CCR Drug Updates

Clinical Cancer Research

Venetoclax in Patients with Previously Treated Chronic Lymphocytic Leukemia

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Abstract

Venetoclax is the first BCL2 inhibitor to enter routine clinical practice. It is an orally bioavailable small molecule that binds BCL2 very specifically. Acting as a pharmacologic mimic of the proteins that initiate apoptosis (a so-called BH3 mimetic), venetoclax rapidly induces apoptosis in chronic lymphocytic leukemia (CLL) cells, which express high levels of BCL2 and rely on it to maintain their survival. As a single agent, daily venetoclax treatment induced durable responses in 79% of patients with relapsed or refractory CLL or small lymphocytic lymphoma in a phase I study, including complete remissions in 20% of patients. Its use was approved by the FDA in April 2016 for patients with previously treated del(17p) CLL on the basis of a single-arm phase II trial demonstrating a 79% response rate and an estimated 1-year progression-free survival of 72% with 400 mg/day continuous therapy. This review focuses on venetoclax, its mechanism of action, pharmacology, and clinical trial data and seeks to place it in the context of rapid advances in therapy for patients with relapsed CLL, especially those with del(17p) CLL. *Clin Cancer Res; 23(16); 4527–33. ©2017 AACR.*

Introduction

Chronic lymphocytic leukemia (CLL) is a malignancy of mature B lymphocytes that is characterized by the gradual accumulation of $CD5^+19^+23^+$ B cells in the blood, lymph nodes, and bone marrow. It is typically a disease in older people, with a median age at diagnosis of 72 years of age, but can occur in young adults.

CLL is a highly heterogeneous disease clinically. A common presentation is as an incidental finding on a routine full blood count, typically without symptoms or clinically apparent lymphadenopathy. Initial treatment is required only when symptoms or complications (e.g., anemia and thrombocytopenia) manifest, so-called "active disease" (1). Combinations of chemotherapy and anti-CD20 mAbs (chemo-immunotherapy) are standard first-line treatments. The choice of initial therapy is influenced particularly by the age and, more importantly, general health of the patient (1–3). The combination of fludarabine/cyclophosphamide/rituximab (FCR) is the standard therapy for young and fit patients (4, 5). In patients with comorbidities, bendamustine/rituximab is an alternative (6), as is chlorambucil/obinutuzumab or chlorambucil/ofatumumab for elderly patients (7, 8).

Although achieving durable remissions in many patients, even the most effective therapies are rarely curative, and relapse is to be expected. Outcome is heavily influenced by genetic abnormalities within the leukemia (9–12), and these acquired genetic factors are now also factored into treatment decisions (13). Propensity to relapse and shorter survival are consistently associated with the presence of loss of parts of the short arm of chromosome 17 [del(17p)] (9), and also with mutation of the *TP53* gene, which is located on 17p (11, 12, 14). In contrast, long-term follow-up data indicate that some patients with *IGHV*-mutated CLL with favorable cytogenetic features can achieve long-term, minimal residual disease (MRD)–negative remissions and possibly cure with FCR (11, 15). This review focuses on treatment for patients whose disease has recurred or progressed after initial therapy because dramatic progress has been made in this area.

Until recently, treatment for relapsed CLL has involved reuse of the initial therapy in patients who had a durable first remission and use of different chemotherapy-based regimens when the initial response was short. Where cytotoxic-based therapy has been poorly tolerated or not induced a long initial response, non-DNA–damaging regimens, including ofatumumab, alemtuzumab, and high-dose corticosteroids, have shown activity (see Table 1). However, no chemo-immunotherapy regimen has been shown to produce long-term remissions in the majority of the relapsed population, in particular, in early relapse or in CLL with 17p deletion/*TP53* mutation.

In recent years, the introduction of ibrutinib (16, 17) and idelalisib (18) into practice has revealed how impactful identification of novel targeted therapies can be (13). Both drugs attack CLL via interruption of B-cell receptor (BCR) signaling pathways. BCR signaling is central to the biology of CLL (19). Pharmacologic inhibition of Bruton tyrosine kinase (BTK) by ibrutinib and PI3K-δ by idelalisib reduces cell survival signals, both directly by reducing activity of the NF-κB and ERK pathways and indirectly by diminishing interactions with the microenvironment (20).

