

Update on Signal Inhibitors in Chronic Lymphocytic Leukemia

Prajwal Boddu, MD, and Nitin Jain, MD

Dr Boddu is a fellow and Dr Jain is an assistant professor with the Department of Leukemia at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Corresponding author:

Nitin Jain, MD

The University of Texas

MD Anderson Cancer Center

Department of Leukemia

1515 Holcombe Boulevard, Unit 428

Houston, Texas 77030

Tel: (713) 745-6080

E-mail: njain@mdanderson.org

Abstract: The last decade has seen major progress in our understanding of the pathobiology of chronic lymphocytic leukemia (CLL) and the identification of potential new therapeutic targets. As a result, researchers have developed novel targeted therapies, several of which are already approved and many of which are in advanced stages of clinical development. These new agents are much less toxic than chemoimmunotherapy and may be preferred for their superior efficacy in patients with certain high-risk features, such as del(17p). The place of these therapies in CLL management is becoming better defined, and they are gradually replacing traditional forms of chemoimmunotherapy. This review provides an update on the clinical data regarding various signal transduction inhibitors in CLL.

Introduction

Chronic lymphocytic leukemia (CLL) is the most common hematologic malignancy in the United States, with an estimated 20,110 new cases reported in 2017.¹ Since the introduction of the initial Rai and Binet clinical staging systems,^{2,3} the development of new molecular diagnostic methodologies has facilitated a much deeper understanding of the pathogenesis of CLL, and multiple high-risk cytogenetic, molecular, and mutational markers have been demonstrated to be variably associated with disease progression and survival.⁴⁻⁶

Until recently, chemoimmunotherapy was the standard treatment for CLL.⁷⁻⁹ Chemoimmunotherapy is not considered curative in CLL, however, and allogeneic stem cell transplant is fraught with morbidity and mortality risks. Additionally, chemoimmunotherapy is of limited efficacy in patients with high-risk cytogenetic features, such as del(17p).^{7,8} The need for improved treatment strategies has resulted in the development of several classes of novel targeted agents, including Bruton tyrosine kinase (BTK) inhibitors, phosphoinositide 3-kinase (PI3K) inhibitors, B-cell lymphoma/leukemia 2 (BCL-2) inhibitors, immunomodulators, monoclonal antibodies, cyclin-dependent kinase (CDK) inhibitors, spleen tyrosine kinase (SYK) inhibitors, checkpoint inhibitors, and genetically modified

Keywords

BCL-2, Bruton tyrosine kinase, ibrutinib, idelalisib, PI3K, venetoclax

chimeric antigen receptor (CAR) T-cell therapies.^{10,11} This report reviews the clinical data on various signal transduction inhibitors in CLL, with a particular focus on the agents targeting the BTK, PI3K, and BCL-2 pathways.

The B-Cell Receptor

B-cell receptor (BCR) signaling plays a key role in B-cell activation, proliferation, and survival. Antigen engagement with the BCR leads to the phosphorylation of immunoreceptor tyrosine-based activation motifs on immunoglobulins alpha and beta (Ig- and Ig-) via the SRC family kinase LYN, thus enabling the transmission of extracellular signals.^{12,13} Phosphorylation of these motifs subsequently leads to the recruitment and sequential activation of a series of nonreceptor protein tyrosine kinases—namely, SYK and BTK.^{14,15} Activated SYK coordinates with BTK and other linker and adaptor proteins in forming a plasma membrane-bound signaling complex, which is a critical event in the amplification and propagation of the activation signal.¹⁶⁻¹⁸ This complex activates and regulates key downstream signaling pathways, including phospholipase C 2/mitogen-activated protein kinase (PLC 2/MAPK), PI3K/AKT/mammalian target of rapamycin (mTOR), and RAS/RAF/ERK.¹⁹ The activation of signal intermediates leads to the activation of downstream transcription factors that promote cell growth and survival. Abnormal, constitutive BCR signaling has been implicated as a key pathway in B-cell leukemogenesis.²⁰ Thus, developing inhibitors that target BCR signaling at various points in the signal pathway is a rational strategy in drug development.²¹

