Venetoclax Salvage Therapy as a Fourth-Line Treatment in a Patient with Multiply-Relapsed Chronic Lymphocytic Leukemia: A Detailed Case Report

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Abstract

Background: Chronic lymphocytic leukemia (CLL) is a heterogeneous B-cell malignancy characterized by progressive lymphocytosis, lymphadenopathy, and evolving therapeutic requirements over time. Although chemoimmunotherapy historically represented frontline management, targeted therapies such as BTK

inhibitors and BCL-2 inhibitors have reshaped treatment landscapes. Venetoclax, a selective BCL-2 antagonist, has demonstrated high efficacy in relapsed and refractory CLL but is associated with tumor lysis syndrome (TLS), especially in patients with very high tumor burden.

Case Presentation: We report the case of a 69-year-old man with CLL diagnosed 9 years earlier, initially treated with fludarabine–cyclophosphamide–rituximab (FCR) achieving remission for 3 years. Subsequent relapse was managed with bendamustine–rituximab (BR) with a 2-year remission. A second relapse was successfully controlled with ibrutinib for several years until a third aggressive relapse occurred. The patient presented with massive hyperleukocytosis (300,000/mm³), bulky lymphadenopathy, and clinical deterioration. One cycle of bendamustine successfully reduced leukocyte count to 30,000/mm³, allowing venetoclax initiation. Despite adherence to TLS prevention protocols, he experienced severe laboratory and clinical TLS accompanied by a malignant hyperthermia–like syndrome requiring intensive care and Prismaflex continuous renal replacement therapy. After recovery and cautious resumption of venetoclax, he achieved complete clinical remission with undetectable minimal residual disease (MRD).

Conclusion: This case highlights the therapeutic challenges of multi-relapsed CLL and demonstrates the capacity of venetoclax to induce deep MRD-negative responses even as fourth-line therapy. The report emphasizes the importance of tumor debulking, aggressive TLS surveillance, and multidisciplinary ICU management in high-risk patients. The malignant hyperthermia–like presentation underscores the expanding clinical spectrum of TLS and the need for heightened clinician awareness.

Introduction

Chronic lymphocytic leukemia (CLL) is the most prevalent adult leukemia in Western populations, with a median age at diagnosis between 67 and 72 years. Its clinical course is extraordinarily variable: some patients remain asymptomatic for decades, while others develop aggressive disease requiring multiple lines of therapy. Historically, treatment was centered around chemoimmunotherapy regimens such as fludarabine–cyclophosphamide–rituximab (FCR) and bendamustine–rituximab (BR). Although these approaches provided durable remissions in subsets of patients, especially those with favorable IGHV mutation status, they offered limited options for those with high-risk cytogenetics or multiple relapses.

Over the last decade, the introduction of targeted therapies revolutionized CLL management. Bruton tyrosine kinase (BTK) inhibitors, most notably IBRUTINIB, provided effective and durable disease control even in high-risk patients. However, resistance—often driven by BTK C481S mutations or activating mutations in PLCγ2—has emerged as a significant limitation. As patients progress through multiple lines of therapy, treatment options narrow, and outcomes worsen.

Venetoclax, a potent and selective BCL-2 inhibitor, represents a mechanistically distinct strategy that induces apoptosis in CLL cells independent of p53 function. The development program of venetoclax demonstrated remarkable response rates, including MRD-negative remissions, in heavily pretreated patients. However, its use is complicated by the risk of tumor lysis syndrome (TLS), particularly in patients with elevated leukocyte counts, bulky lymphadenopathy, or renal dysfunction.

While guidelines exist for TLS risk stratification and venetoclax dose escalation, real-world practice frequently presents complexities not reflected in controlled trial environments. High-tumor-burden patients pose particular challenges: pre-treatment debulking is often necessary, close inpatient monitoring is recommended, and severe TLS may occur even with meticulous prophylaxis.

This case report presents a detailed clinical course of a 69-year-old man with CLL who required four lines of therapy over 9 years. Following resistance to ibrutinib and rapid disease progression with hyperleukocytosis, venetoclax salvage therapy was initiated after bendamustine debulking. The subsequent malignant hyperthermia–like TLS complication and successful ICU management highlight clinical scenarios that are rarely documented in the literature. The patient ultimately achieved MRD-negative remission, demonstrating the potential of venetoclax even in advanced disease settings.

