REGULAR ARTICLE

blood advances

Safety of venetoclax rapid dose escalation in CLL patients previously treated with B-cell receptor signaling antagonists

Kristin L. Koenig,[1] Ying Huang,[1] Emily K. Dotson,[2] Shane Sheredy,[2] Seema A. Bhat,[1] John C. Byrd,[1] Emily Desmond,[1] Jill Ford,[1] Shauna Iarocci,[1] Jeffrey A. Jones,[1] Margaret S. Lucas,[1] Mollie E. Moran,[1] Tracy E. Wiczer,[2] Jennifer A. Woyach,[1] Farrukh T. Awan,[3,*] and Kerry A. Rogers[1,*]

[1]Division of Hematology and [2]Department of Pharmacy, The Ohio State University, Columbus, OH; and [3]Division of Hematology and Oncology, University of Texas Southwestern Medical Center, Dallas, TX

Key Points

- Venetoclax RDE is associated with a significant but manageable risk of TLS in chronic lymphocytic leukemia patients progressing after BTKi's.
- Rapid decline in ALC at each dose increase is associated with increased TLS risk and can be used to guide patient management.

Venetoclax has efficacy in patients relapsing after B-cell receptor pathway inhibitors (BCRis); however, because of the risk of tumor lysis syndrome (TLS), a 5-week dose ramp-up is required to attain the target dose. Patients relapsing after BCRis frequently have proliferative disease, requiring a faster time to target dose than this scheme allows. This limitation can potentially be overcome with rapid dose escalation (RDE). We analyzed 33 chronic lymphocytic leukemia patients who underwent venetoclax RDE after prior BTKi treatment. Median time to target dose was 9 days. Seventeen patients (52%) developed laboratory TLS, and 5 (15%) developed clinical TLS, all as a result of renal injury. TLS was seen in more patients with a higher initial tumor burden. TLS occurred at all dose levels, with most episodes occurring at the 50- and 100-mg doses. Most interestingly, a decrease in absolute lymphocyte count (ALC) from pre–venetoclax dose to 24 hours post–venetoclax dose of $10 \times 10^3/\mu L$ was associated with an increased risk of TLS (hazard ratio, 1.32; $P = .02$), after controlling for venetoclax dose level. Venetoclax RDE with close in-hospital monitoring at experienced centers and in select patients is feasible. The rapidity with which ALC drops helps predict TLS and could help guide dose-escalation decisions.

Introduction

Despite sustained disease control observed with B-cell receptor pathway inhibitors (BCRi's), particularly Bruton tyrosine kinase inhibitors (BTKis), patients with chronic lymphocytic leukemia (CLL) who relapse after treatment with these agents often have rapidly progressive symptomatic disease.[1-4] The BCL-2 inhibitor venetoclax demonstrated an overall response rate of 65% and median progression-free survival (PFS) of 24 months in patients relapsing after ibrutinib in a phase 2 trial and is currently the most effective standard therapy in this patient population.[5] This study was performed in a high-risk patient population that was heavily pretreated, with a median of 4 prior therapies (range, 1-15 therapies). These patients also had a significant tumor lysis syndrome (TLS) risk (26 patients [29%] with high TLS risk and 31 [34%] with medium TLS risk per venetoclax prescribing information).

The most substantial risk with venetoclax is TLS with treatment initiation. To mitigate this, a 5-week dose ramp-up to the target dose of 400 mg with close monitoring and prophylaxis demonstrated reduced incidence of TLS, from 18% to 1.7%.[6] However, the kinetics of relapse after BCRi's can frequently outpace attainment of an effective venetoclax dose. In the same phase 2 trial of venetoclax in this population, 11% of patients who discontinued for progressive disease did so within the first 5 weeks.[5] This limitation of venetoclax in this CLL patient population can potentially be overcome with more rapid

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*F.T.A. and K.A.R. contributed equally to this work.

Send data sharing requests via e-mail to the corresponding author, Kerry A. Rogers (kerry.rogers@osumc.edu).

The full-text version of this article contains a data supplement.

Table 1. TLS occurrence per amount of tumor burden

Tumor burden	Tumor burden at start of venetoclax, n (%)	Developed laboratory TLS, n (%)
Low	8 (24)	3 (38)
Medium	20 (61)	11 (55)
High	5 (15)	3 (60)

dose escalation (RDE) of venetoclax. We have adopted this approach at our institution for select patients in whom there is a rapid need to achieve the target dose of venetoclax, and we performed this retrospective cohort study to report our experience.