BTK Inhibition

BTK is a nonreceptor kinase that belongs to the TEC kinase family and plays a key role in B-cell signaling and proliferation. Ibrutinib (Imbruvica, Pharmacyclics/Janssen) is an oral BTK inhibitor that irreversibly inhibits BTK phosphorylation. Early clinical activity of ibrutinib was first demonstrated as a part of first-in-human dose-escalation study in B-cell malignancies.^{22,23} Byrd and colleagues first reported on the outcomes of 85 patients with relapsed/refractory (R/R) CLL treated with 420 or 840 mg of ibrutinib in their phase 1b/2 study (Table).²⁴ Of all patients, 57% had Rai stage 3 or 4 disease, 69% harbored del(17p) or del(11q), and 79% had unmutated immunoglobulin heavy chain variable region (*IGHV*) status. The results were highly encouraging, with overall response rates (ORRs) of 71% in the 2 dosing groups; furthermore, an additional 20% and 15% of patients in the 420- and 840-mg groups, respectively, achieved a partial response with lymphocytosis (PR-L). These responses

were durable, with an estimated progression-free survival (PFS) rate of 75% at 26 months, and were found to be independent of the clinical and genomic risk factors present before treatment, including del(17p). Toxicities were acceptable, with the majority of patients experiencing grade 1 or 2 diarrhea, fatigue, or respiratory infections. In an extended follow-up of these patients over 5 years,²⁵ reported adverse events (AEs) of grade 3 or higher were hypertension, pneumonia, neutropenia, and atrial fibrillation. The ORRs were 86% for all treated patients, 84% for patients with treatment-naïve (TN) disease, and 86% for patients with R/R disease. The 30-month PFS rates with ibrutinib in the del(17p) group were inferior to those of the patients without any aberration (48% vs 74%, respectively), indicating the effect of cytogenetics on ibrutinib responsiveness. Patients who had del(11q) had superior PFS and OS compared with patients who had del(17p), but they still fared poorly compared with those who had no cytogenetic abnormalities.

These findings led to the phase 3 RESONATE trial comparing ibrutinib (n=195) with ofatumumab (Arzerra, Novartis; n=196) in R/R CLL.²⁶ The ibrutinib arm demonstrated much higher ORRs and improved overall survival (OS) compared with the ofatumumab arm. The results of this pivotal trial led to the US Food and Drug Administration (FDA) approval of ibrutinib in patients with R/R CLL who had received at least one prior therapy and in all patients with del(17p) CLL. In the 4-year follow-up data, the rate of drug discontinuation owing to AEs was 4.1% in the ibrutinib arm, with 86% of patients continuing ibrutinib treatment.²⁷

The role of ibrutinib was assessed in a phase 1b/2 trial involving patients older than 65 years who had TN CLL and required therapy.²⁸ After a median follow-up of 22.1 months, the ORR was 71% (22 of 29 patients enrolled). A complete response (CR) occurred in 4 patients, a partial response (PR) in 17, and a nodal PR in 1. Toxicities were acceptable and primarily grade 1/2.

Most recently, the randomized phase 3 RESONATE-2 trial compared ibrutinib and chlorambucil in older patients with TN disease. A total of 269 patients were enrolled whose median age was 71 years. During a median follow-up of 18.4 months, ibrutinib proved superior to chlorambucil in terms of ORR (86% vs 35%), PFS (median PFS, not reached vs 18.9 months), and OS (2-year OS rate, 98% vs 85%).²⁹

The rationale of synergy secondary to different mechanisms of action suggests that combining ibrutinib with chemoimmunotherapy may prove to be an attractive approach. Ibrutinib plus bendamustine/rituximab (BR) was compared with BR alone in a phase 3 study of R/R CLL called HELIOS.³⁰ The study enrolled 578 patients with CLL/small lymphocytic lymphoma (SLL) who had

Table. Monotherapies With Novel Targets in Refractory/Relapsed Chronic Lymphocytic Leukemia

