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How I Treat

How I manage CLL with venetoclax-based treatments

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Targeted therapies for chronic lymphocytic leukemia (CLL) include venetoclax, the oral inhibitor of B-cell lymphoma-2, and inhibitors of kinases in the B-cell receptor signaling pathway, like Bruton tyrosine kinase and phosphatidylinositol 3 kinase. Randomized clinical trials clearly demonstrated improved progression-free survival with targeted therapy over chemoimmunotherapy in first-line and treatment of relapsed/refractory CLL. Comparative trials of venetoclax-based vs other targeted therapies have not been conducted. Differentiating features and considerations with targeted therapies include goals of treatment and therapeutic approach as well as side effect and toxicity profiles. With targeted therapy options for first-line and relapsed CLL, it is ever more important to develop sound rationale and strategy for selecting first-line and treatment of relapsed disease and for long-term management of the disease, including therapeutic sequencing. Fixed-duration therapy with a treatment-free remission is a particularly appealing prospect, since it avoids continuous exposure to treatment and potential for toxicity. We discuss rationale and practical application of venetoclax in first-line and treatment of relapsed and refractory CLL. Venetoclax is highly active at achieving deep remission for most treated patients with CLL, including those with high-risk disease such as del(17p) CLL. (*Blood*. 2020; 135(17):1421-1427)

Introduction and background

Remarkable progress has been made over the past 6 years in targeted therapy for patients with chronic lymphocytic leukemia (CLL). Prior evolution in chemoimmunotherapy (CIT) led to development of progressively more effective combinations, but at the cost of myelosuppression and risk for infection and long-term marrow damage. High levels of B-cell lymphoma-2 (BCL2) protein are expressed in CLL, contributing to resistance to apoptosis. Venetoclax is an oral BCL2 inhibitor (BCL2i) that is highly potent at inducing apoptosis in CLL cells by a p53-independent mechanism and was initially approved for treatment of relapsed/refractory (R/R) del(17p) CLL (M13-982; Table 1)[1-5] and then more broadly with rituximab in relapsed CLL based on the phase 3 MURANO trial that showed improved progression-free survival (PFS) over CIT-based therapy (Table 1).[6] First-line treatment with venetoclax plus obinutuzumab showed improved PFS vs CIT in patients with comorbidities who tended to be older (CLL14; Table 1).[7] Bruton tyrosine kinase (BTK) is an important molecule in the B cell receptor signaling pathway. The era of targeted therapy for CLL was ushered in with development of the irreversible oral small-molecule inhibitor of BTK (BTKi) ibrutinib. Multiple phase 3 trials recently reported improved PFS with BTKi-based treatment vs CIT, comparing across the spectrum of patient age, comorbidities and CIT intensity.[8-11] Acalabrutinib, a second-generation BTKi, was recently approved for treatment of both first-line and relapsed CLL. No trial has shown clear clinical benefit with early treatment of CLL, including with targeted therapy; therefore, treatment is only initiated when patients develop active disease requiring treatment according to the standard International Working Group on CLL criteria.[12]

The therapeutic strategy with CIT was to treat with several courses (typically 6) to remission, and then observation in remission until progression and retreatment for recurrent active, progressive disease; CIT was not considered curative for most patients. Venetoclax-based treatment is highly potent at eliminating CLL and able to achieve deep remission with fixed-duration therapy.[6,7] Retreatment at relapse, progression, and active disease is anticipated, and limited data support this concept.[13] BTKi-based treatment is highly effective at gaining disease control and reducing bulk of disease, especially nodal disease; deep remissions are uncommon but can occur with very prolonged therapy, and treatment is typically continuous, until progression.[14-17] Both venetoclax- and BTKi-based treatments are effective for high-risk CLL, particularly del(17p) and *TP53*-mutated CLL, where CIT should not be used.[14,18] Furthermore, they are effective in treating immunoglobulin heavy chain variable gene (IGHV)-unmutated CLL. Venetoclax- and BTKi-based treatments each have unique toxicities and side-effect profiles that must be considered in selecting treatment; resistance mechanisms are also unique. Because neither is currently considered curative and owing to the chronicity of CLL, therapeutic sequencing is an important consideration and should be kept in mind, including when selecting first-line treatment. Table 1 summarizes studies with venetoclax-based treatments, including trials in first-line and R/R CLL and monotherapy and combinations with continuous and fixed-duration treatment.