Methods

All patients undergoing venetoclax RDE from May 2016 to December 2018 were retrospectively reviewed under an institutional review board–approved protocol and in accordance with the Declaration of Helsinki. Venetoclax dose was increased in stepwise fashion from 20 to 400 mg in a rapid manner, based on patient tolerability and TLS, with close in-hospital monitoring. Laboratory parameters were evaluated every 4 to 8 hours. There were no standard criteria employed for when to increase the dose, but attempts were made by practitioners to escalate every 1 to 2 days if TLS did not occur.

Allopurinol was initiated at least 1 day before venetoclax. Maintenance fluids (eg, dextrose 5%/sodium chloride 0.45%) at a rate of 150 mL per hour were administered at least 12 hours before first venetoclax dose. If the uric acid level was >8 mg/dL despite IV fluids and allopurinol, a dose of rasburicase was considered before venetoclax. If uric acid was >8 mg/dL after venetoclax dose, rasburicase was administered. Phosphate binders were routinely used upfront. Kayexalate, furosemide, and insulin with dextrose were used as needed for rising potassium.

The Cairo-Bishop definition of TLS was used to define both laboratory and clinical TLS.[7] Clinical TLS was defined as laboratory TLS plus ≥1 clinical manifestations: cardiac arrhythmia, death, seizure, or acute kidney injury with an elevated serum creatinine level >1.5 times the upper limit of normal. TLS risk was assessed by tumor burden per venetoclax prescribing information.[8]

Patient baseline characteristics and absolute lymphocyte count (ALC) pre– and post–venetoclax dose were summarized using descriptive statistics. Generalized linear mixed model with logit link function was used to determine an association between change in ALC and odds of developing TLS, and patient-level characteristics were linked with the same outcome using univariable logistic regression. PFS and overall survival (OS) were calculated from venetoclax start date to date of event (progression/death for PFS; death for OS), censoring event-free patients at time of last known follow-up. PFS and OS were estimated using the Kaplan-Meier method and correlated with risk factors through univariable Cox regression models. All analyses were generated using SAS software (version 9.4).

Results

Thirty-three patients with relapsed/refractory CLL received venetoclax RDE. Median age was 65 years (range, 48-86 years). Most patients had genetically high-risk CLL (complex karyotype, 45%; del17p, 52%; unmutated IGHV, 86%) and were heavily pretreated, with a median of 5 prior lines of therapy (range, 2-18 lines). All patients received prior BCRi's, with 75.6% most recently treated with BTKi (supplemental Table 1). Risk for TLS with venetoclax was increased with higher tumor burden, as defined per venetoclax prescribing information, or decreased renal function (supplemental Table 2).[8] Five patients (15%) had high tumor burden, and 20 (61%) had medium tumor burden (Table 1).[8] Median baseline creatinine level was 0.95 mg/dL (range, 0.6-2.0 mg/dL).

Median time to target dose of venetoclax was 9 days (range, 5-32 days), and only 1 patient did not reach target dose. Most patients had a target venetoclax dose of 400 mg daily. Three patients had a target dose of 200 mg as a result of concomitant antifungal therapy. In these patients, the dose was adjusted because of drug-drug interactions so that venetoclax exposure was similar to the 400-mg dose. One patient had a target dose of 200 mg because of concomitant radiation therapy for renal cell carcinoma brain metastases. One patient died before completing dose escalation after developing venetoclax-associated neutropenic septic shock, bacteremia, and respiratory failure.

Oral and IV hydration are key in reducing injury from TLS, and our RDE approach requires several days of hydration. This had consequences; median weight gain from admission was 1.9 kg (range, −10.5 to 11.3 kg), and median net fluid balance was 6.7 L (range, 0-33.7 L). Nineteen patients (57.6%) received diuretics during admission, and 2 patients were discharged with a new or increased prescription for diuretics.

Seventeen patients (52%) developed laboratory TLS, and 5 (15%) developed clinical TLS. All cases of clinical TLS were due to renal injury, ranging from grade 0 to 3 in severity.[7] Thirty-eight percent of patients with low initial tumor burden developed laboratory TLS, whereas 55% and 60% of patients with medium and high tumor burden developed laboratory TLS, respectively

Table 2. Change in ALC with venetoclax and association with TLS at each venetoclax dose