Drug	Study Phase	Patient Age, y	Patients Enrolled, No.	Patients With Disease Characteristics, %	Dosing Scheme	Best ORR	Survival Outcomes	Notable Serious AEs
BTK inhibitors								
Ibrutinib ^{26,92}	1b/2	64	101	69% with del(17p)/del(11q), 79% with um <i>IGHV</i>	420/840 mg daily	71% (7% CR, 80% PR, 3% PR-L)	30-mo PFS: 74%, 48% in del(17p); 30-mo OS: 95%, 65% in del(17p)	Hypertension, pneumonia, neutropenia, thrombocytopenia, infections, bleeding, atrial fibrillation
Acalabrutinib ⁵¹	1/2	62	61	31% with del(17p), 75% with um <i>IGHV</i>	100-400 mg OD (esc phase); 100 mg BID (exp phase)	95% (85% PR, 10% PR-L), 100% in del(17p)	16-mo PFS: 96%	Diarrhea, weight gain, pyrexia
Spebrutinib ⁵³	1	66.5	84	45% with del(17p)/del(11q), 54% with um <i>IGHV</i>	25-1000 mg OD (esc phase); 375-500 mg BID (exp phase)	63% (53% CR/PR, 10% PR-L), 69% in del(17p)	mDOR: 5.6-11 mo, 5.6 mo in del(17p)	Neutropenia, thrombocytopenia, diarrhea, fatigue
ONO-4059 ⁵⁴	1b	67	25	46% with del(17p)/del(11q), 89% with um <i>IGHV</i>	20-600 mg OD; 375-500 mg BID	96%, 100% in del(17p)	mDOR: 20 mo	Neutropenia, thrombocytopenia
PI3K inhibitors								
Idelalisib ⁶³	1	63	54	24% with del(17p), 91% with um <i>IGHV</i>	50-350 mg OD/BID	79% (PR 39%, PR-L 33%), 54% in del(17p)	mDOR: 16.2 mo, 36-mo OS: 75%, mDOR in del(17p): 3 mo	Pneumonia, neutropenic fever, diarrhea, transaminitis
Duvelisib ⁷⁶	1	66	54	49% with del(17p)/ <i>TP53</i> , 89% with um <i>IGHV</i>	8-75 mg BID	55% (1 CR, 26 PRs), 50% in del(17p)	18-mo PFS: 60%, median PFS in del(17p): 14 mo	Neutropenia, thrombocytopenia, febrile neutropenia, pneumonia, transaminitis
TGR-1202 ^a	1	63	20	—	800-1200 mg daily	92% (nPR with 50% PR)	—	Neutropenia, diarrhea, cough, fatigue

(Table continued on next page)

received at least one prior systemic therapy and randomly assigned them to receive either ibrutinib or placebo with 6 cycles of BR. Interim analysis showed that BR/ibrutinib was associated with an 80% decreased risk for progression and death, along with superior PFS, compared with BR alone.³¹ The results of RESONATE-2 led to the approval

of ibrutinib in all phases of CLL. The role of ibrutinib in patients with TN CLL who are asymptomatic but at high risk for progression is unclear, but more clarity may be obtained from the phase 3 trial of ibrutinib vs placebo (NCT02863718).

As alluded to earlier, the most common toxicities

Table. (Continued) Monotherapies With Novel Targets in Refractory/Relapsed Chronic Lymphocytic Leukemia

Drug	Study Phase	Patient Age, y	Patients Enrolled, No.	Patients With Disease Characteristics, %	Dosing Scheme	Best ORR	Survival Outcomes	Notable Serious AEs
BCL-2 inhibitors								
Navitoclax ⁸⁰	1	67	29	72% with del(17p)/del(11q)	100-300 mg daily	35% (all PR), 33% in del(17p)	Median PFS: 25 mo	Neutropenia, thrombocytopenia, TLS, MI, PML
Venetoclax ⁸⁵	1	66	56	30% with del(17p), 27% with del(11q), 45% with um <i>IGHV</i>	150-1200 mg daily (esc phase); 400 mg daily (exp phase)	92% (20% CR), 71% in del(17p)	Median PFS: 25 mo, median PFS in del(17p): 16 mo	Neutropenia, pneumonia, URTI, thrombocytopenia, TLS

*NCT01767766; 2015 ASCO abstract 7069.

AE, adverse event; BID, twice a day; BCL-2, B-cell lymphoma/leukemia 2; BTK, Bruton tyrosine kinase; CDK, cyclin-dependent kinase; CR, complete response; CRS, cytokine release syndrome; mDOR, median duration of response; esc, escalation; exp, expansion; *IGHV*, immunoglobulin heavy chain variable region; MI, myocardial infarction; mo, months; No., number; nPR, nodal partial response; OD, once daily; ORR, overall response rate; OS, overall survival; PI3K, phosphoinositide 3-kinase; PFS, progression-free survival; PML, promyelocytic leukemia; PR, partial response; PR-L, partial response with lymphocytosis; TLS, tumor lysis syndrome; um, unmutated; URTI, upper respiratory tract infection; y, years.

include diarrhea, rash, joint pain, bleeding, atrial fibrillation, hypertension, infection, and cytopenia. The complication of bleeding has been intensively studied. Bleeding most commonly occurs early in treatment, with major episodes in about 5% of patients.^{32,33}