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Table 1. Drug activity in relapsed or refractory CLL

	Phase	*N*	ORR	CRR	PFS estimates	Comment	Reference
Relapsed/refractory CLL							
Small molecules							
Venetoclax	I	116	79%	20%	69% (59–77) @ 15 mths	Doses 150–1,200 mg/d; PFS estimate is for pts treated with 400 mg/d	42
Ibrutinib	I/II	85	88%	2%	75% @ 26 mths	Dose 420 or 840 mg/d	17
	I/II	101	90%	7%	69% @ 30 mths	Composite at RP2D	52
	III	195	63%	0%	88% @ 6 mths	IRC-assessed results	16
mAbs							
Rituximab	III	100	13%	0%	Median 6 mths	IRC-assessed results	18
Ofatumumab	II	138	52%[a]	1%[a]	Median 6 mths	Either fludarabine-refractory or bulky CLL	62
	III	196	4%	0%	Median 8 mths	IRC-assessed results	16
Alemtuzumab	I	93	33%[a]	2%[a]	NR		63
Obinutuzumab	II	20	30%	5%	Median 11 mths		64
Combination therapies							
Venetoclax/rituximab	Ib	49	86%	51%	80% @ 2 yrs		61
Idelalisib/rituximab	III	110	81%	0%	93% @ 6 mths	IRC-assessed results	18
Ibrutinib/rituximab	II	39	95%	8%	78% (61–89) @ 18 mths	Included four pts with untreated del(17p) CLL	65
Ibrutinib/ofatumumab	Ib/II	71	83%	2%	83% (72–90) @ 1 yr		66
Alemtuzumab/rituximab	II	40	53%[a]	18%[a]	NR	Median time-to-failure 6 mths	67
	I	28	14%	NR	Median 26 mths		68
Benda/ofatumumab	II	49	72%	17%	Median 24 mths		69
Benda/rituximab	II	78	59%	9%	Median 15 (13–18) mths		70
Benda/rituximab	III	289	68%	3%	Median 13 (11–14) mths		71
Ibrutinib/benda/rituximab	III	289	83%	10%	79% (73–83) @ 18 mths	Pts with >20% del(17p) excluded	71
FCR	II	284	74%	30%	Median 21 (19–28) mths		72
Fludarabine/benda/rituximab	I/II	51	67%	36%	Median 19 mths		73
Deletion 17p CLL/SLL							
Small molecules							
Venetoclax	I	31	71%	16%	Median 16 mths (11–25)	Doses 150–1,200 mg/d	42
	II	107	79%	8%	72% @ 1 yr	400 mg/d; IRC-assessed results	50
Ibrutinib	I/II	34	79%	6%	Median 28 mths (18–NE)	Dose 420 or 840 mg/d	52
	II	144	83%	3%	79% @ 1 yr; 63% @ 2 yr	Dose 420 mg/d; IRC ORR 63%; CRR 0%	53
	III	62	NR	NR	83% @ 6 mths	IRC-assessed results	16
mAbs							
Rituximab	III	50	NR	NR	Median 4 mths	del(17p) and/or TP53 mutant	18
Ofatumumab	III	61	NR	NR	Median 6 mths	IRC-assessed results	16
Alemtuzumab	II	30	39%	NR	Median 6 mths	Fludarabine-refractory CLL	74
Combination therapies							
Venetoclax/rituximab	Ib	9	89%	67%	NR		61
Idelalisib/rituximab	III	46	NR	NR	66% @ 1 yr	del(17p) and/or TP53 mutant; PFS same as for all pts on trial	18, 75
Ibrutinib/rituximab	II	20	90%	10%	72% (46–88) @ 18 mths	Pts had del(17p) or TP53 mutation; all CRs in previously untreated pts	65
Ibrutinib/ofatumumab	Ib/II	31	74%	NR	NR		66
Alemtuzumab/methylpred	II	22	77%	14%	Median 6.5 mths		76
Alemtuzumab/rituximab	I	9	33%	NR	Median 35 mths		68
Alemtuzumab/pentostatin/rituximab	II	36	56%	28%	Median 7 (5–18) mths	20 pts del(17p) and/or TP53 mutation	77
CFAR	II	14	29%	14%	Median 3 mths		78
Benda/ofatumumab	II	8	38%	0%	NR		69
Benda/rituximab	II	14	7%	7%	NR	Event-free survival median <6 mths	70
FCR	II	20	35%	0%	Median 5 mths	del(17p) by karyotype	72