Table 1. Efficacy of venetoclax-based treatment of CLL

Study	Phase	Treatment	Population	n	ORR, %	CR/CRi, %	uMRday 4, %	mPFS, mo	24-mo PFS, % (mo)	OS, % (mo)	NCT #
M12-175[2]	1/2	VEN cont	R/R	116	79	20	NP	25	69 (15)	84 (24)	01328626
M13-365[6,13]	1b	VEN cont	R/R	49	86	51	57 (BM)	NR	56 (60)	NP	01682616
M13-982[1,18]	2	VEN cont	R/R Del(17p)	158	77	20	30 (PB)	27.2	54	73 (24)	01889186
M14-032[3,4]	2	VEN cont	R/R								02141282
			BTKi Ref/Intol	91	65	9	26 (PB)	24.7	80 (12)	NR	
			PI3Ki Ref/Intol	36	67	8	20 (PB)	NR	79 (12)	NR	
MURANO[6,28]	3	VEN 24 cycles RIT 6 cycles	R/R	194	92.3	8.2	62.4 (PB) 27.3 (BM)	NR	84.9	91.9 (24)	02005471
		vs									
		BEN 6 cycles OBIN 6 cycles		195	72.3	3.6	13.3 (PB) 1.5 (BM)	17	36.3	86.6 (24)	
GNE[27]	1/2	VEN 12 cycles OBIN 6 cycles	TN	32	100	78	78/78 (PB/BM)	NR	90.6	NP	01685892
			R/R	43	95	37	63/62 (PB/BM)		85.4	NP	
CLL14[7]	3	VEN 12 cycles OBIN 6 cycles	TN	216	84.7	49.5	75.5 (PB) 56.9 (BM)	NR	88.2	NR	02242942
		vs									
		CHLOR 12 cycles OBIN 6 cycles		216	71.3	23.1	35.2 (PB) 17.1 (BM)	NR	64.1	NR	
MDACC[34]	2	VEN 24 cycles IBR 27+ cycles	TN	80	100 (1 y)	88 (1 y)	61 (1 y) (BM)	NR	98 (12)	99 (12)	02756897
CLARITY[33]	2	VEN 12 cycles IBR 12 cycles	R/R	53	89 (1 y)	51 (1 y)	53 (PB) 36 (BM)	NR	NP	100	NP
CLL2-BAG[5]	2	BEN 2 cycles	TN	34	100	9	91 (PB) 12 (BM)	NR	100 (15)	100 (15)	02401503
		OBIN 6 cycles,M VEN cont	R/R	29	90	7	83 (PB) 14 (BM)	NR	83 (15)	90 (15)	

BEN, bendamustine; BM, bone marrow; cont, continuous; CR/CRi, complete remission/complete remission with incomplete count recovery; GNE, Genentech sponsored study; IBR, ibrutinib; M, maintenance; MDACC, MD Anderson Cancer Center; mPFS, median PFS; number; NP, not provided; NR, not reached; ORR, overall response rate; PB, peripheral blood; Ref/Intol, refractory and/or intolerant; RIT, rituximab; TN, treatment naive; VEN, venetoclax.

Table 2. Strategy for selecting first-line CLL treatment

TP53 status (del(17p)/*TP53* mutation)	Age/ fitness	IGHV MS	First-line treatment (in order of authors' preference)
TP53 deleted and/ or mutated	All	Either	(1) BTKi ± OBIN (continuous), (2) VEN + OBIN (fixed duration), no CIT
TP53 intact	Younger/ fit	Mutated	(1) FCR (fixed duration), (2) VEN + OBIN (fixed duration), (3) BTKi ± OBIN (continuous)
		Unmutated	(1) VEN + OBIN (fixed-duration), (2) BTKi ± OBIN (continuous)
	Older/ unfit	Mutated	(1) VEN + OBIN (fixed duration), (2) BTKi ± OBIN (continuous)
		Unmutated	(1) BTKi ± OBIN (continuous), (2) VEN + OBIN (fixed-duration)

FCR, fludarabine, cyclophosphamide, and rituximab; MS, mutation status; OBIN, obinutuzumab.

Factors affecting first-line treatment selection

A thoughtful strategy for managing CLL requires selecting first-line treatment based on patient characteristics, especially given multiple current treatment options, including CIT and BTKi- and venetoclax-based treatments. Owing to multiple treatment options and approaches, it is ever more important to clearly articulate the rationale and goals for treatment selection. Essential considerations for fist-line treatment are patient age and comorbidities, *TP53* status (including del(17p) and *TP53* mutation status), IGHV mutation status, and goal(s) of treatment (Table 2). In addition, cardiac history and status, concomitant medications, renal function, bulk of CLL, and financial and patient and logistic access are important. In selecting targeted therapy according to goals of treatment, fixed-duration treatment achieving deep remission and prolonged treatment-free interval is appealing over continuous therapy, given the reduced exposure time, reduced potential for toxicities, and long-term convenience with fixed-duration therapy (Table 2). With venetoclax-based treatment, there is an initial requirement for close monitoring on initiation and ramp-up, but once on the target dose, monitoring is similar to BTKi-based treatment.