Although lymphocytosis is usually transient, up to 20% of patients taking ibrutinib have prolonged lymphocytosis beyond 1 year on ibrutinib.³⁴ The development of lymphocytosis does not correlate with inferior survival. This finding is not unique to BTK inhibition; it is also seen with drugs from other classes, including PI3K inhibitors.³⁵⁻³⁷ Patients with persistent lymphocytosis are placed in a separate response category—namely, PR-L—to account for this phenomenon unique to selective novel agents.³⁸

Responses to ibrutinib are not uniform; they vary depending on several disease characteristics. In ex vivo studies, responses to ibrutinib vary widely, with heightened sensitivities in unmutated *IGHV*, *ZAP70*, and trisomy 12 samples.³⁹ A complex karyotype predicts even more strongly than del(17p) an inferior response to ibrutinib in R/R CLL.⁴⁰ Normalization of κ_2 -microglobulin within 6 months predicts superior PFS.⁴¹

Mechanisms of resistance to ibrutinib are an area of active research. Resistance most commonly involves the acquisition of a BTK cysteine-to-serine mutation at a key ibrutinib-binding locus (C481S).⁴² Another resistance mechanism involves gain-of-function mutations (R665W and L845F) in the downstream PLC 2

signaling molecule, leading to its constitutive activation. Several in vitro and ex vivo studies have attempted to circumvent these resistance pathways by combining novel agents with ibrutinib and by potentiating the cytotoxicity of ibrutinib. Preclinical data appear promising with some of these agents, such as venetoclax (Venclexta, AbbVie/Genentech; apoptosis associated with BCL-2 inhibition).⁴³ Ibrutinib is under study in phase 1/2 trials with various novel agents, including the BCL-2 inhibitors venetoclax (NCT02756897) and GDC-0199 (NCT02427451); the PI3K inhibitors buparlisib (NCT02614508) and TGR-1202 (NCT02268851); the checkpoint inhibitors nivolumab (Opdivo, Bristol-Myers Squibb; NCT02420912) and pembrolizumab (Keytruda, Merck; NCT02332980); the immunomodulatory agent lenalidomide (Revlimid, Celgene) plus rituximab (Rituxan, Genentech/Biogen; NCT02160015); exportin 1 (XPO1) inhibitors such as selinexor (NCT02303392); and the monoclonal antibodies momalizumab (NCT02557516) and BI 836826, the latter of which is an anti-CD37 antibody (NCT02759016). Interim results of the phase 1 study of ibrutinib in combination with lenalidomide and rituximab were presented at the 2017 annual meeting of the American Society of Hematology.⁴⁴ A total of 12 patients with R/R CLL were enrolled. The ORR was 66.7%, with the best response seen in most patients at their first assessment, conducted 10 weeks after the start of therapy. Importantly, the combination was associated

with sustained grade 4 neutropenia; furthermore, the ORR was not significantly improved compared with that in previous reports of lenalidomide plus rituximab alone, resulting in the termination of the study.

As ibrutinib becomes a standard first-line treatment in CLL, especially for patients who have del(17p) or are older and frail, consideration must be given to the cost of therapy, treatment logistics, and toxicities. Ibrutinib and other targeted agents for CLL are expensive, and their use dramatically increases individual out-of-pocket and societal expenses.^{45,46}

Up to 28% of patients may discontinue ibrutinib, with survival rates varying according to the reason for discontinuation.⁴⁷ Disease progression on ibrutinib is associated with inferior survival, ranging from a median of 3.5 months in patients with Richter's transformation (RT) to 17.6 months in patients with progressive CLL.⁴⁸ Progressive CLL but not RT seems to correlate with acquired inhibitor resistance, suggested by the acquisition of BTK and PLC 2 mutations in almost all cases of progressive CLL compared with none in patients in whom RT develops.

Ibrutinib was also evaluated in combination with anti-CD20 therapies. It was first tried in combination with rituximab in a phase 2 single-arm trial. The study enrolled 40 patients with TN CLL that was either R/R or del(17p). Results were promising, with a 95% ORR (8% CR rate, 87% PR rate) and an 18-month PFS rate of 78%. The effect of combining ibrutinib with rituximab is being investigated in ongoing phase 2/3 trials, specifically a phase 3 trial of ibrutinib vs rituximab (NCT01973387) and a phase 2 trial of ibrutinib/rituximab vs rituximab alone (NCT02007044).