NOTE: The table only includes drugs that have had regulatory approval for marketing. Responses were reported by International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria unless otherwise specified. Data rounded to nearest whole number for percentages and for months. del(17p) was assessed by FISH unless otherwise specified. Data in () indicate 95% confidence intervals of estimate.

Abbreviations: Benda, bendamustine; CFAR, cyclophosphamide/fludarabine/alemtuzumab/rituximab; CR, complete remission; CRR, complete response rate; d, day; IRC, independent review committee; methylpred, methylprednisolone; mths, months; *N*, number of patients; NE, not estimable; NR, not reported; ORR, overall response rate; pts, patients; RP2D, recommended phase II dose; SLL, small lymphocytic lymphoma; yr/yrs, year/years.

[a]National Cancer Institute Working Group (NCI-WG) criteria for response only reported.

In parallel to the BCR, the prosurvival protein BCL2 also has a fundamental place in CLL biology. BCL2 is constitutively expressed in the counterpart normal B cells (21). Although there is interindividual and intraindividual variation, BCL2 is highly expressed by CLL cells in all patients, often at elevated levels compared with normal $CD19^+$ cells (22–24). Loss of the repressive miRNAs *miR-15* and *miR-16*, located on chromosome 13q14, may drive BCL2 overexpression in many cases of CLL (25).

With the generation of venetoclax (26), potent and selective targeting of BCL2 has become possible. Preclinical data indicated potent killing of CLL cells *in vitro*, with relative sparing of normal T cells, granulocytes, and platelets (26–28).

Mechanism of Action

The key function of the intracellular protein BCL2 is to prevent cells from undergoing apoptosis (29, 30). Its overexpression is associated with inappropriate cell survival (29, 31), tumor formation (as in CLL and follicular lymphoma; ref. 32), and diminished sensitivity to chemotherapy (33). In healthy cells, BCL2 and its other prosurvival relatives, such as BCL2L1 (BCLxL) or MCL1, prevent apoptosis by keeping the cell death mediators BAX and BAK in check (30). However, when cells are no longer required or undergo significant stresses, such as that triggered by genotoxic damage, apoptosis is initiated by activation of the naturally occurring antagonists of prosurvival BCL2 proteins, the BH3-only proteins [e.g., BCL2L11 (BIM), BBC3 (PUMA), and BAD]. These proapoptotic proteins bind and inhibit BCL2 or its close relatives (see Fig. 1; ref. 34). Once the prosurvival BCL2 proteins have been targeted this way, BAX and BAK are no longer constrained and are thus able to drive apoptotic cell death by causing mitochondrial damage. As binding of the BH3-only proteins such as BIM to BCL2 or its prosurvival relatives is the pivotal step for initiating apoptosis, small molecules that potently mimic their action were developed to pharmacologically inhibit the prosurvival proteins (35).

The most advanced of such BH3 mimetic compounds is venetoclax (formerly ABT-199 or GDC-0199; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-*N*-({3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)benzamide; ref. 26). Venetoclax was developed by structure-informed reverse engineering of navitoclax, a first-generation BH3 mimetic compound that targets BCLxL as well as BCL2 (36). Although navitoclax had demonstrated significant clinical activity against CLL, with a 35% response rate in heavily pretreated patients in a phase I study (37), a barrier to broad clinical application was dose-limiting thrombocytopenia due to antagonism of BCLxL, which maintains platelet viability (38). Designed to have much greater selectivity for BCL2 through reduction in affinity for BCLxL, venetoclax showed enhanced potency against CLL but spared platelets in preclinical studies (26).