Patient 1

Patient 1 is a 77-year-old physically active, retired physician with hypertension and coronary artery disease (prior cardiac stent) and a Cumulative Illness Rating Scale (CIRS) score of 5. CLL was diagnosed 8 years ago (currently, no palpable lymph nodes, no del(17p), *TP53* wild-type, IGHV mutated [5.6% deviation from germline]; absolute lymphocyte count [ALC] 145 × 10^9/L, hemoglobin [Hgb] 10.6 g/dL, platelet [PLT] count 137 × 10^9/L, and creatinine clearance [CrCl] 65 mL/min). Indications for treatment included progressive anemia and fatigue.

First-line treatment options for this older patient with comorbidities include lower-intensity CIT, BTKi-based, and venetoclax-based regimens. Improved PFS, but not overall survival (OS), was demonstrated in phase 3 first-line trials with both targeted therapies over CIT.[7-10] Although this patient had intact *TP53*, a *TP53* abnormality (either deletion or mutation) would certainly exclude CIT as a treatment option. PFS has been considered a surrogate for OS with traditional fixed-duration CIT, and differences in OS are difficult to appreciate in first-line trials for CLL; longer follow-up may be needed to identify the superior treatment in this regard for targeted therapy trials. The authors' selection of venetoclax over BTKi is based on advanced age, history of cardiac disease, IGHV-mutated status, and desire for fixed-duration treatment. The deep remission that is expected with fixed-duration venetoclax-based treatment in a patient with IGHV-mutated may eliminate the need for any future treatment in this 77 year old.

TLS risk mitigation and management This patient was treated with venetoclax-based treatment according to the CLL14 regimen.[7] Allopurinol was initiated before treatment and course 1 treatment was with obinutuzumab monotherapy, which typically results in rapid resolution of lymphocytosis. Indeed, treatment of course 1 with obinutuzumab monotherapy can effectively decrease tumor lysis syndrome (TLS) risk category, notably bringing most high- and medium-risk patients down to medium- and low-risk TLS category, respectively.[7,19] We typically also begin herpesvirus prophylaxis prior to starting therapy. There is no clear indication for routine *Pneumocystis jirovecii* pneumonia bacterial or fungal prophylaxis in the first-line setting. Prior to initiating venetoclax in course 2, the patient should have had a staging computed tomography (CT) of chest, abdomen, and pelvis to fully evaluate risk for TLS upon starting the venetoclax ramp-up. Course 1 of obinutuzumab typically resolves lymphocytosis in most patients and has variable effect in reducing nodal disease; therefore, it is the authors' opinion that CT is best performed toward the end of course 1 and prior to course 2. Venetoclax ramp-up is initiated with course 2 with TLS monitoring based on extent of CLL and according to prescribing information for risk mitigation. First-line, fixed-duration treatment begins course 1, day 1 with obinutuzumab, and venetoclax ramp-up begins on course 1, day 22. Total therapy consists of 12 courses; the first 6 courses include obinutuzumab (8 doses total), and venetoclax (28-day courses) continues through course 12, according to CLL14 trial design. Patient 1 had CrCl of 65 mL/min, no lymph nodes >2 cm on CT, and ALC <25 × 10^9/L and was therefore managed as a low-risk for TLS with venetoclax initiation. If he were medium or higher risk for TLS, he might need admission and monitoring for first dose and first dose escalation. Weekly dose escalations can be monitored as outpatient. Risk for clinically significant TLS is very low if the prescribing information is followed for venetoclax ramp-up.

There was no age restriction for enrollment on CLL14, only requirement for CIRS >6, but patients treated on this trial tended

to be older, with median age of 72 yrs.[7] For patients such as Patient 1, with no abnormality in *TP53* [no del(17p) or mutated *TP53*] and IGHV-mutated, the complete remission (CR) rate was 51.3%, blood undetectable minimal residual disease (uMRD) (10^{-4} sensitivity) rate was 73.7% and 24-month PFS rate was ~90% with 1 year of fixed-duration treatment. While the 24-month PFS rate was not significantly different for venetoclax-based treatment vs CIT for patients with IGHV-mutated, the blood uMRD rate was nearly twice (74% vs 43%, respectively). With this difference in uMRD, there is an expectation for improved PFS with venetoclax-based treatment with longer follow-up. Overall, rates of grade ≥3 neutropenia (52.8% vs 48.1%, respectively) and infection (17.5% and 15.0%, respectively) were not significantly different, and there was no difference in OS (24-month survival of 91.8% vs 93.3%, respectively) in this trial with venetoclax- vs chlorambucil-based first-line treatment.