Jaglowski and colleagues reported outcomes with ibrutinib/ofatumumab in their phase 1b/2 study.⁴⁹ The study enrolled 66 patients, and 3 different dosing schedules were used. The group that received an ibrutinib lead-in followed by ofatumumab had the best response, with an ORR of 100% and a 12-month PFS rate of 89%. A phase 3 randomized study (GENUINE) to assess the efficacy and safety of ublituximab/ibrutinib vs ibrutinib alone in high-risk del(17p), del(11q), or mutant *TP53* R/R CLL is currently under way (NCT02301156). Early-phase trial data on 126 patients showed a higher ORR in the ublituximab/ibrutinib arm (78%) than in the ibrutinib-alone arm (45%).⁵⁰ Similarly, various phase 3 trials of patients with TN CLL are studying ibrutinib, either alone or in combination (NCT022644574, NCT02048813, and NCT01886872).

Acalabrutinib (Calquence, AstraZeneca) is a second-generation BTK inhibitor that has been observed to be highly selective and more potent than ibrutinib in pre-clinical models. Byrd and colleagues reported phase 1/2

trial data on acalabrutinib in 61 patients with R/R CLL.⁵¹ Patients received 100 to 400 mg once daily in the dose-escalation phase and 100 mg twice daily in the expansion phase. These patients had predominantly high-risk disease: 31% with del(17p) and 75% with unmutated *IGHV*. The ORR was 95% (85% PR, 10% PR-L). The most common AEs were headache, diarrhea, and weight gain. Interestingly, the ORR was 100% in the del(17p) cohort. A phase 3 trial comparing acalabrutinib vs ibrutinib in patients with previously treated high-risk CLL is currently recruiting subjects (NCT02477696). Additional trials will further help to establish the role of acalabrutinib in CLL management, including a phase 1 trial of acalabrutinib plus the PI3K inhibitor ACP-319 (NCT02157324), a phase 1/2 trial of acalabrutinib plus the checkpoint inhibitor pembrolizumab (NCT02362035), and a phase 3 trial of chlorambucil/obinutuzumab (Gazyva, Genentech) vs acalabrutinib vs acalabrutinib/obinutuzumab (NCT02475681).

Spebrutinib is another potent, irreversible BTK inhibitor that has shown promising activity in preclinical in vitro models.⁵² Brown and colleagues reported on outcomes in 84 patients with R/R CLL/SLL in a phase 1 dose-escalation study. The ORR was 63% (53% PR/CR, 10% PR-L); the most common grade 3/4 AEs were neutropenia and thrombocytopenia, and the most common nonhematologic treatment-emergent AEs were diarrhea and fatigue.⁵³

Another selective BTK inhibitor in active clinical development is ONO-4059. Walter and colleagues reported on outcomes in 25 patients who had R/R CLL treated with this agent in a dose-escalation phase 1b study.⁵⁴ The study included 9 dose-escalation cohorts given doses ranging from 20 to 600 mg. The ORR was high (96%), with the majority of patients (84%) remaining on treatment at the end of the study. Most of the AEs were grade 1 or 2, with grade 3/4 AEs typically transient and nonlimiting.

BGB-3111 is an irreversible BTK inhibitor that is much more selective and potent than ibrutinib and has been shown to achieve more complete target inhibition than ibrutinib. In a phase 1 first-in-human trial study⁵⁵ evaluating this compound in 25 patients with R/R B-cell malignancies (8 with CLL), an objective response was noted in 6 of the patients with CLL (0 CRs), and all 8 patients were continuing treatment at a median follow-up of 6.5 months. The reported ORR in an update was 96%⁵⁶ and reached 100% among patients with high-risk molecular characteristics. This agent is under evaluation in combination regimens with obinutuzumab (NCT02569476) and programmed death 1 (PD-1) inhibitors (NCT02795182). Early phase 1b trial data of this drug in combination with obinutuzumab (20 TN,

25 R/R) have reported the combination to be well tolerated, with no fatal AEs reported.⁵⁷

Another BTK inhibitor compound of interest is SNS-062, a reversible inhibitor that does not require BTK C481 for its inhibitory activity. C481S is an important acquired mechanism of resistance to the efficacy of BTK inhibitors, and SNS-062 retains its activity against CLL cells with the C481S mutation.⁵⁸ A phase 1/2 study testing the safety and efficacy of this compound is recruiting patients (NCT03037645).

