

Real-world outcomes and management strategies for venetoclax-treated chronic lymphocytic leukemia patients in the United States

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ABSTRACT

Venetoclax is a BCL2 inhibitor approved for 17p-deleted relapsed/refractory chronic lymphocytic leukemia with activity following kinase inhibitors. We conducted a multicenter retrospective cohort analysis of patients with chronic lymphocytic leukemia treated with venetoclax to describe outcomes, toxicities, and treatment selection following venetoclax discontinuation. A total of 141 chronic lymphocytic leukemia patients were included (98% relapsed/refractory). Median age at venetoclax initiation was 67 years (range 37-91), median prior therapies was 3 (0-11), 81% unmutated *IGHV*, 45% del(17p), and 26.8% complex karyotype (≥ 3 abnormalities). Prior to venetoclax initiation, 89% received a B-cell receptor antagonist. For tumor lysis syndrome prophylaxis, 93% received allopurinol, 92% normal saline, and 45% rasburicase. Dose escalation to the maximum recommended dose of 400 mg daily was achieved in 85% of patients. Adverse events of interest included neutropenia in 47.4%, thrombocytopenia in 36%, tumor lysis syndrome in 13.4%, neutropenic fever in 11.6%, and diarrhea in 7.3%. The overall response rate to venetoclax was 72% (19.4% complete remission). With a median follow up of 7 months, median progression free survival and overall survival for the entire cohort have not been reached. To date, 41 venetoclax treated patients have discontinued



Haematologica 2018
Volume 103(9):1511-1517

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Received: March 17, 2018.

Accepted: June 5, 2018.

Pre-published: June 7, 2018.

doi:10.3324/haematol.2018.193615

Check the online version for the most updated information on this article, online supplements, and information on authorship & disclosures: www.haematologica.org/content/103/9/1511

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therapy and 24 have received a subsequent therapy, most commonly ibrutinib. In the largest clinical experience of venetoclax-treated chronic lymphocytic leukemia patients, the majority successfully completed and maintained a maximum recommended dose. Response rates and duration of response appear comparable to clinical trial data. Venetoclax was active in patients with mutations known to confer ibrutinib resistance. Optimal sequencing of newer chronic lymphocytic leukemia therapies requires further study.

Introduction

Venetoclax is an oral second-generation BCL2 inhibitor with demonstrated activity and durable responses in relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL), including those with chromosome 17p deletion (del(17p)), unmutated IGHV, fludarabine-resistance, bulky disease, and progression on or following ibrutinib or idelalisib.¹⁻⁵ Overall response rate (ORR) to venetoclax monotherapy was 79% in the phase II trial in del(17p) R/R CLL.³ Moreover, ORRs were 65% and 67% in R/R CLL following ibrutinib or idelalisib, respectively.^{4,5} In addition to data with monotherapy, progression free survival (PFS) was superior for patients treated with venetoclax and rituximab compared to bendamustine and rituximab in R/R CLL, and more venetoclax-treated patients achieved undetectable minimal residual disease (MRD) (83.5% vs. 23.1%).⁶

Knowledge about venetoclax efficacy, dose-escalation, and toxicity in CLL patients has almost entirely been informed by experiences from clinical trials.³ As several real-world evidence series showed that toxicity profiles and outcomes for kinase inhibitor-treated patients may differ from those reported in the clinical trial setting, studying whether these differences apply to venetoclax-treated patients is essential.⁷⁻¹¹ Furthermore, there is one study to date regarding strategies for early identification of high-risk patients, particularly those previously treated with kinase inhibitor based therapy, for progression on venetoclax and how treatment is selected after its discontinuation is selected.²

We aimed to better understand disease characteristics and toxicities of CLL patients treated with venetoclax in clinical practice and contrast their outcomes to those reported in key clinical trials. We explored prognostic factors that predict early progression on venetoclax and studied treatment selection following discontinuation. To our knowledge, this analysis reports the largest series of CLL patients treated with venetoclax in a real-world setting with a focus on outcomes following venetoclax discontinuation.