Patient 2

Patient 2 is a 60-year-old architect with no notable comorbidities but with progressive fatigue resulting in elimination of regular exercise and drenching night sweats occurring twice weekly on average. CLL was diagnosed 4.5 year ago (currently, bilateral palpable 2-cm axillary lymph nodes, no del(17p), *TP53* wild-type, IGHV unmutated [0% deviation from germline]; ALC 70 × 10^9/L, Hgb 11.3 g/dL, PLT count 103 × 10^9/L, CrCl 92 mL/min).

Patient 2 was symptomatic with progressive cytopenias indicating active CLL needing treatment. Options for treatment of this patient included CIT and BTKi- and venetoclax-based treatment. Factors important for selecting first-line treatment of this patient included his younger age and IGHV-unmutated status (Table 2). The most effective CIT is FCR. The median PFS with FCR is ~55 months compared with 42 months with bendamustine plus rituximab, with >90% expected to progress with follow-up for patients with IGHV unmutated.[20] CIT employs genotoxic therapy, and its use is associated with a risk for secondary hematologic malignancies such as myelodysplastic syndrome and acute myeloid leukemia in 3% to 5% of patients who receive FCR.[21,22] A phase 3 trial evaluated first-line ibrutinib and rituximab to standard FCR in untreated patients <70 years old.[11] This trial showed improved PFS for ibrutinib and rituximab vs FCR (hazard ratio, 0.35; $P < .001$) and OS of 98.8% vs 91.5% at 3 years (hazard ratio for death, 0.17; $P < .001$). The expected 5-year PFS is 70% with first-line ibrutinib-based continuous treatment,[9] and the expected 2-year PFS is 88% with venetoclax-based 1-year fixed-duration first-line treatment.[7] Both BCL2i- and BTKi-based therapies have superior PFS over CIT and eliminate exposure to genotoxic treatment. The authors prefer nongenotoxic, targeted, fixed-duration therapy and are comfortable extrapolating the outcomes expectations of CLL14 to a younger, fit population. Therefore, venetoclax plus obinutuzumab was chosen to treat patient 2. Of note, the long-term risk for secondary myelodysplastic syndrome/acute myeloid leukemia and for Richter transformation with targeted therapy is unknown and requires further long-term follow-up in large numbers of patients treated with these treatments.

Managing venetoclax-associated neutropenia Allopurinol was started, and then treatment was initiated with course 1 obinutuzumab and CT of the chest, abdomen, and pelvis was performed to assess TLS risk with venetoclax. Venetoclax ramp-up was initiated with course 2 to the target dose of 400 mg/day, according to the prescribing information, to avoid TLS. The patient was noted to have an absolute neutrophil count (ANC) of 0.467 × 10^9/L at the 200 mg/day dose during the venetoclax ramp-up. Pegylated filgrastim was administered and continued intermittently to maintain ANC >1 × 10^9/L through ramp-up to the target 400 mg/day dose and for first 3 months of treatment without venetoclax dose interruption to maintain the venetoclax target dose. Intermittent filgrastim may be similarly effective and sufficient but requires blood count checks and closer monitoring for dosing. The rationale for achieving the venetoclax target dose, not interrupting venetoclax dosing, and maintaining target dose with the use of neutrophil growth factor support to maintain ANC >1 × 10^9/L is that the CLL bone marrow burden is initially high, and maintaining venetoclax dose intensity early will clear the marrow and allow for better recovery of counts. Venetoclax is myelosuppressive; 53% of patients treated with venetoclax and obinutuzumab in CLL14 experienced grade ≥3 neutropenia, and 14% experienced grade ≥3 thrombocytopenia.[7] Infection grade ≥3 occurred in 18% of patients treated with venetoclax-based therapy in this study.