PI3K Inhibition

PI3K is major mediator of the PI3K/AKT pathway, which is essential for B-cell proliferation and survival. Following antigen engagement, LYN phosphorylates the CD19 cytoplasmic domain, which subsequently binds PI3K and activates it.⁵⁹ This results in the production of phosphatidylinositol 3-phosphate, which recruits multiple signal intermediates to the plasma membrane and activates them. Exploiting this pathway is thus a rational strategy for developing novel inhibitors.

Idelalisib (Zydelig, Gilead) is a selective inhibitor of the PI3K- isoform, the predominant mediator of most PI3K signaling in CLL cells.⁶⁰ It binds reversibly through a noncovalent linkage to PI3K.⁶¹ Idelalisib inhibits MCL1 upregulation, AKT phosphorylation, and nuclear factor B (NF B) pathway activation.⁶² Brown and colleagues reported on the outcomes of phase 1 trial of idelalisib in R/R CLL.⁶³ A total of 54 patients were evaluated; the patients had received a median of 5 therapies, and most had high-risk features. They were treated at 6 dose levels, ranging from 50 to 350 mg. The ORR was 79% (PR rate, 39%; PR-L rate, 33%), and the median PFS was 15.8 months. Pneumonia, neutropenic fever, and diarrhea were the most common AEs. The responses were durable and lasted for at least 17 months in half of the treated patients.⁶⁴ This trial was followed by a multicenter, randomized phase 3 study assessing the safety and efficacy of rituximab with or without idelalisib.⁶⁵ A total of 220 patients were enrolled in the study, and idelalisib was administered at a dose of 150 mg twice daily. An interim analysis showed a significant improvement in PFS in the rituximab/idelalisib arm. The rituximab/idelalisib arm also had a better ORR (81% vs 13%) and superior 12-month OS (92% vs 80%). The rates of serious AEs did not differ significantly between the 2 arms: 40% in the patients receiving rituximab/idelalisib and 35% in those receiving rituximab/placebo. These results led to FDA approval of idelalisib as the first-in-class PI3K inhibitor for relapsed CLL.⁶⁶ Idelalisib was also studied in a phase 3 trial in combination with BR in R/R CLL.⁶⁷ This study randomly assigned 416 patients with R/R CLL to either

idelalisib/BR or placebo/BR. Preliminary results from the study reported a significant improvement in PFS in idelalisib arm (23.1 vs 11.1 months). The benefit was consistent across subgroups, including patients with del(17p)/*TP53* mutation.

In addition, idelalisib has been evaluated in the frontline setting. A phase 2 study involving 27 patients with CLL who were older than 65 years and received 150 mg of idelalisib twice daily reported an ORR of 97%. Toxicities were frequent, with colitis, pneumonia, rash, and transaminitis being the most common grade 3/4 AEs. The rate of transaminitis was far higher (grade 3 in 53% of patients) in another phase 2 study, in which idelalisib was given for 2 months followed by idelalisib and ofatumumab for 6 months.⁶⁸ The difference between the rates of transaminitis was most likely due to differences in the ages of patients in the 2 study groups; the second study included patients younger than 65 years. Younger age and mutated *IGHV* were determined to be predictive of early hepatotoxicity.

A single-arm phase 2 study assessed idelalisib/rituximab in patients with TN CLL.⁶⁹ A total of 64 older patients with TN CLL received idelalisib/rituximab continuously for 48 weeks. Patients who completed 48 weeks without progression could continue to receive idelalisib in an extension study. The median time on treatment was 22.4 months (range, 0.8-45.8+). The ORR was 97%, including a CR rate of 19%. The ORRs were 100% in patients with del(17p)/*TP53* mutation and 97% in those with unmutated *IGHV*. Responses were durable, with a 3-year PFS rate of 83%. Toxicities were common and included transaminitis, diarrhea/colitis, rash, fever, nausea, chills, cough, and fatigue.

The most notable toxicities with idelalisib include potentially fatal immune-mediated colitis, pneumonitis, and transaminitis. These events mandate either dose reduction or discontinuation of the drug.⁷⁰⁻⁷² Given the immune-mediated nature of these reactions, corticosteroids remain the mainstay of treatment.⁷³ In March 2016, several frontline trials with idelalisib were halted owing to an increased risk for infection and death.