Data from model systems strongly suggest that cells that harbor high levels of BCL2 are particularly susceptible to its inhibition by venetoclax (26). Like the native BH3-only proteins, venetoclax binds with tight affinity to BCL2, thereby relieving constraints on BAX/BAK activation and initiating apoptosis. The high levels of BCL2 in CLL cells also appear to be a reservoir for bound (and thereby) inhibited endogenous BH3-only proteins, such as BIM (39, 40). Treatment with BCL2 inhibitors such as venetoclax releases BIM from BCL2 to indirectly target the other prosurvival proteins, such as MCL1 (41).

Pharmacology

Venetoclax is orally bioavailable, highly plasma protein bound (>99%) and has a terminal half-life of 16 to 19 hours (42–44). In clinical trials, dosing has been daily, and steady state is typically reached within a week. Accumulation over time is minor (44) and has not been an observed problem (43). At doses ranging between 300 and 900 mg/day, pharmacokinetic parameters are dose proportional (43). Age and race have no effect on venetoclax pharmacokinetics (44). Minor sex differences have been observed but have minimal effects on exposure. Peak concentrations are

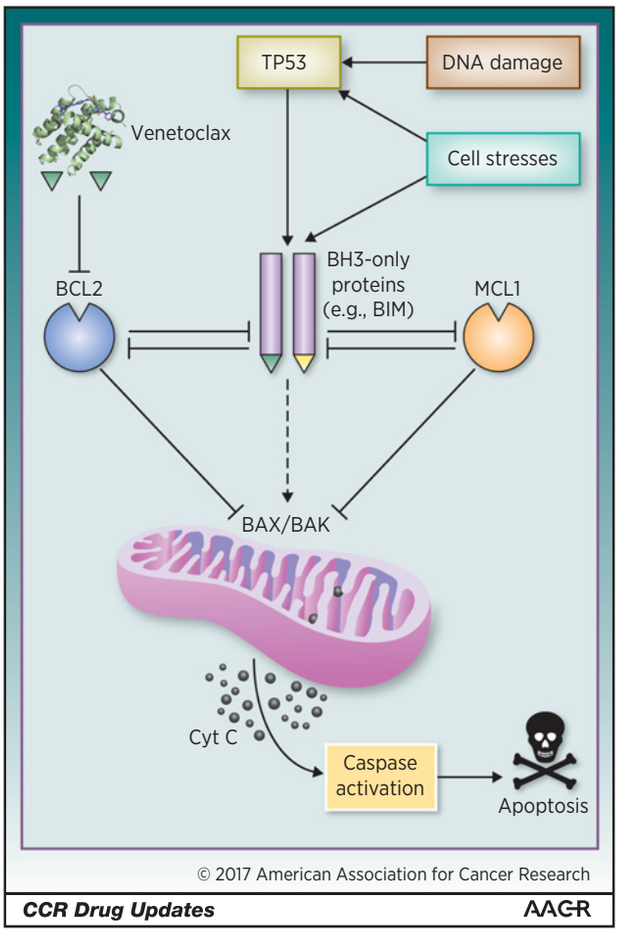

Figure 1.