Methods

We conducted a multicenter, retrospective cohort study of all CLL patients treated with venetoclax across 19 United States academic and community cancer centers. The study was approved by the institutional review board at each US institution. Investigators conducted a detailed review of the institutional electronic medical records to identify patients with CLL treated with venetoclax. Collected data included demographics, clinical and genetic prognostic factors, venetoclax dose-escalation management, long-term dosing, toxicities, tumor lysis syndrome (TLS) prophylaxis strategies and outcomes, ORR, complete response (CR), survival out-

comes, and reasons for discontinuation. Investigators were asked to follow the National Cancer Institute working group international workshop guidelines for CLL (iwCLL) published in 2008 to define rates of response and progression of disease.¹² Disease burden as a predictor for TLS risk was categorized as low, medium, and high per the treating physician. Physicians were asked to use the venetoclax package insert to guide the categorization, which was developed based on United States approval of the drug in 2016.¹³ TLS events were defined as per Howard criteria, which specify criteria for laboratory and clinical TLS.¹⁴ Adverse events (AEs) were graded using the NCI Common Toxicity Terminology Criteria for Adverse Events v4.0 (CTCAE v4.0). Cytogenetics, FISH results and next generation sequencing (NGS) were reported for patients where available.

The primary endpoint was PFS, defined as the time from venetoclax initiation until progression or death from any cause as per the Kaplan Meier method.¹⁵ Patients were censored at the time of last follow up or at the time of next therapy regardless of progression status. Outcomes were stratified by prognostic characteristics where available, including del(17p) status, complex karyotype (>3 abnormalities), and venetoclax monotherapy *versus* combinations. Secondary endpoints included overall survival (OS), venetoclax dosing and toxicities, TLS incidence, dose escalation schema, response rates, and reasons for discontinuation.

Comparisons of survival outcomes data were made using the long rank (LR) test.¹⁶ Hazard ratios were estimated using Cox regression analyses.¹⁷ Other analyses were descriptive. Tests were two-sided at the 5% level. Statistical analyses were performed using STATA 10.1 (Stata Statistical Software: Release 10, 2007; StataCorp LP, College Station, TX).

Results

Patient characteristics

We identified 141 CLL patients treated with venetoclax. Males and Caucasians represented most patients at 66% and 87%, respectively. The median age at diagnosis was 59 years (range 30-88), and median age at venetoclax initiation was 67 years (range 37-91). The population consisted almost entirely of patients with R/R CLL, with only 2 (1.4% of 141) of patients being treatment-naïve. Patients had received a median of 3 prior therapies (range 0-11). Venetoclax was administered in combinations in 18.4% (n=26 of 141) of patients. Ibrutinib (36%), obinutuzumab (32%), and rituximab (24%) were the most commonly used drugs with venetoclax. Almost 89% of patients were treated with a B-cell receptor signal transduction inhibitor prior to venetoclax; 82% (n=115/141) received ibrutinib. Patient characteristics are summarized in Table 1.

Most patients in this cohort had at least one traditionally poor-risk feature: 45% (n=61/136 tested) patients had chromosome del(17p), 26% (n=34/131) had deletion of chromosome 11q (del(11q)), 44% (n=42/95) had p53 mutations, 26.8% (n=52/130) had a complex karyotype

(>3 chromosomal abnormalities) and 26.8% (n=15/56) had a *NOTCH1* mutation. Thirty-one patients (22%) had del(17p) and *TP53* mutation, and 16 patients (11%) had del(17p), *TP53* mutation, and complex karyotype.

Venetoclax dosing and adverse events

All patients underwent 5-week dose escalation of venetoclax. During dose-escalation, 85% (n=120/141) of patients achieved a maximum dose of 400 mg daily, with 75% of the cohort (n=103/137) maintaining 400 mg daily as a long-term stable dose. Dose interruptions occurred in 30% of patients and 21% required dose reduction. Details are available in *Online Supplementary Table S1*. Reasons for interruptions were not available. Hematologic events were the most common AEs with neutropenia (defined as ANC < 1000 cells/microL) occurring in almost half of patients (47.4%, n=65/137) and thrombocytopenia (defined as platelets < 50,000 cells/microL) occurring in over one-third of patients (36.0%, n=49/136). Other AEs included TLS (13.4%, n=18/134), neutropenic fever (11.6%, n=16/138), and grade ≥ 2 diarrhea (7.3%, n=10/138). Opportunistic infections (OI) while on venetoclax were reported in 11 patients (7.8%) with the three most common being pneumocystis jirovecii pneumonia (PJP) (n=6), invasive fungal (n=2), and toxoplasmosis (n=2). Nine OI events occurred in patients with prior exposure to any kinase inhibitor, 8 OI events occurred in patients with prior exposure to ibrutinib, and 6 OI events occurred in patients with prior exposure to two prior kinase inhibitors. The median time from venetoclax start to OI event was 5 months (0.2 – 16 months).

