ORR: 38%, CR: 14%) and DLBCL (ORR: 18%, CR: 12%), and the median duration of response of DLBCL was only 3.3 months (Table 4) [48].

3. Future

Recently, many molecular targeting drugs have been

developed so far and will be done in the future. However, these drugs need to be selected to match each patient or each disease. For instance, DLBCL represents the most common type of non-Hodgkin lymphoma. Although histologically well defined, DLBCL is heterogeneous at the molecular level. Patients with DLBCL have variable response to standard RCHOP therapy, which cures about 50% of the patients. There is robust evidence for oncogenic cooperation between MYC, BCL2, and activated PI3K signaling pathway in lymphomagenesis, providing an opportunity for developing mechanism-based therapy for MYC+/BCL2+/DLBCL (Fig. 2) [49]. Mechanism-based combination regimens including these drugs may be required for a future direction.

4. Conclusions

Now, many molecular targeting drugs for the treatment of B-cell lymphoma are available in clinical

practice. In the future, mechanism-based combination regimens including these drugs may be required for the treatment of B-cell malignancies.

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