Duvelisib (IPI-145), unlike idelalisib, is a dual PI3K- and PI3K- isoform inhibitor.⁷⁴ Duvelisib is effective even against CLL lines that have become resistant to ibrutinib by acquiring the C481S mutation.⁷⁵ Duvelisib has been investigated in both the frontline setting and the setting of relapsed CLL. A phase 1 dose-escalation study included 54 patients who had R/R CLL treated with duvelisib at doses ranging from 8 to 75 mg twice daily.⁷⁶ The median age of the patients was 66 years; 49% had del(17p)/*TP53* mutation and 89% had unmutated *IGHV* status. The ORR was 55% (1 CR, 26 PRs) and the 18-month PFS rate was 60%. The median PFS in the del(17p) group was

14 months. Most of the toxicities were grade 1 or 2, with the most common grade 3 AEs being neutropenia (31%), thrombocytopenia (11%), febrile neutropenia (15%), and pneumonia (11%). Duvelisib is currently being compared with ofatumumab in R/R CLL in a phase 3 trial (NCT02004522).

TGR-1202 is a second-generation PI3K inhibitor with specifically designed structural modifications to reduce the incidence of transaminitis, an AE frequently observed with idelalisib and duvelisib.⁶⁰ Burris and colleagues reported on outcomes with TGR-1202 monotherapy and the double combination with ublituximab in 152 patients with non-Hodgkin lymphoma, including 40 patients with R/R CLL, in a dose-escalation phase 1 study.⁷⁷ A total of 109 patients (27 with CLL) received the targeted therapeutic dose and were evaluable for efficacy. The ORR in the patients with CLL was 89% (1 CR, 23 PRs). The median PFS was 24 months for the monotherapy and was not reached for the combination. Clinical trials are being actively undertaken and should further establish the role of TGR-1202 in TN CLL.

BCL-2 Inhibitors

The BCL-2 family is a group of antiapoptotic proteins that are primarily responsible for inhibiting apoptosis in CLL cells. The expression of antiapoptotic proteins such as BCL-2, BCL-xL, and MCL1 is increased in CLL samples, and increased levels of messenger RNA are correlated with clinical progression of disease.⁷⁸ These findings have resulted in the development of targeted therapies via either antisense approaches or the synthesis of molecules that mimic the proapoptotic BH3 domains of the antiapoptotic proteins.⁷⁹

Navitoclax

Navitoclax (ABT-263) is an orally available, small-molecule inhibitor of BCL-2 and BCL-xL. It was first evaluated as monotherapy in R/R CLL in a phase 1 dose-escalation study.⁸⁰ The 29 patients who were enrolled received doses that ranged from 100 to 300 mg once daily. Of the 26 patients treated with a dose of 110 mg or higher, 9 achieved a PR. The median PFS was 25 months, with activity observed even in patients who had poor-risk features. The major dose-limiting toxicity was thrombocytopenia, which was attributed to the accelerated senescence of platelets caused by BCL-xL inhibition.

Oblimersen

Oblimersen is a BCL-2 antisense oligonucleotide that is unlike other small-molecule inhibitors in this class.⁸¹ O'Brien and colleagues first reported outcomes with

oblimersen as monotherapy in a phase 3 study of 40 patients with R/R CLL, 14 in phase 1 and 26 in phase 2. Responses were modest, with 2 of 26 evaluable patients achieving a PR. Cytokine release syndrome, characterized by fever, hypotension, and back pain, was observed at higher doses. A phase 3 trial randomly assigned 241 patients with R/R CLL to either fludarabine/cyclophosphamide (n=121) or fludarabine/cyclophosphamide plus oblimersen (n=120).⁸² The ORR was higher with fludarabine/cyclophosphamide plus oblimersen (17%) than with chemotherapy only (7%). The response rate in the oblimersen group was higher in the patients with fludarabine-sensitive disease, and achievement of a response correlated with extended time to progression and longer survival. In a 5-year survival analysis, achievement of response translated to a survival benefit.⁸³

Venetoclax

Venetoclax (ABT-199) is a highly selective BCL-2 inhibitor that was designed to prevent BCL-xL-mediated platelet senescence.⁸⁴ Roberts and colleagues reported outcomes with venetoclax in R/R CLL in a phase 1 dose-escalation study.⁸⁵ A total of 56 patients were treated in 8 groups that received doses ranging from 150 to 1200 mg daily after a test dose of 20 mg. An additional 60 patients in an expansion cohort were started at a dose of 20 mg daily, with a weekly dose ramp-up to a final dose of 400 mg. The ORRs were 92% (CR rate, 20%) in the entire group and up to 79% in the high-risk subgroups. The 15-month PFS rate was 69%. Common toxicities were diarrhea, upper respiratory tract infection, nausea, and neutropenia. A notable complication in the dose-escalation cohort was tumor lysis syndrome in 3 of 56 patients, a complication not observed in any of the 60 patients who received a steady dose ramp-up in the expansion cohort.

