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Clinical Relevance of the Recommended Intensive Laboratory Monitoring during the Standard Ramp-up at Time of Venetoclax Initiation for CLL: A Real-World Experience

Correspondence should be addressed to: gbaek@fredhutch.org

Grace Baek[1,2], Ivan Huang[1,2], Jonathan Cohen[1,2], Sirin Khajaviyan[1], Stephanie Louie[1], Laura Samples[1,2], Stephen Smith[1,2], Brian Till[1,2], Houston Warren[1,2], Ajay Gopal[1,2], Christina Poh[1,2], Ryan Lynch[1,2], Chaitra Ujjani[1,2], Mazyar Shadman[1,2]

[1]Fred Hutchinson Cancer Center, Seattle, WA; [2]UW Medicine, Seattle, WA

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Background

- Venetoclax has become a standard of care for chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) as one of several preferred treatment options for newly diagnosed or relapsed/refractory disease with or without del(17p)/*TP53* mutation. [1,2]
- Significant risk of clinical tumor lysis syndrome (TLS) – a potentially fatal complication characterized by hyperuricemia, extreme electrolyte abnormalities, and related complications such as acute kidney failure – has been previously well characterized for B-cell directed therapies in CLL/SLL.[3,4,5]
- Given the risk of TLS observed in early-phase development, venetoclax initiation for CLL/SLL includes a five-week venetoclax ramp-up schedule as the labeled/standard dosing schema, as well as scrupulous supportive care measures and monitoring. [2,3,4,6] It is recommended that patients at highest risk for TLS be admitted for close observation, but use of the standard ramp-up schedule in ambulatory care settings has demonstrated safety and effectiveness for the majority of patients. [6,7]
- The requirements for intensive monitoring, which require frequent patient visits, is a limiting factor that has contributed to the relatively low utilization of this effective drug.
- Prior characterization of TLS events demonstrate occurrence most frequently within the first week of therapy. [9]
- The clinical relevance of such intensive monitoring for venetoclax in clinical practice, especially in patients with low or medium risk for TLS, is unknown. Alternative ramp-up schedules for venetoclax are being investigated.

Objectives

- Evaluate real-world incidence of clinical and laboratory TLS in CLL/SLL patients undergoing standard venetoclax ramp-up to elucidate at-risk sub-populations and identify opportunities to optimize venetoclax ramp-up.
- Offer insight as to evolving best practices for intensive monitoring and logistics required with initiation of therapy, a potentially limiting constraint for patients and providers compared to alternative therapies.

Methods

Study Design

- IRB-approved, single-center, retrospective study
- Clinical interventions reported for laboratory or clinical findings were documented for each week of the ramp-up

Definitions

- TLS: Cairo-Bishop criteria [10]
- Laboratory abnormalities: based on absolute threshold

Primary Endpoint

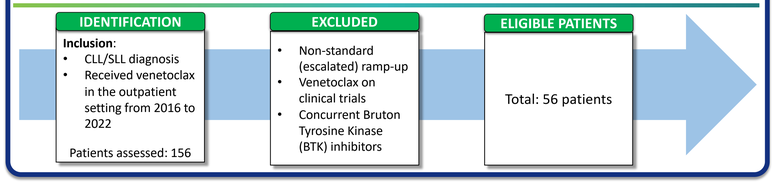
- Incidence of laboratory and clinical TLS and clinical interventions that were done based on laboratory findings during the ramp-up

- Long duration of venetoclax ramp-up schedule
- Intensive monitoring requirements

+ Emerging data demonstrating low incidence of clinical TLS with a rapid ramp-up schema [9]

→ What is the real-world incidence of TLS with standard venetoclax ramp-up for CLL/SLL?