TLS: prophylaxis and hospitalization practice patterns

Of 134 patients with TLS data, 44.8% were low-risk (n=60), 35.8% were intermediate risk (n=48), and 19.4% were high risk (n=26). Eighty-nine of 131 patients (64.3%) had pre-venetoclax lymph node assessment by CT scan to inform TLS risk. To minimize the occurrence of TLS, allopurinol was used in almost all cases regardless of risk category (93.1% low risk, 87.5% intermediate risk, 100.0% for high risk), as was intravenous normal saline (82.1% low risk, 91.7% intermediate risk, 100.0% high risk). Rasburicase use as TLS prophylaxis varied by risk category: 17.2% of low risk, 31.3% of intermediate risk, and 46.2% of high risk patients. TLS risk stratification, prophylaxis patterns, and incidence are summarized in Table 2.

Most patients had one or more planned hospitalizations during dose escalation regardless of risk category (*Online Supplementary Table S2*). Twenty-seven patients were not hospitalized at any point, including 20 of 58 (34.5%) low risk patients and 7 of 48 (14.6%) intermediate risk patients. All high-risk patients were hospitalized at least once for TLS monitoring and prophylaxis during the dose escalation phase. Among high-risk patients, 32.0% (n=8 of 25) were hospitalized for all five dose escalations. The mean number of days hospitalized during the 5-week dose escalation period for low risk, intermediate risk, and high-risk patients were 1.5, 1.7, and 3.1, respectively.

Overall, the incidence of TLS events (laboratory and clinical) was 13.4% (n=18/134) with 5 events (3.7%) reported in low-risk, 4 (3.0%) in intermediate-risk, and 9 (6.7%) in high-risk patients. Of these events, 6 were recorded as clinical TLS events (2 low risk patients, 1 intermediate risk patient, and 3 high risk patients), and the

Table 1. Baseline characteristics of 141 patients treated with venetoclax.

Patient characteristics	Median (range)
Median age at diagnosis, years	59 (30-88)
Median age at venetoclax start, years	67 (37-91)
Median prior lines of therapy	3 (0-11)
Follow up, months*	7 (0.1-38.4)
CLL characteristics	Frequency (n with characteristic/ total n with available data)
Relapsed/Refractory	198.6% (139/141)
Treatment naive	1.4% (2/141)
CLL genetics	
Del(17p)	44.9% (61/136)
Del(11q)	26.0% (34/131)
<i>TP53</i> mutation	44.2% (42/95)
<i>NOTCH1</i> mutation	26.8% (15/56)
Complex karyotype, ≥ 3 mutations	26.8% (52/130)
Unmutated <i>IGHV</i>	83.3% (60/72)
Prior ibrutinib exposure	81.6% (115/141)
Ibrutinib resistance mutations	
<i>BTK</i> mutation	35.3% (12/34)
PLC γ 2 mutation	12.5% (4/32)
Venetoclax administered in combination	18.4% (26/141)
Venetoclax and ibrutinib	36% (9/26)
Venetoclax and obinutuzumab	32% (8/26)
Venetoclax and rituximab	24% (6/26)

*Median follow up calculated using overall survival.

remainder were laboratory events (n= 12). Of the clinical TLS patients, 4 of 6 achieved 400 mg venetoclax dosing. No TLS patient required hemodialysis. One TLS death was reported in a patient who was re-challenged with venetoclax after a delayed interruption without utilizing a dose escalation schedule or hospitalization for venetoclax re-escalation. We were unable to correlate TLS events with a threshold dose of venetoclax.

