Venetoclax in Patients with Previously Treated Chronic Lymphocytic Leukemia

Andrew W. Roberts1,2,3,4, Stephan Stilgenbauer5, John F. Seymour1,3,4, and David C.S. Huang2,3

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 mimic), 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).
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 intranidividual 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).

<table>
<thead>
<tr>
<th>Table 1. Drug activity in relapsed or refractory CLL</th>
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<td><strong>Phase</strong></td>
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**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/ys, year/years.

*aNational Cancer Institute Working Group (NCI-WG) criteria for response only reported.*
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 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., BCL2L1 (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 mimic 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-2H-pyran-4-yl)methyl]aminophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yl)benzamide; ref. 26). Venetoclax was developed by structure-informed reverse engineering of navitoclax, a first-generation BH3 mimic 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 mimic 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 demobilize 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 MCL1 (41)], which demobilize 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 MCL1 (41)].

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observed after 4 to 5 hours in fasting patients and delayed by approximately 2 hours when taken with a meal. $C_{\text{max}}$ and AUC were 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 (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 (45) 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 data suggesting more durable disease control be managed by intermittent uses of short-acting G-CSFs or dose ramp-up with CLL. Concomitant therapy with weak CYP3A inhibitors, such as some azole antifungals, should therefore be avoided, but if necessary, then should trigger a ≥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 (45) 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).

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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 ≥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 ibritunib, 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 ibritunib 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 (antiocoagulants 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 ibritunib 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 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 ibritunib (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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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.W. Roberts

Writing, review, and/or revision of the manuscript: A.W. Roberts, S. Stilgenbauer, J.F. Seymour, D.C.S. Huang

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

Other (approval of final version): J.F. Seymour

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