The figure depicts key interactions between molecules that regulate the mitochondrial pathway to apoptosis and how venetoclax induces apoptosis by acting as a BH3 mimetic to inhibit BCL2. Apoptosis occurs when BAX and BAK are activated on the mitochondrial outer membrane, leading to depolarization, release of cytochrome C (cyt C), and activation of caspases, which demolish the cell (30, 40). In healthy cells, BAX and BAK are maintained in an inactive state through inhibition by BCL2 and similar proteins (including MCL1 and BCLxL). In turn, this repression of BAX and BAK is relieved by the actions of BH3-only proteins [including BIM, BAD, PUMA, and PMAIP1 (NOXA)] when cells undergo major stresses, such as DNA damage (34). TP53 is a major sensor of cellular stress and transcriptionally upregulates some BH3-only proteins. CLL cells maintain high levels of BCL2, in equilibrium with a pool of BH3-only proteins (particularly BIM), and low levels of MCL1 and negligible BCLxL. The expression of MCL1 and BCLxL is increased when CLL cells are stimulated by environmental growth factors, such as CD40 ligand. CLL cells with loss of TP53 function [as is common in del(17p) or *TP53* mutation] have diminished capacity to activate apoptosis, particularly after DNA-damaging chemotherapy. Venetoclax acts as a mimic of BH3-only proteins, binding to BCL2 in the same fashion as BIM, thereby relieving repression of BAX and enabling displaced BIM to interact and inhibit other prosurvival proteins, such as MCL1 (26, 39, 41). In this way, venetoclax is able to overcome the protective effect of high levels of BCL2 and to initiate apoptosis independently of TP53 (49), explaining its efficacy in del(17p) CLL. Venetoclax is depicted as both a ribbon structure and as a stylized green triangle that represents its ability to bind with high affinity to a groove in the stylized BCL2 protein. The BH3-only proteins are represented by purple cylinders with variably colored triangular heads to signify their ability to bind selectively in specific grooved regions of BCL2, MCL1, BCLxL, and other prosurvival proteins.

observed after 4 to 5 hours in fasting patients and delayed by approximately 2 hours when taken with a meal. C_{max} and AUC are also increased 3- to 5-fold when taken with food, especially a high-fat meal (45). The favored explanation for the food effect is that lipids in food increase venetoclax intestinal lymphatic transport. This not only increases the fraction of drug absorbed but also bypasses the hepatic first-pass effect and hence increases the systemic exposure. Ultimately, these food-associated differences in exposure are similar to the 2- to 3-fold differences observed between the 400 and 1,200 mg/day dose levels, both of which are tolerable. Consequently, it is recommended that venetoclax be administered once daily with a meal. No special dietary adjustment is thought necessary (45). At steady state, the peak concentration of venetoclax at the recommended dose of 400 mg/day is 2.1 ± 1.1 μg/mL when taken with a low-fat meal (42, 43).

Venetoclax is metabolized by CYP3A4/5 and is a substrate for the P-glycoprotein efflux pump (43, 46). Concomitant therapy with strong CYP3A inhibitors, such as some azole antifungals, should therefore be avoided, but if necessary, then should trigger a $\geq$75% venetoclax dose reduction (44). Concomitant use of moderate CYP3A inhibitors (e.g., erythromycin and ciprofloxacin) or P-glycoprotein inhibitors (e.g., azithromycin and cyclosporine) also requires dose modifications of at least 50% (43, 44). Venetoclax clearance does not appear to be affected in patients with mild to moderate renal or hepatic impairment (47) but has not been studied in patients with severe abnormalities of kidney or liver function. There is minimal excretion of intact venetoclax in the urine (43).

In the absence of an assay to measure saturation of intracellular BCL2 binding, it is unknown what plasma concentration corresponds with complete inhibition of BCL2 function. Consequently, the recommended dose is based on the balance of efficacy and toxicity (42), supported by pharmacokinetic and pharmacodynamic modeling (47). An MTD has not been defined, with 1,200 mg/day tolerated in an ongoing study in lymphoma (48). For CLL, the approved dose is 400 mg/day (44).

Clinical Data

Efficacy

In the first-in-human phase I trial, venetoclax induced objective responses in 79% of patients with relapsed or refractory CLL and small lymphocytic lymphoma (SLL; ref. 42). Four features distinguished the drug's activity. Firstly, antileukemic effects occurred rapidly. Reductions in circulating absolute lymphocyte count (ALC) were observed after single doses as low as 20 mg, and caspase activation and apoptotic CLL cells were detected in the blood of patients within 6 to 24 hours of the first dose (49). Clinical tumor lysis syndrome (TLS) was observed after single doses of 50 mg in two patients with bulky lymphadenopathy. As the degree of cytoreduction in the first few days of treatment was proportional to dose, therapy is most safely initiated at low doses. Formal objective responses by International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria (1) were typically documented at the time of the first scheduled CT scan (median, 6 weeks).