Outcomes

The reported ORR and CR rate, stratified by selected risk factors, are summarized in Table 3. The ORR for the entire cohort was 72.1% and 19.4% of patients achieved a CR. The median time to best response was 2.1 months. Venetoclax had a similar ORR across several high-risk groups including patients with age ≥ 65 (ORR = 74.3%), del(17p) (71.4%), prior ibrutinib therapy (69.1%), *BTK* mutation (91.6%), and PLC γ 2 mutation (75.0%). At a median follow up of 7 months, the median PFS and OS have not been reached for the entire cohort (Figure 1a and 1b). The projected PFS and OS for the entire cohort at 12 months were 68% and 88%, respectively. Patients with a *TP53* interruption (del(17p) and/or *TP53* mutation) had significantly shorter PFS than those with intact *TP53* (Figure 1c), though OS for the two groups was not significantly different (*Online Supplementary Figure S1*).

In univariate analyses, we identified *TP53* interruption as a predictor of inferior PFS (HR 2.7, 95% CI 1.08-6.7, $P=0.034$) but not OS (HR 1.78, 95% CI .55-5.74, $P=.332$).

Complex karyotype (HR 1.36, 95% CI 0.66-2.84, $P=0.4$), prior ibrutinib therapy (1.74, 95% CI 0.61-5.0, $P=0.3$), and unmutated *IGHV* (HR 0.29, 95% CI 0.04-2.3, $P=0.25$) were not significantly associated with inferior PFS. *TP53* interruption remained a significant predictor for inferior PFS in a multivariate analyses which included *TP53* interruption, complex karyotype and prior ibrutinib therapy (HR 2.8, CI 1.22-6.4, $P=0.03$). The presence of del(11q) did not impact OS and had an observed protective effect on PFS (HR 0.31, 95% CI 0.11-0.90, $P=0.03$).

Venetoclax discontinuations and treatment selection following venetoclax

Venetoclax was discontinued in 41 patients (29%). Progression of disease was the most common reason for discontinuation (53.8%, $n=21$) followed by toxicity (20.5%, $n=9$), two-thirds of which were hematologic. Other reasons for discontinuation included death not related to progressive disease (10.25%, $n=4$), second cancer (5.1%, $n=2$), physician/patient preference (2.5%, $n=1$), Richter's transformation (2.5%, $n=1$), and planned alternate therapy including CD19 directed chimeric antigen receptor T cells (CAR-T, 2.5%, $n=1$) and transplantation (2.5%, $n=1$).

Table 4 summarizes therapy selection and outcomes for individual cases following venetoclax. Notably, 17 of 34 patients (50%) who discontinued venetoclax and remain alive have not required a subsequent therapy. Reasons for discontinuation in the group of patients who have not yet been treated following venetoclax discontinuation

include toxicity ($n=6$), progression of CLL ($n=4$), death not secondary to toxicity or progression ($n=4$), secondary malignancy ($n=2$), and doctor or patient preference ($n=1$). Ibrutinib-based therapy was the most common choice after venetoclax; five of 24 (21%) patients receiving ibrutinib. Three of five of patients treated with ibrutinib had prior ibrutinib exposure. Of these five patients, 1 had a partial response, 2 had stable disease, and 2 had progressive disease. Other therapies selected included rituximab monotherapy (12.5%, $n=3$), anthracycline based regimens (12.5%, $n=3$), allogeneic stem cell transplant (12.5%, $n=3$), idelalisib-based therapy (8.3%, $n=2$), and CAR-T (8.3%, $n=2$). Subsequent lines of therapies with their corresponding responses are detailed in *Online Supplementary Table S3*.

Discussion

In the largest series of venetoclax-treated CLL patients treated in the U.S., response rates (ORR 72.1%) and survival data are comparable to those reported in published clinical trials.^{1,3-5} Toxicities were similar with hematologic toxicities being the most frequently observed. Rates of TLS were higher than prior reports. Collectively, these results suggest that the efficacy and safety profile of venetoclax demonstrated in the clinical trials setting are comparable to what has been observed in the real world.

Consistent with previously published data, the ORR for the del(17p) population remained high at 71.4%. Whereas

Table 2. Tumor lysis syndrome prophylaxis and events.