Table 3. Strategy for selecting treatment of R/R CLL

Prior treatment			Recommendation for next treatment	Allo-SCT planning
CIT	BCL2i	BTKi		
Yes	No	No	VEN + RIT (fixed duration) or BTKi (continuous)	No
		Yes (intolerant)	Alternative BTKi (continuous) or PI3Ki ± CD20 mAb (continuous)	No
		Yes (refractory)	VEN + RIT	Short-term
	Yes	No	BTKi (continuous)	Yes
		Yes (intolerant)	Alternative BTKi (continuous) or PI3Ki ± CD20 mAb (continuous)	Yes
		Yes (refractory)	Clinical trial CIT if no *TP53* abnormality to debulk	Immediate
No	No	Yes (intolerant)	Alternative BTKi (continuous) or PI3Ki ± CD20 mAb (continuous)	No
		Yes (refractory)	VEN + RIT (fixed duration)	Yes
	Yes	No	BTKi (continuous)	No
		Yes (intolerant)	Alternative BTKi (continuous) or PI3Ki ± CD20 mAb (continuous)	No
		Yes (refractory)	Clinical trial CIT if no *TP53* abnormality to debulk	Immediate

Allo-SCT, allogeneic stem cell transplant; BCL2i, BCL2 inhibitor; mAb, monoclonal antibody; PI3Ki, PI3K inhibitor.

The authors' practice is to reduce the dose of venetoclax if there is recurrent neutropenia beyond the first 3 or 4 months on the highest tolerated dose of venetoclax with neutrophil growth factor support or if treatment with neutrophil growth factor dose not result in improvement in ANC. Grade >3 obinutuzumab-related infusion reactions occurred in 9% of patients treated on CLL14. Although uncommon, grade 4 thrombocytopenia may require venetoclax dose reduction.[23] Venetoclax is a cytochrome P450 3A (CYP3A) substrate, and when taken concurrently with CYP3A inhibitors, such as "azole" antibiotics, the pharmacokinetics are altered, leading to increased exposure. Therefore, venetoclax dose reduction by 50% and 75% is recommended when combined with moderate and strong inhibitors of CYP3A, respectively.[24]

uMRD and depth of remission Consistent with CLL14, the intended treatment course for patient 2 is obinutuzumab for the first 6 courses and venetoclax for a total of 12 courses, followed by response assessment with CT scan, blood count, and blood MRD evaluation (10^{-4} sensitivity). This enables estimation of PFS and time off treatment; uMRD is correlated with longer PFS. Follow-up monitoring is every 3 to 6 months with routine clinic visit and blood counts. Patients are not monitored with scheduled CT scans or bone marrow evaluations during follow-up.

Selecting treatment of R/R CLL

Patient 3

Patient 3 is a 75-year-old retired teacher with hypertension and reflux disease and a CIRS score of 7. CLL was diagnosed 5 years ago; ibrutinib was started 3 years ago for active del(17p) CLL and was well tolerated with no dose adjustments (currently, ALC is increasing with a newly noted 2-cm palpable cervical lymph node, del(17p), *TP53* mutated, IGHV unmutated [0%], BTK-mutated [C481S]; ALC 55 × 10^9/L, Hgb 10.6 g/dL, PLT count 145 × 10^9/L, CrCl 70 mL/min).

This patient is developing ibrutinib-refractory CLL with rising ALC and newly noted lymph node and rising ALC while on ibrutinib and mutation in BTK (C481S); a new treatment is indicated for this patient with high-risk CLL. CIT is contraindicated for this patient with defective *TP53*; switching to an alternative irreversible BTKi is contraindicated due to the presence of BTK mutation, and switching to an alternative inhibitor of the B-cell receptor signaling pathway such as phosphatidylinositol 3 kinase (PI3K) inhibitor is unlikely to result in a response. BCL2i-based therapy with venetoclax has shown durable responses in patients who develop BTKi-refractory CLL, and is the best treatment choice for this patient. Continuous venetoclax monotherapy was initially approved for patients with R/R del(17p) CLL, like this patient. Table 3 illustrates considerations for selecting treatment of R/R CLL, which are heavily dependent on prior treatment and refractoriness to treatment. In addition, while not the case for this patient, suspicion for Richter transformation should be evaluated with positron emission tomography/CT followed by biopsy of fluorodeoxyglucose-avid nodes (standardized uptake value >5).[25]