A phase 2 single-arm study of 107 patients who had R/R CLL with del(17p) and were treated with venetoclax on a ramp-up schedule showed an ORR of 79.4%.⁸⁶ The most common grade 3/4 AEs were neutropenia, anemia, thrombocytopenia, and infections. Other complications included pyrexia, autoimmune hemolytic anemia, pneumonia, and febrile neutropenia; 4 patients died of an AE. On the basis of promising preclinical evidence,⁴⁵ venetoclax is being investigated in combination with ibrutinib in a phase 2 trial in R/R CLL (NCT01682616). Venetoclax was also studied in combination with rituximab in a phase 1b⁸⁷ trial of 49 patients with R/R CLL; the ORR was 86%, and the rate of negativity for minimal residual disease (MRD) was 57% (20 of 25 complete responders). None of the 11 MRD-negative patients who discontinued venetoclax had disease progression while off therapy, although the follow-up was short. The CLARITY study is currently evaluating the safety and efficacy

of combining venetoclax and ibrutinib, with the primary endpoint of MRD eradication.⁸⁸ The study has enrolled 50 patients and is currently ongoing. A phase 1b study is evaluating venetoclax in combination with ibrutinib and obinutuzumab. Of 12 patients with R/R disease treated in the phase 1b portion of the trial, 6 have reached response assessment after completing 8 cycles, with objective responses observed in all: 5 PRs and 1 CR⁸⁹; accrual to the phase 2 cohorts continues. Venetoclax is also being evaluated in the phase 3 CLL14 trial, which is comparing venetoclax/obinutuzumab vs chlorambucil/obinutuzumab in TN CLL.⁹⁰ Of the 11 patients among 12 evaluable who completed treatment with venetoclax and obinutuzumab, all have responded, with CRs noted in 58% and MRD negativity in 83%. At 15 months, no patients had progressed, and there were no deaths.

Role of Targeted Therapies in Specific Stages of CLL

Relapsed/Refractory CLL

The outlook for patients with R/R CLL has changed dramatically with the development of novel targeted therapies. As was discussed in detail in the previous sections, these new agents have marked efficacy in R/R CLL, with durable responses even in patients who have high-risk disease features such as del(17p). Ibrutinib, idelalisib (in combination with rituximab), and venetoclax are the currently approved treatments for R/R CLL, with venetoclax approved only for patients with del(17p).⁹¹ A number of other agents have shown promising clinical activity in R/R CLL (Table), and ongoing trials will clarify their role in R/R CLL. In this context, the timing of allogeneic stem cell transplant remains undefined, and the approach must be individualized after a consideration of each patient's disease features and response status. Of note, several other therapies—including CDK inhibitors, LYN inhibitors, SYK inhibitors, CAR T-cell therapies, checkpoint inhibitors, immunomodulators, and chemokine receptor signal inhibitors, among others—are being explored in preclinical and clinical settings in CLL. A review of these agents is not included in this discussion.

Del(17p)/TP53 CLL

Having been shown to produce superior responses to intensive chemotherapy in both TN and R/R CLL, ibrutinib is the currently approved treatment for del(17p) CLL.^{92,93} Acalabrutinib was shown to be highly active in R/R CLL, and its benefit vs ibrutinib in high-risk TN CLL will be clarified in an ongoing phase 3 trial comparing these 2 agents (NCT02477696). Venetoclax is FDA-approved for patients with R/R CLL and del(17p) CLL.⁹¹

Conclusions

Thanks to the rapid clinical development of effective novel therapies, an encouraging picture is emerging for the future of patients with CLL. Ongoing phase 2/3 trials will further establish the role of these therapies in years to come. It must be stressed that as the treatment paradigms in CLL shift rapidly toward personalized medicine, there is a concurrent need to identify biomarkers predictive of resistance and response to these therapies.⁹⁴

Disclosures

The authors have no relevant conflicts of interest. The manuscript was supported in part by The University of Texas MD Anderson Cancer Center Leukemia Support Grant (CCSG) CA016672, and the CharifSouki Cancer Research Fund.

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