TLS risk category n=134	TLS prophylaxis			Total	TLS events	
	Allopurinol	Rasburicase	Normal saline		Laboratory	Clinical
Low 44.8% (n=60)	93.1% (n=54/58)	17.2% (n=10/58)	82.1% (n=46/56)	5	3	2
Intermediate 35.8% (n=48)	87.5% (n=42/48)	31.3% (n=15/48)	91.7% (n=44/48)	4	3	1
High 19.4% (n=26)	100.0% (n=26/26)	46.2% (n=11/26)	100.0% (n=25/25)	9	6	3

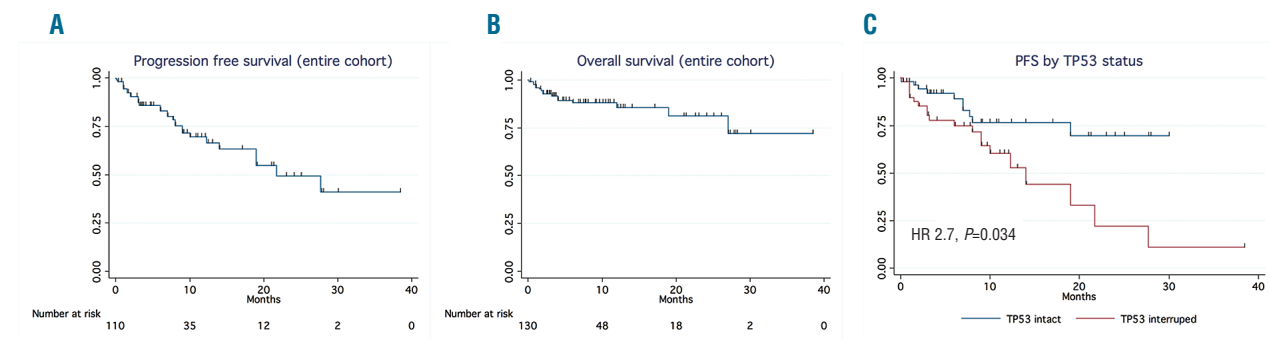


Figure 1. Survival analyses for patients following venetoclax initiation. (A) Progression free survival for the entire cohort. Median PFS has not been reached with median follow up of 7 months. Projected 12-month PFS is 68%. (B) Overall survival for the entire cohort. Median OS has not been reached with median follow up of 7 months. Projected 12-month OS is 88%. (C) Progression free survival by *TP53* status. PFS is significantly superior for patients with intact *TP53* compared to patients with *TP53* interruption, either *TP53* mutation or del(17p).

TP53 interruption was significantly associated with inferior PFS, OS was not compromised. Complex karyotype was not associated with inferior PFS, despite being shown to be a risk factor for progression in patients receiving venetoclax in a recent study by Anderson *et al.*² It is possible that our shorter follow up accounts for this discrepancy. Interestingly, del(11q) did not adversely affect PFS. Similar findings were reported by Kipps *et al.* in 620 patients treated with ibrutinib stratified by del(11q) status (HR 0.73, $P=0.08$).¹⁸ In subgroup analysis, the response rate for patients previously treated with ibrutinib was 69.1%, similar to the 65% demonstrated by Jones *et al.* in patients who were treated with venetoclax following ibrutinib.⁵ Finally, we did not observe a difference in PFS whether venetoclax was given alone or in combination.

TLS has been suggested as the most critical toxicity with venetoclax, contributing to early treatment-related deaths in clinical trials, particularly before the current dose ramp-up schedule was implemented in trials to minimize TLS risk. In our study, TLS rates were higher than those reported in most recent trials. In this cohort, 18 patients (13.4%) had TLS; 12 (9.0%) cases were laboratory TLS events and 6 (4.5%) cases were clinical events. In the initial phase I venetoclax study, 18% of patients experienced TLS (12.5% laboratory, 5.6% clinical). However, once the dosing schedule was modified to minimize TLS risk, 1.7% of patients had laboratory TLS and none had clinical TLS.³ More recently reported clinical trials using the standard dose ramp-up protocol have shown laboratory TLS rates of 2.2%⁵ and 4.7%³ and clinical TLS rates of 0%.³⁻⁵ Despite the higher rates of TLS observed in our study, only 19.4% of patients were deemed high risk for TLS *versus* 25-49% of patients classified as high risk in the clinical trials setting.³⁻⁵

Overall, adherence to TLS prophylaxis recommendations was excellent. The majority (92%) received allopurinol, which is recommended for all patients regardless of risk category.¹³ Guidelines per the US venetoclax prescribing information document also recommend oral hydration and intravenous normal saline for high risk patients, which was followed for all patients in our cohort. Similarly, rasburicase is recommended for patients with elevated baseline uric acid. This was used in over one-quarter of all cases and almost half of the high-risk cases. All high-risk patients had at least one planned hospitalization during dose escalation. Three of 25 high-risk patients forwent the second recommended hospitalization given lack of TLS development during the first hospitalization.