Venetoclax with CD20 mAb and duration of treatment in R/R CLL Although not formally demonstrated in a randomized clinical trial, it is the opinion of the authors that the addition of a CD20 mAb improves efficacy of venetoclax therapy. Therefore, this patient was treated with venetoclax plus rituximab similar to in the MURANO trial, which included patients previously treated with BTKi-based treatment. Due to this patient having progressive CLL while on ibrutinib, ibrutinib should be continued through venetoclax ramp-up for overlap of these agents to avoid the explosive CLL disease flare that is commonly seen with BTKi discontinuation in patients who are progressing on BTKi.[26] TLS risk assessment is important for this patient; therefore, a staging CT scan should be performed prior to initiating venetoclax, and the patient must be started on allopurinol or equivalent. TLS risk mitigation measures should be taken according to the prescribing information. Venetoclax ramp-up was initiated first, with rituximab planned to begin during course 2 when up to 400 mg/day dose. An alternative CD20 mAb to consider is obinutuzumab, which is a superior CD20 mAb for treating CLL; however, it is not currently US Food and Drug Administration approved for R/R CLL, but it has been studied with venetoclax in a limited number of patients with R/R CLL.[27] Rituximab was given for 6 monthly doses as in MURANO. Although the MURANO trial studied 24-course fixed-duration treatment, there are 2 situations where continuing venetoclax beyond this could be considered: (1) in relapsed patients with defective *TP53*, such as patient 3; and (2) in patients who are blood MRD positive after 24 courses of venetoclax. Both are at risk for shorter PFS if venetoclax is discontinued.[28] Patient 3 was both MRD positive after 24 courses and had defective *TP53* and therefore continued venetoclax monotherapy. He experienced neutropenia (ANC 0.755 × 10^9/L) in course 9 of venetoclax. Pegylated filgrastim was given, but neutropenia recurred 1 month later, so the venetoclax dose was decreased to 300 mg/day without recurrence of neutropenia.

The median PFS for R/R del(17p) CLL with venetoclax monotherapy was 24 months, but this might be improved with the addition of rituximab. Of note, while not useful in selecting next therapy, a prognostic model to predict OS for relapsed patients going on targeted therapy was developed based on β-2 microglobulin, lactate dehydrogenase, Hgb, and time from last therapy.[29] Patient 3 has very-high-risk CLL by virtue of having defective *TP53*, relapsed, and BTKi-refractory disease; therefore, long-term disease control should consider allo-SCT as an option. This patient is older and may not have a suitable available donor. Allo-SCT should be considered when patient achieves best response with venetoclax-based treatment, if this is an option. In addition, clinical trials of CD19-chimeric antigen receptor T-cell therapy, reversible BTKi, or another novel strategy are reasonable considerations for this patient.

Current and future states

While CLL14 enrolled patients with comorbidities who tended to be older, the authors are comfortable extrapolating the efficacy results of this trial to younger fit patients, making venetoclax plus obinutuzumab a highly active first-line fixed-duration treatment option also available for these patients who might not want continuous BTKi-based therapy or CIT. Bone marrow and blood uMRD status has been associated with longer PFS and OS, and it is a treatment goal with venetoclax-based therapy to allow fixed-duration therapy with treatment-free interval. We now have a treatment with venetoclax, which can be administered to older

patients with comorbidities to achieve blood uMRD remission in the majority of these patients, many of whom may never need another treatment given their advanced age.

Characteristics associated with lower complete remission rate and shorter duration of response with venetoclax-based treatment in R/R CLL include presence of bulky lymph nodes (≥5 cm) and refractoriness to BTKi.[30] Shorter duration of response was also associated with abnormality in *TP53* and mutated *NOTCH1*.[30] These might be patients for whom active allo-SCT planning is initiated. Longer duration of response was clearly associated with achieving uMRD status. Consideration for continued venetoclax monotherapy after combination with rituximab for relapse/refractory CLL should be given to patients with persistent MRD at the end of 24 cycles of venetoclax and for those with *TP53* abnormality (deletion or mutation), since these patients are more likely to progress sooner upon discontinuing venetoclax.[28]

Further progress in treatment of CLL will come with developing treatments that achieve a higher proportion of patients with uMRD remission with shorter fixed-duration treatment. Deeper remissions are expected with longer PFS and OS and may result in immune-reconstitution and reduced risk for infection, autoimmunity, and second cancers. Key objectives include reducing and eliminating the risk of developing (1) Richter transformation, (2) CLL clonal evolution, and (3) refractory disease. Access and affordability of these highly effective treatments are key considerations. Treatment with combined targeted agents certainly has the potential to increase cost, so we must strive for shorter fixed-duration treatments to be feasible and practical.

The rationale for combining BTKi with BCL2i was built on clinically complimentary activity; BTKi's are highly active in treating and shrinking nodal disease, and BCL2i is highly effective at clearing blood and bone marrow. In vitro studies demonstrated reduced MCL1 with BTKi treatment potentially making cells more vulnerable to BCL2i-induced apoptosis.[31] Promising early results with this combination were reported in first-line and relapsed CLL.[32-34] Remaining questions with this strategy include the role of CD20 mAb, predictive markers for response and outcomes, optimal duration of combined therapy, how to manage relapsed disease, and clinical characteristics of CLL refractory to targeted therapy. Indeed, a randomized comparison of venetoclax plus obinutuzumab vs venetoclax plus BTKi is planned by the German CLL Study Group with CLL17.