			Pre-ALC		Post-ALC		Decrease in ALC (pre to post)	
Venetoclax dose level, mg	Patients, n	Patients with TLS, n (%)	Median (range), $\times 10^3/\mu L$	n	Median (range), $\times 10^3/\mu L$	n	Median (range), $\times 10^3/\mu L$	n
20	33	6 (18)	30.8 (0.5-307.3)	33	17.8 (0.5-138.6)	33	4.3 (−21.1 to 168.7)	33
50	33	8 (24)	15.9 (0.5-138.6)	33	10.3 (0.1-103.3)	32	3.7 (−5.3 to 68.4)	32
100	33	8 (24)	5.8 (0.4-62.2)	32	3.9 (0.3-64.9)	33	1.6 (−4.7 to 45.4)	32
200	32	4 (13)	3.4 (0.3-36.4)	29	2.5 (0.4-45.3)	29	0.7 (−9 to 13.1)	29
400	28	3 (11)	1.1 (0.4-45.3)	20	1.1 (0.4-39.9)	19	0.2 (−0.4 to 5.4)	19

Odds of developing TLS increased by 32% for each 10-unit drop in ALC (odds ratio, 1.32; 95% confidence interval [CI], 1.04-1.68; $P = .02$), even after accounting for venetoclax dose level. Many patients were leukopenic by the time they received 200- and 400-mg doses, leading to lower overall risk for TLS and limited ability to calculate ALC in some cases.

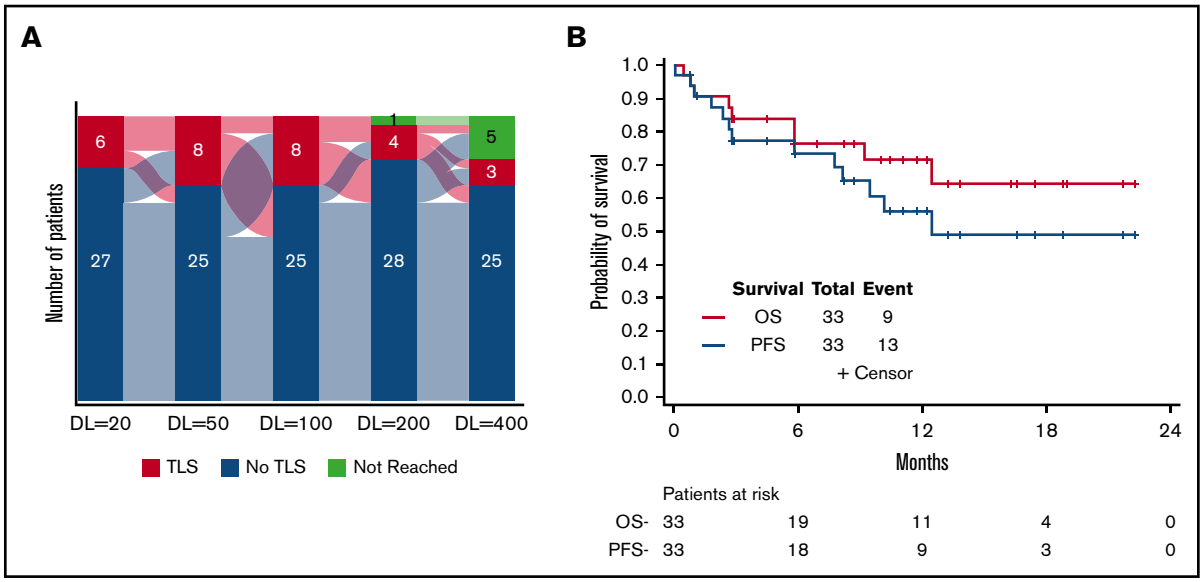

Figure 1. Progression-free and overall survival after starting venetoclaxTLS occurrence by dose level and PFS and OS after starting venetoclax. (A) Sankey plot shows what fraction of patients developed TLS at each dose level (DL). Connecting lines show individual patients who changed category, and width of each line is based on number of patients. (B) PFS and OS estimated in Kaplan-Meier curve. Median PFS was 14.1 months (95% CI, 8.1 months to not reached), and 1-year PFS was 56% (95% CI, 35% to 73%). Median OS was not reached, and 1-year OS was 72% (95% CI, 51% to 85%). Median follow-up for PFS was 10.7 months (range, 0.8-22.3 months); for OS, it was 11.1 months (range, 0.8-22.3 months).

(Table 1). Two patients (6.1%) received a prophylactic dose of rasburicase for elevated uric acid before starting venetoclax, and 5 (15.2%) required rasburicase during venetoclax RDE. No patient required renal replacement therapy.

