Venetoclax Consolidation after BTKi Discontinuation for Patients with Chronic Lymphocytic Leukemia

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Background

- Bruton Tyrosine Kinase Inhibitors (BTKi) can yield long-term disease control for patients (pts) with chronic lymphocytic leukemia (CLL) but requires indefinite therapy that can lead to cumulative side effects, especially cardiovascular.[1]
- Venetoclax (Ven) is a BCL-2 inhibitor (BCL-2i) that produces deep responses with high rates of undetectable minimal residual disease (uMRD) for pts with CLL, thus allowing for fixed duration therapy.[2]
- We performed a single institution retrospective analysis of pts treated ven based regimens following BTKi evaluating feasibility and efficacy.

Methods

20 Pts between 2015-2023 initially treated with a BTKi stopped therapy either due to intolerance or personal preference. Pts who had progression on BTKi were excluded.

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Ven-based treatment (tx) consisted of single agent ven (400mg) or in combination with obinutuzumab.

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Response assessment was performed using iwCLL criteria. Minimal residual disease (MRD) was assessed by multi- parametric peripheral blood flow cytometry with a sensitivity of 10^{-4}.

Results

- 80% of pts were treated with ibrutinib and 20% of patients were treated with acalabrutinib.
- 75% of pts were previously treated, 1 previously treated with ven.
- Reasons for stopping BTKi included: atrial fibrillation 25%; desired for fixed duration therapy 25%; diarrhea 15%; completion of planned treatment 15%; infection 10%; arthralgia 5%; and hemorrhage 5%.
- Tumor lysis risk (TLS) prior to starting BTKi was low 60%; intermediate 30%; and high 10%. (Table 1)

Table 1: Patient Characteristics

	Overall N = 20 (%)
Median Age, y (Range)	64 (41 – 82)
Rai Stage	1: 4 (20) 2: 10 (50) 3: 1 (5) 4: 5 (25)
Cytogenetic Abnormalities	del13q: 11 (55) del11q: 7 (35) Trisomy 12: 5 (25) Normal: 3 (15) del17p: 2 (10) Complex: 2 (10)
IGHV Mutational Status Mutated Unmutated	 5 (35.7) 9 (64.3)
Prior CLL Treatment	15 (75)
Median # of prior CLL Treatments, n (Range)	1 (0 – 5)

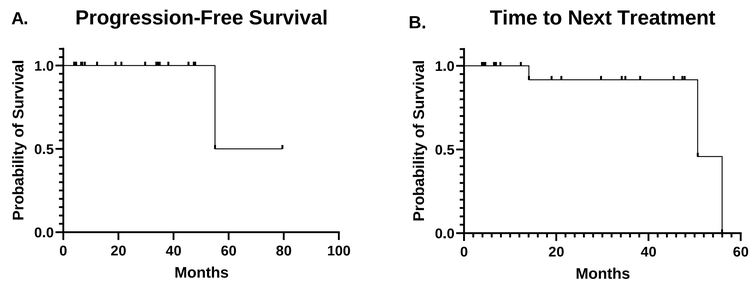
- 15% of pts underwent dose reduction of BTKi prior to switching to ven.
- Response to BTKi therapy was partial response (PR) in 89.5% of pts and stable disease (SD) in 10.5% of pts.
- 95% pts were low-risk TLS after BTKi.
- Pts achieved high-rates of uMRD irrespective of ven-based therapy that were durable. (Table 2)

Table 2: MRD Results

	Overall N = 20 (%)
Median Number of Months of BTKi Tx	32 (1.3 – 70.3)
TLS Risk After Stopping BTKi Low Intermediate	 19 (95) 1 (5)
Median Number of Months of Ven-Based Tx	13 (3.9 – 63.2)
Ven-Based Treatment Ven Monotherapy Ven + Obinutuzumab	 14 (70) 6 (30)
Best MRD Response uMRD Low MRD High MRD	 13 (92.9) 1 (7.1) 0
Best MRD Response Based on Tx *Ven Monotherapy* uMRD *Ven + Obinutuzumab* uMRD Low MRD	 10 (100) 3 (75) 1 (25)
MRD Response after 1 Year of Completion of Ven uMRD Low MRD High MRD	 4 (57.1) 2 (28.6) 1 (14.3)

- Nine pts currently remain on ven.
- Four patients required dose reductions of ven secondary to neutropenia and diarrhea, but no pts had grade ≥3 infections.
- Only one pt had progression after ven-based therapy, while three received subsequent therapy. The median progression-free survival and time to next treatment were 67.3 months and 50.7 months, respectively. (Figure 1)

Figure 1: Survival



Conclusions

- CLL pts treated with ven after BTKi discontinuation due to intolerance/patient preference is a feasible treatment strategy, with high uMRD rates irrespective of the type of ven-based therapy.
- Currently, clinical trials have focused on combination BCL-2i and BTKi. However, this increases the risk of hematologic and gastrointestinal side effects.[3]
- Initial BTKi administration may facilitate sufficient debulking of CLL to facilitate administration of single-agent ven, avoiding the use of combination therapy, decreasing the risk for side effects and infectious complications. This was evident in our cohort, as all but one pt had low-risk TLS prior to initiation of ven.
- Our analysis demonstrates that sequential ven after BTKi is a feasible and effective treatment strategy for pts with CLL that deserves further evaluation in prospective clinical trials.

References

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[3] Tam CS, et al. *Blood.* 2022; 139(22):3278–3289.

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