Another important concept is understanding the therapeutic plateau with targeted therapy. With BTKi-based treatment, there is continued clinical benefit and disease control with continued exposure, and deeper remissions are reported with prolonged (years) exposure, but remissions typically are not deep enough to consider discontinuing treatment of the majority of patients, and there is a concern for selecting for resistance with cycling off and on BTKi treatment. With venetoclax-based treatment, there is patient heterogeneity in kinetics of response; the optimal exposure duration has not been defined and is likely multifactorial. Responses with venetoclax-based treatment tend to take longer, and duration of response is generally shorter during the treatment-free follow-up for patients with R/R CLL compared with patients receiving first-line treatment. Patients with R/R CLL tend to have more proliferative disease, and deeper remissions are likely necessary to have a reasonable remission duration off treatment. Venetoclax appears to be a very appealing partner for combination therapies, given the potency in reducing bulk of CLL and its apparent ability to lower the threshold for apoptosis and potentially synergize with most therapeutic agents.

Conclusions

Venetoclax offers a targeted therapy that is extremely potent at eliminating CLL, including high-risk del(17p)/mutated-*TP53* CLL and CLL refractory to CIT. Venetoclax initiation and ramp-up require TLS risk assessment and risk-stratified monitoring and mitigation measures, which can be cumbersome but allow for universally safe initiation and escalation. Extended, fixed-duration venetoclax treatment is well tolerated, with potential for mild myelosuppression and infrequent need for dose-adjustment for toxicity (most commonly neutropenia). The addition of CD20 mAb is thought to improve responses, and fixed-duration treatment is recommended for first-line treatment and treatment of standard-risk relapsed CLL. There are clear data supporting use of obinutuzumab with venetoclax in first-line treatment and with rituximab in relapsed CLL, but no data supporting use of obinutuzumab with venetoclax in relapse disease. Undetectable MRD status with fixed-duration treatment is achieved in the majority of patients treated with venetoclax-based treatment. This is appealing, since it offers potential for a treatment-free interval of remission for most patients, which could be very long for patients with favorable disease features, such as intact *TP53* and IGHV mutated. Indeed, current work is focused on developing regimens with combined targeted therapy that achieve the highest uMRD rate with shorter fixed-duration treatment. It will require longer follow-up to assess potential for cure with this strategy and clarify outstanding questions delineated above.

Authorship

Contribution: W.G.W. reviewed the literature, developed patient cases, constructed and assembled content, wrote the review, and reviewed the manuscript; and F.P.T. reviewed the literature, developed patient cases, wrote the review, and reviewed the manuscript.