Doses of venetoclax at which TLS occurred are listed in Table 2 and Figure 1A. Although TLS was seen at all venetoclax dose levels, it was more frequent at 50- and 100-mg doses (8 patients; 24% each), but it was also seen at the 20-mg dose (6 patients; 18%; Figure 1A). Controlling for venetoclax dose level, we found an association between decrease in ALC from predose to 24 hours after venetoclax dose and risk of developing TLS, which increased by 32% for each $10 \times 10^3/\mu L$ drop in ALC (odds ratio, 1.32; 95% CI, 1.04-1.68; $P = .02$; supplemental Table 3). Because ALC was highest before starting venetoclax and decreased the most during the first dose levels, TLS was more frequent at the lower doses (Table 2). No patient characteristics, including baseline tumor burden, were associated with developing TLS on univariable analysis; however, this study was not powered to detect correlation, and this analysis was exploratory in nature (supplemental Table 4). Furthermore, the number of days a patient received the prior dose level was not significantly associated with TLS occurrence at the current dose level (supplemental Table 4).

PFS and OS are shown in Figure 1B. One-year PFS and OS for this cohort were 56% (95% CI, 35% to 73%) and 72% (95% CI, 51% to 85%), respectively, and median PFS was 12.5 months (7.8 months to not reached). Median OS was not reached for this cohort. Three patients died within 30 days of starting venetoclax: 1 from progressive disease and 2 from sepsis.

Discussion

Our results support that venetoclax RDE with close in-hospital monitoring at experienced centers with appropriate resources is feasible in select patients. We were successful in shortening the duration of dose escalation, which took a median of only 9 days. However, high rates of both laboratory (52%) and clinical TLS (15%) were seen, and these were higher than rates with weekly dose escalation (6%). Given this increased TLS rate, it is important to note that RDE venetoclax is not a generalizable approach; it should be used only when necessary to achieve rapid disease control in patients with proliferative disease. That being said, this approach is important for obtaining disease control in carefully chosen patients with aggressive or proliferative disease in whom prompt disease control is needed. Although the risk of TLS is increased with RDE, we were able to use this approach without the need for renal replacement therapy and without death resulting from TLS. The medical consequences of TLS were not severe, and patients were successfully discharged on venetoclax. This suggests our approach of hospitalizing patients for management was also successful in limiting the consequences of any TLS that occurred.

Detailed methods regarding standardization of RDE venetoclax are beyond the scope of this report, because ours was a retrospective study; however, the physician group at an institution should agree upon a standardized approach for its specific practice setting, and prospective study of a rapid escalation scheme may be needed to better define methods. RDE should not be attempted at centers with limited experience or resources, because it is a resource-heavy endeavor and requires significant ancillary support.

Despite having only 1 patient with progressive disease within 30 days, suggesting better early disease control with RDE, PFS in this limited patient cohort was short, and new therapeutic approaches are needed for CLL patients relapsing after BTKi's. Furthermore, our study only involved a small number of patients, and before RDE venetoclax can be used in a larger number of CLL patients,

a prospective study is warranted to determine the true safety data from this approach.

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Authorship

Contribution: K.L.K., J.C.B., F.T.A., and K.A.R. designed the study; S.A.B., J.C.B., E.D., E.K.D., J.F., S.I., J.A.J., M.S.L., M.E.M., T.E.W., J.A.W., F.T.A., and K.A.R. cared for the patients; K.L.K., E.K.D., and S.S. collected the data; Y.H. performed the statistical analysis and designed the figures; K.L.K. wrote the initial draft of the manuscript; and all authors interpreted the data analysis, reviewed the work, and agreed to submit the manuscript.

Conflict-of-interest disclosure: E.K.D. has consulted for AbbVie. S.A.B. served on advisory boards for Pharmacyclics and Jannsen. J.C.B. receives grant support from Janssen, Genentech, Acerta, and Pharmacyclics. J.A.J. is employed by and owns stock in Celgene. M.S.L. participated in the Gilead 2018 Oncology Medical Scientist Medical Affairs Advisory Program. J.A.W. has received research funding from Pharmacyclics, Janssen, Karyopharm, Morphosys, Verastem, Loxo, and AbbVie and is a consultant or serves on advisory boards for Janssen, Pharmacyclics, AstraZeneca, and Arqule. F.T.A. has provided consultancy to Genentech, Astrazeneca, AbbVie, Janssen, Pharmacyclics, Gilead Sciences, Kite Pharma, Dava Oncology, Celgene, Blueprint Medicines, Sunesis, Karyopharm, and MEI Pharma. K.A.R. receives research funding from Genentech, AbbVie, and Janssen and has consulted for Acerta Pharma, AstraZeneca, and Pharmacyclics. The remaining authors declare no competing financial interests.

ORCID profiles: K.L.K., 0000-0002-2071-3169; F.T.A., 0000-0003-1813-9812; K.A.R., 0000-0001-5748-7874.

Correspondence: Kerry A. Rogers, The Ohio State University, 410 W 12th Ave, Room 458, Columbus, OH 43210; e-mail: kerry.rogers@osumc.edu.

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