Most low and intermediate-risk patients were hospitalized at least once, suggesting a conservative approach was utilized in this series during the dose ramp-up as outpatient dosing, with close monitoring. As per United States Food and Drug Administration (FDA) label guidelines, low and intermediate-risk patients can also be managed in the outpatient setting without hospitalization and we suspect future real-world series will demonstrate a higher proportion of low and intermediate-risk patients managed in the clinic during the dose ramp-up period.

Potential reasons for increased TLS events may include difficulty in adhering to the exact dose-ramp up schedule or lack of physician/patient education surrounding importance of suggested prophylaxis, laboratory monitoring, and interventions for all patients. Patients may have had differences in comorbidities, such as impaired renal function, which would have made them ineligible for a venetoclax clinical trial and possibly at increased risk for TLS. Deviations in clinical practice initiation of venetoclax from that recommended in the FDA label, in particular the limited use of CT assessment (64.3%) to establish TLS risk prior to venetoclax initiation, could have led to risk misclassification. Additionally, while investigators were asked to use the Howard criteria to define TLS, it is possible that this mandate was not strictly followed when capturing data, leading to misclassification bias.

To date, little is known regarding reasons for venetoclax discontinuation in clinical practice. In our study, 28% of all patients discontinued therapy; 53.8% of these patients discontinued due to progression of CLL excluding Richter's transformation (RT) and 20.5% discontinued due to toxicity. As in clinical trials, we found CLL progression to be the most common reason for venetoclax discontinuation. In the phase I study of venetoclax for R/R CLL, the overall discontinuation rate of 56%, with 35% of discontinuations due to CLL progression (non RT) and 20% due to toxicity.¹ In the phase II study of patients treated with prior B-cell receptor signal transduction inhibitors, the discontinuation rate was 49.5% at 14 months median follow up. CLL progression represented 49% of these discontinuations and AEs represented 11% of discontinuations.⁵ In this same series, RT was reported in 5% of patients who discontinued venetoclax. The median time to CLL progression was 8.4 months, and median time to RT was approximately one year.¹⁹ Anderson *et al.* reported that, in a group of heavily pretreated patients, 37% of patients progressed on venetoclax at a median follow up of 23 months, and that 8.2% of patients discontinued therapy

Table 3. Response rates.

	Overall population n=129	Age >65 years n=82	Age <65 years n=47	Del 17p present n=56	Del 17p absent n=69	Prior ibrutinib therapy n=107	No prior ibrutinib therapy n=22	BTK mutation present n=12	BTK mutation absent n=22	PLCγ2 mutation present n=4	PLCγ2 mutation absent n=28
ORR	72.1%	74.3%	68%	71.4%	72%	69.1%	86.2%	91.6%	72.6%	75.0%	78.6%
CR	19.4%	18.3%	21.2%	25.0%	16.0%	17.7%	27.2%	8.3%	18.1%	0.0%	14.3%
PR	52.7%	56.0%	46.8%	46.4%	56.5%	51.4%	59.0%	83.3%	54.5%	75.0%	64.3%
SD	17.8%	17.1%	19.1%	16.1%	18.8%	19.6%	9.0%	8.3%	18.1%	25.0%	14.3%
PD	10.1%	8.5%	12.7%	12.5%	8.7%	11.2%	4.5%	0%	9.0%	0%	7.1%

CR: complete response; ORR: overall response rate; PD: progressive disease; PR: partial response; SD: stable disease.

Table 4. First treatment following venetoclax discontinuation and treatment outcomes.