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Footnote

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REFERENCES

1. Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. *Lancet Oncol*. 2016;17(6):768-778.
2. Roberts AW, Davids MS, Pagel JM, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2016;374(4):311-322.
3. Jones JA, Mato AR, Wierda WG, et al. Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2018;19(1):65-75.
4. Coutre S, Choi M, Furman RR, et al. Venetoclax for patients with chronic lymphocytic leukemia who progressed during or after idelalisib therapy. *Blood*. 2018;131(15):1704-1711.
5. Cramer P, von Tresckow J, Bahlo J, et al. Bendamustine followed by obinutuzumab and venetoclax in chronic lymphocytic leukaemia (CLL2-BAG): primary endpoint analysis of a multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2018;19(9):1215-1228.
6. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med*. 2018;378(12):1107-1120.
7. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med*. 2019;380(23):2225-2236.
8. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. *N Engl J Med*. 2018;379(26):2517-2528.
9. Burger JA, Barr PM, Robak T, et al. Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study [published online ahead of print 18 October 2019]. *Leukemia*. doi:10.1038/s41375-019-0602-x
10. Moreno C, Greil R, Demirkan F, et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019;20(1):43-56.
11. Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib-rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. *N Engl J Med*. 2019;381(5):432-443.
12. Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood*. 2018;131(25):2745-2760.
13. Brander DM, Seymour JF, Kipps TJ, et al. Durability of responses on continuous therapy and following drug cessation with venetoclax and rituximab: long-term follow-up analysis of a phase 1b study in patients with relapsed CLL [abstract]. *Blood*. 2019;134(suppl 1):3036. Abstract 3036.
14. O'Brien S, Furman RR, Coutre SE, et al. Ibrutinib as initial therapy for elderly patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: an open-label, multicentre, phase 1b/2 trial. *Lancet Oncol*. 2014;15(1):48-58.
15. Byrd JC, Furman RR, Coutre SE, et al. Three-year follow-up of treatment-naïve and previously treated patients with CLL and SLL receiving single-agent ibrutinib. *Blood*. 2015;125(16):2497-2506.
16. Coutré SE, Furman RR, Flinn IW, et al. Extended treatment with single-agent ibrutinib at the 420 mg dose leads to durable responses in chronic lymphocytic leukemia/small lymphocytic lymphoma. *Clin Cancer Res*. 2017;23(5):1149-1155.
17. O'Brien S, Furman RR, Coutre S, et al. Single-agent ibrutinib in treatment-naïve and relapsed/refractory chronic lymphocytic leukemia: a 5-year experience. *Blood*. 2018;131(17):1910-1919.
18. Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax for patients with chronic lymphocytic leukemia with 17p deletion: results from the full population of a phase II pivotal trial. *J Clin Oncol*. 2018;36(19):1973-1980.
19. Kater AP, Kersting S, van Norden Y, et al; HOVON CLL study group.. Obinutuzumab pretreatment abrogates tumor lysis risk while maintaining undetectable MRD for venetoclax + obinutuzumab in CLL. *Blood Adv*. 2018;2(24):3566-3571.
20. Eichhorst B, Fink AM, Bahlo J, et al; German CLL Study Group (GCLLSG). First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. *Lancet Oncol*. 2016;17(7):928-942.
21. Benjamini O, Jain P, Trinh L, et al. Second cancers in patients with chronic lymphocytic leukemia who received frontline fludarabine, cyclophosphamide and rituximab therapy: distribution and clinical outcomes. *Leuk Lymphoma*. 2015;56(6):1643-1650.
22. Thompson PA, Tam CS, O'Brien SM, et al. Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in IGHV-mutated chronic lymphocytic leukemia. *Blood*. 2016;127(3):303-309.
23. Davids MS, Hallek M, Wierda W, et al. Comprehensive safety analysis of venetoclax monotherapy for patients with relapsed/refractory chronic lymphocytic leukemia. *Clin Cancer Res*. 2018;24(18):4371-4379.
24. Freise KJ, Shebley M, Salem AH. Quantitative prediction of the effect of CYP3A inhibitors and inducers on venetoclax pharmacokinetics using a physiologically based pharmacokinetic model. *J Clin Pharmacol*. 2017;57(6):796-804.
25. Falchi L, Keating MJ, Marom EM, et al. Correlation between FDG/PET, histology, characteristics, and survival in 332 patients with chronic lymphoid leukemia. *Blood*. 2014;123(18):2783-2790.
26. Jain P, Keating M, Wierda W, et al. Outcomes of patients with chronic lymphocytic leukemia after discontinuing ibrutinib. *Blood*. 2015;125(13):2062-2067.
27. Flinn IW, Gribben JG, Dyer MJS, et al. Phase 1b study of venetoclax-obinutuzumab in previously untreated and relapsed/refractory chronic lymphocytic leukemia. *Blood*. 2019;133(26):2765-2775.
28. Kater AP, Seymour JF, Hillmen P, et al. Fixed duration of venetoclax-rituximab in relapsed/refractory chronic lymphocytic leukemia eradicates minimal residual disease and prolongs survival: post-treatment follow-up of the MURANO phase III study. *J Clin Oncol*. 2019;37(4):269-277.
29. Soumerai JD, Ni A, Darif M, et al. Prognostic risk score for patients with relapsed or refractory chronic lymphocytic leukaemia treated with targeted therapies or chemoimmunotherapy: a retrospective, pooled cohort study with external validations. *Lancet Haematol*. 2019;6(7):e366-e374.
30. Roberts AW, Ma S, Kipps TJ, et al. Efficacy of venetoclax in relapsed chronic lymphocytic leukemia is influenced by disease and response variables. *Blood*. 2019;134(2):111-122.
31. Cervantes-Gomez F, Lamothe B, Woyach JA, et al. Pharmacological and protein profiling suggests venetoclax (ABT-199) as optimal partner with ibrutinib in chronic lymphocytic leukemia. *Clin Cancer Res*. 2015;21(16):3705-3715.
32. Rogers KA, Huang Y, Ruppert AS, et al. Phase 1b study of obinutuzumab, ibrutinib, and venetoclax in relapsed and refractory chronic lymphocytic leukemia. *Blood*. 2018;132(15):1568-1572.
33. Hillmen P, Rawstron AC, Brock K, et al. Ibrutinib plus venetoclax in relapsed/refractory chronic lymphocytic leukemia: the CLARITY study. *J Clin Oncol*. 2019;37(30):2722-2729.
34. Jain N, Keating M, Thompson P, et al. Ibrutinib and venetoclax for first-line treatment of CLL. *N Engl J Med*. 2019;380(22):2095-2103.