Second, the reductions in tumor burden in blood, nodes, and bone marrow were substantial and consistent in most patients, with the depth of response increasing over time, especially in the bone marrow and nodes. Doses ranging from 150 to 1,200 mg/day resulted in complete remissions (CR) in 20% of patients, and CRs negative for MRD by flow cytometry analysis of bone marrow were documented in some patients. Third, objective response rates were similarly high independent of the presence of a range of previously negative prognostic indices, including older age, disease refractoriness to fludarabine, del(11q), unmutated *IGHV*, and bulky adenopathy. Finally, responses were just as common and deep in patients with del(17p), consistent with the drug's ability to kill cells independently of TP53 function (49).

These observations led to a phase II study in patients with relapsed CLL bearing del(17p) (50). In 107 patients, the response rate according to iwCLL criteria, as judged by an independent review panel, was 79%. In 18 of 45 patients assessed, peripheral blood was negative for MRD by sensitive 4-color flow cytometry. The overall response and progression-free survival (PFS) estimate at 12 months [72% (95% confidence interval (CI), 62–80)] did not vary markedly by the proportion of CLL cells with del(17p), presence of *TP53* mutation, or other characteristics typically associated with poor outcomes, including refractoriness to prior therapy. As for the phase I study, responses were rapid and deepened over time. The median time was 0.8 months to first documented response, 8 months to CR, and 9 months to peripheral blood MRD negativity.

Safety

Venetoclax is generally well tolerated, although mild gastrointestinal side effects, such as nausea and loose bowel movements, are common, especially early in the course of treatment (42, 50). The most serious and potentially life-threatening toxicity, clinical TLS, is a function of its marked clinical activity. Tumor lysis requires active prevention when treatment first commences. In patients with CLL and SLL, dosing should commence with 20 mg/day for a week, followed by a weekly ramp-up in dosing through 50, 100, and 200 mg/day to the recommended dose of 400 mg/day (44, 50). Admission to hospital for intravenous hydration and intensive serial blood test monitoring for rises in phosphate and potassium is advisable for patients at particularly high risk of TLS, those with very bulky lymphadenopathy, with or without marked lymphocytosis (42). Patients without high-risk features and normal renal function can be safely managed as ambulatory patients but do require blood test monitoring for biochemical evidence of tumor lysis 6 to 8 hours and 24 hours after initiating the drug and with each ramp-up in dose (44, 50).

Neutropenia is also common in heavily pretreated patients with CLL (42, 50). Although venetoclax can selectively inhibit granulocytic progenitors (51), key contributors to the 40% to 50% incidence of grade 3/4 neutropenia on the two early-phase studies likely were the extent of previous marrow-damaging chemotherapy and the degree of bone marrow infiltration with CLL. Consistent with this, lower rates of neutropenia were reported in patients with non-Hodgkin lymphoma receiving higher doses of venetoclax (48). Neutropenia is generally well tolerated and can be managed by intermittent uses of short-acting G-CSFs or dose reduction (42). The latter is infrequently required with dosing at 400 mg/day, and data suggesting more durable disease control with doses of $\geq$400 mg support the preference for maintaining dose intensity. Serious infections are infrequent and occur most commonly in the first 3 months of treatment (42, 50). In the phase I trial, 17% of patients with CLL experienced a grade 3 or 4 infection at an exposure-adjusted rate of 1.4 per 100 patient-months (42). The incidence of >grade 3 infections in the phase II

trial was 20%, with respiratory tract infections accounting for the majority (50). No increased propensity to atypical infection has yet emerged (42, 48, 50). In contrast to the dose-limiting thrombocytopenia observed with navitoclax (37), thrombocytopenia is significantly less common during venetoclax therapy. In the phase II trial, no patients discontinued due to thrombocytopenia, and only 2% of patients required a dose reduction from 400 mg (50).