Treatment	Number treated with agent (Percentage of 24 patients who received subsequent line of therapy)	Patient level responses (n)
Ibrutinib-based	5 (20.8%)	PR (1), SD (2), PD (2)
Idelalisib-based	2 (8.3%)	CR (1), No response assessment (1)
Rituximab monotherapy	3 (12.5%)	PR (2), PD (1)
CAR-T	2 (8.3%)	No response assessment (2)
Anthracycline-based (R-CHOP/R-EPOCH)	3 (12.5%)	PD (2), no response assessment (1)
Allogeneic SCT	3 (12.5%)	CR (2), no response assessment (1)
Other	6 (25%)	PR (1), SD (1), PD (2), no response assessment (2)

due to other reasons with no patients discontinuing due to toxicity.² We also note these results differ from recent real world BCR inhibitor series where AEs were the most common reason for drug discontinuation, followed by CLL progression.²⁰

Even less is known about sequencing of therapies following venetoclax discontinuation. Anderson *et al.* report outcomes on 25 patients who progressed following venetoclax, 8 with progressive CLL and 17 with RT. In this series, 6 CLL patients with progression, all of whom were ibrutinib naïve, were treated with a BTK inhibitor as the first therapy after discontinuation. Five of six (83%) initially achieved a partial response.²

Our study is unique in that we report patient level treatment data on 24 CLL patients progression following venetoclax, which represents the largest series reported to date. These patients are representative of the U.S. population currently treated with venetoclax in that they are treated in the R/R setting, and 89% had been exposed to a BCR inhibitor prior to venetoclax treatment, most commonly ibrutinib. We found that, following progression on venetoclax, ibrutinib was most commonly selected agent, accounting for 20.8% of the cases. However, idelalisib-based, rituximab monotherapy, CAR-T, anthracycline based therapy, and allogeneic stem cell transplant were also selected as next therapy in other cases. Interestingly, 3 patients underwent allogeneic stem cell transplant as first therapy after venetoclax. Two achieved a CR and 1 did not have an available response assessment. One patient received an allogeneic SCT as second therapy following venetoclax and achieved CR. Although interpretation of the SCT results are subject to selection bias, they suggest that there is a potential role for effective cellular therapies and should be explored. Our data demonstrate that no clear consensus exists for therapy selection following venetoclax failure and highlights the importance addressing sequencing strategies in future clinical trials. This will become increasingly important as more patients in practice are treated with venetoclax alone or in combination with antibodies and/or ibrutinib.

Our study has several limitations. Data were collected retrospectively by multiple physicians and are subject to differences in clinical experience, practice style, and inconsistencies in chart review. Missing data varied with individual data points and were infrequent. To address this, we included absolute numbers and percentages to highlight any data that was not reported for individual data points. Additional data, including performance status, could offer additional insight but was not collected. Variables and out-

comes, including TLS risk categorization, TLS events, and response were documented per physician assessment. Although we recommended the use of iwCLL response criteria, Howard criteria for TLS, and tumor burden classification per package insert, central review of outcomes was outside the scope of this study and, therefore, outcomes may have been subject to misclassification bias. While the case report form captured information on TLS prophylaxis and events, it was not designed to discern the detailed information that would be required to understand rate of TLS by management strategy. This was beyond the scope of this study but future research should consider examining this important information. Additionally, AE assessment was not comprehensive and included data on select AEs such as TLS, hematologic, infection or gastrointestinal toxicities. Applying CTCAE criteria retrospectively may result in underreporting of events and caution is emphasized in interpreting these findings. Indications for treatment were based on treating physicians' discretion and were not specified. Detailed information regarding reason for discontinuation of line of therapy prior to venetoclax was not captured. As we know from prior studies, outcomes can differ significantly in patients who discontinue a kinase inhibitor due to toxicity as compared to progression.⁸ Future studies of venetoclax should consider stratifying patients by these subgroups. While we did include data from community practices, the fact that most patients were treated in academic centers could introduce a selection bias. Our median follow up of 7 months is short and does not capture progressions on venetoclax that occur later.

Despite its inherent limitations, this series represents the largest real-world cohort of CLL patients treated with venetoclax. Neutropenia and thrombocytopenia were the most common toxicities, and progression was the leading cause of venetoclax discontinuation. Venetoclax was active in patients with mutations known to confer ibrutinib resistance as well as in patients with other poor risk features. However, *TP53* interruption was associated with an inferior PFS. While we report the largest series of post-venetoclax outcomes, we demonstrate no clear sequencing pattern. Because the number of patients who discontinue venetoclax due to disease progression or toxicity within the first 2 years of initiating therapy is not trivial, understanding how these patients should be subsequently treated is a critical area of future research.

Acknowledgments

The authors would like to thank Joseph and Cindy Riggs for their support.

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