Patient Screening and Exclusion



Results

Incidence of TLS and Clinical Interventions

	Lab TLS, n(%)	Clinical TLS, n(%)
Week 1, Day 1$^{\Delta}$	1 (1.8%)	0
Week 1, Day 2	0	0
Week 2	0	0
Week 3	0	0
Week 4	0	0
Week 5	0	0
Total Events	1	0

	Any clinical intervention, n(%)	IV fluids, n(%)	Intervention other than IV fluids, n(%)	Hospitalization
Week 1, Day 1$^{\Delta}$	1 (1.8%)	0	1 (1.8%)*	0
Week 1, Day 2	1 (1.8%)	0	1 (1.8%)*	0
Week 2	2 (3.6%)	0	2 (3.6%)*,**	0
Week 3	1 (1.8%)	0	1 (1.8%)*	0
Week 4	1 (1.8%)	1 (1.8%)	0	0
Week 5	0	0	0	0
Total Events	6 (across 3 patients)	1	5 (across 2 patients)	0

Abbreviations: IV, intravenous; TLS, tumor lysis syndrome. [Δ On day 1, after initiating venetoclax ramp-up ; *Received phosphate-lowering intervention ; **Received calcium supplementation]

- **Criteria for laboratory TLS were met with 1 patient (1.8%) overall**
- **No lab or clinical TLS in the medium and high TLS risk patient populations throughout venetoclax ramp-up**

Excluded from analysis:

- Laboratory deviations from normal limits but did not meet Cairo-Bishop criteria: 3 patients total
  - Patient A: day 1 (after venetoclax initiation), week 3, and week 4
  - Patient B: week 2
  - Patient C: week 2
- Met laboratory TLS criteria but not attributed to venetoclax: 1 patient
  - Hyperphosphatemia and hypocalcemia in week 5; patient was on dialysis throughout ramp-up and concern with compliance with nephrologist-directed sevelamer therapy

A Closer Look

- One episode of lab TLS (hypoCa and hyperPhos) occurred in the first week of venetoclax ramp-up. Profile: relapsed/refractory CLL, had undergone debulking with anti-CD20 mAb, low TLS risk, no empiric IV fluids. Interventions: Phos binding therapy initiated → normal serum Phos for subsequent weeks.
- Elevated baseline median SCr not a deciding factor for empiric IV fluids during week 1. Baseline median SCr similar between empiric IV fluid group vs. none: 0.95 mg/dL (empiric) vs. 0.97 (none).
- Two patients (both relapsed/refractory disease) completed 5-week ramp-up at a final dose of venetoclax 200 mg daily: one due to hypoCa, hyperPhos, and hyperK → added IV fluids; one with new-onset knee/tailbone pain, achiness, and sweats.

Demographics

	(N=56)
Age	
Median (IQR)	64 (58,70)
Min-Max	39-81
Sex, n(%)	
Male	42 (75)
Female	14 (25)
TLS Risk, n(%)	
Low	42 (75)
Intermediate	13 (23)
High	1 (2)
Line of Therapy	
Median (IQR)	0 (0, 1)
Min-Max	0, 5
Prior Debulking Therapy, n(%)	
Total	46 (82)
Obinutuzumab	21 (46)
Rituximab	25 (53)
CLL Risk (Pre-Treatment), n(%)	
Favorable	27 (48.2)
Intermediate	10 (17.8)
Unfavorable	18 (32)
Not available	1 (2)
TLS Prophylaxis, n(%)	
Any oral anti-hyperuricemic agent	56 (100)
Allopurinol	55 (98)
Febuxostat	1 (2)
IV Fluids	
Week 1	40 (73)
Week 2	31 (55)
Week 3	19 (34)
Week 4	11 (20)
Week 5	11 (20)
Creatinine Clearance, mL/min	
Median (IQR)	89.2 (69.7, 129.85)
Min-Max	14, 224.1

Abbreviations: IV, intravenous; TLS, tumor lysis syndrome

Conclusions

- Intensive laboratory monitoring during the 5-week ramp-up in CLL/SLL patients with majority low or medium-risk TLS risk resulted in very low rates of laboratory and clinical TLS, as well as clinical interventions. These rates in a predominantly newly diagnosed patient population were similar, or lower than, previously reported real-world results, which were often reported with r/r CLL patients.
- Higher TLS risk did not translate into higher incidence of laboratory or clinical TLS.
- No episodes of laboratory or clinical TLS occurred among our newly diagnosed patient sub-population. Newly diagnosed CLL/SLL patients with prior debulking therapy may be candidates for less intensive laboratory monitoring during venetoclax ramp-up.
- Further research into strategies to de-intensify laboratory monitoring requirements and abbreviate venetoclax ramp-up for CLL/SLL should be considered. This may potentially increase the utilization of venetoclax.

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