Perspectives and Context with Other Drugs

The registration of venetoclax for previously treated patients with del(17p) CLL adds to treatment options that physicians and patients can consider. To date, there are no comparative trials between ibrutinib, idelalisib plus rituximab, and venetoclax. Table 1 summarizes available data for these and other drugs, alone and in combination. For context, information is also summarized for drugs studied in the broader relapsed or refractory CLL/SLL population. Data for ibrutinib overall are more mature and indicate that although CRs are very uncommon, responses are generally durable, albeit somewhat shorter among patients with del(17p) (52, 53). Administration as monotherapy is usually straightforward after the exclusion of patients taking medications that are either potentially interacting or that increase the risk of bleeding (anticoagulants and platelet function inhibitors). The major novel toxicities are bruising and an increased incidence of atrial fibrillation (16, 52). Fewer data are available for idelalisib in combination with rituximab for durability of response, and delayed onset diarrhea, colitis, and pneumonitis can be problematic (18). Second-generation BTK inhibitors are now being developed and demonstrate excellent efficacy in early trials (54).

Venetoclax offers a distinctly different mechanism of cell killing (26, 49). Although the initiation of therapy requires attention to detail and may include hospitalization, BCL2 inhibition achieves an unprecedented CR rate in heavily pretreated patients (42), including those with del(17p) and/or *TP53* mutation (49, 50). Although experience is limited, there is no prima facie evidence of cross-resistance between ibrutinib and venetoclax, and sequential use is a reasonable option (55, 56).

As for most cancer therapies, combination therapies are anticipated to improve response rates and reduce progressions on therapy. In theory, BCL2 inhibitors, such as venetoclax, should be additive or synergistic with drugs that create intracellular stresses that prime the cell for death (57), such as DNA-damaging chemotherapy (51, 58), mAbs (26, 59), and BCR inhibitors (60). For patients with CLL, combinations with anti-CD20 antibodies and with BTK inhibitors have particular attraction. To date, only data for the combination of venetoclax and rituximab are sufficiently mature to consider here (61). In a phase Ib study of patients with relapse or refractory CLL/SLL, the addition of six 4-weekly doses of rituximab to venetoclax had minimal effect on the adverse event profile and no effect on venetoclax pharmacokinetics. An objective response rate of 86% and a CR rate of 51% were observed, with 40% of patients achieving MRD-negative CR status. The 2-year estimate for PFS was 80% and 90% for ongoing response. Trials combining venetoclax with ibrutinib (NCT02756897), obinutuzumab (NCT02242942 and NCT01685892), or both (NCT02427451 and NCT02758665) are now underway.

Conclusions and Future Directions

Venetoclax is the first selective BCL2 inhibitor and the first BH3 mimetic drug to receive FDA approval. Consistent with the central role BCL2 plays in maintaining survival of these leukemia cells, venetoclax is highly active against CLL, irrespective of the presence of adverse clinical or genetic features. Current FDA approval is for use in previously treated patients with del(17p) CLL, and the drug also induces durable responses in the broader population of patients with relapsed or refractory CLL. We anticipate that novel combination therapies, including venetoclax, will further transform the landscape of treatment for patients with relapsed CLL, particularly those with del(17p) CLL.

Disclosure of Potential Conflicts of Interest

A.W. Roberts reports receiving commercial research grants from AbbVie, Genentech, Janssen, and Servier. A.W. Roberts and D.C.S. Huang are employees of the Walter and Eliza Hall Institute of Medical Research that receives milestone and royalty payments related to venetoclax. S. Stilgenbauer reports receiving commercial research grants and speakers bureau honoraria from and is a consultant/advisory board member for AbbVie, Genentech, Gilead, Janssen, Pharmacyclics, and Roche. J.F. Seymour reports receiving commercial research grants from AbbVie and Janssen, speakers bureau honoraria from AbbVie, Celgene, Gilead, and Roche, and is a consultant/advisory board member for AbbVie, Celgene, Genentech, Gilead, Janssen, Roche, and Takeda.

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S. Stilgenbauer
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