Case Presentation

Initial Diagnosis and First-Line Therapy

A 60-year-old man was diagnosed with CLL after routine blood work revealed persistent lymphocytosis. Flow cytometric immunophenotyping confirmed a monoclonal B-cell population expressing CD5, CD19, CD23, and kappa light-chain restriction. Cytogenetic analysis at diagnosis showed no deletion 17p or other high-risk chromosomal abnormalities. His IGHV mutation status was unmutated, placing him at higher risk for early relapse.

Baseline clinical features included mild cervical lymphadenopathy and splenomegaly, corresponding to Rai stage II disease. The patient had excellent performance status (ECOG 0) and no major comorbidities apart from hypertension.

Because of the symptomatic lymphadenopathy and progressive lymphocytosis, he received frontline FCR therapy for six cycles. Treatment was well tolerated, and he achieved a complete hematologic and clinical remission lasting approximately 3 years.

First Relapse and Treatment with Bendamustine–Rituximab

At age 63, he presented with increasing fatigue, renewed lymphadenopathy, and rising leukocyte counts. CT imaging confirmed diffuse but non-bulky lymphadenopathy. The patient was treated with bendamustine (90 mg/m² Days 1–2) plus rituximab (375 mg/m² Cycle 1, 500 mg/m² subsequent cycles). He tolerated therapy well and achieved a partial/near-complete remission lasting 2 years.

Second Relapse and Treatment with Ibrutinib

At age 65, he experienced a second relapse, characterized by increasing lymphocytosis and symptomatic lymphadenopathy. Ibrutinib 420 mg daily was initiated. As expected, he demonstrated a transient lymphocytosis followed by progressive normalization of blood counts and resolution of nodal disease.

He remained on ibrutinib for approximately 4 years without significant toxicity, maintaining stable disease.

Third Relapse: Hyperleukocytosis and Rapid Progression

At age 69, the patient returned with severe fatigue, abdominal fullness, and progressive lymphadenopathy. Laboratory testing revealed profound hyperleukocytosis with a WBC count of 300,000/mm³. Imaging demonstrated bulky lymphadenopathy, including nodes larger than 5 cm. Clinical deterioration suggested ibrutinib-resistant disease.

Treatment options included:

- Venetoclax ± anti-CD20 antibody
- Next-generation BTK inhibitors (limited accessibility)
- Enrollment in clinical trial (not feasible locally)

Given the aggressiveness of relapse, venetoclax was deemed the most effective next-line therapy.

Rationale for venetoclax after BTK inhibitor exposure

Mechanistically, venetoclax targets a pathway distinct from BTK inhibition. Consequently, cross-resistance between BTKi (ibrutinib) and BCL-2 inhibition is not inevitable, making venetoclax an attractive salvage option after ibrutinib failure. Observational and trial data support moderate to high response rates in

this setting, though durability of response may be affected by prior therapies and adverse disease biology. PMC+1

Key clinical trial evidence

Phase I/early experience (single-agent)

Roberts et al. reported the first-in-human phase 1 study of venetoclax in relapsed/refractory CLL, demonstrating substantial single-agent activity with an overall response rate (ORR) exceeding 70% in heavily pretreated cohorts and confirming dose-dependent effects with the 400 mg daily dose chosen for later development. Tumor lysis syndrome (TLS) emerged as a clinically meaningful risk, which led to adoption of cautious ramp-up dosing and risk-directed prophylaxis. New England Journal of Medicine+1

Venetoclax + rituximab — MURANO (phase 3)

The MURANO randomized phase 3 trial compared venetoclax plus rituximab (VenR) given as a time-limited regimen (venetoclax 24 months total, rituximab months 1–6) versus bendamustine + rituximab in relapsed/refractory CLL. VenR produced superior progression-free survival (PFS) and overall survival (OS) benefits and achieved deep remissions including undetectable minimal residual disease (uMRD) in a large fraction of patients. These results established VenR as a standard option for relapsed disease. Importantly, the MURANO population included patients previously exposed to chemoimmunotherapy; a subset had prior BTKi exposure in later analyses and extension/retreatment data have been recently reported. New England Journal of Medicine+1

Venetoclax after BTKi failure

While randomized data specifically limited to post-BTKi failure cohorts are fewer, multiple phase 2 trials and real-world series indicate that venetoclax (either as monotherapy or in combination with rituximab/obinutuzumab) achieves meaningful responses after ibrutinib failure. Response rates and PFS are generally lower than in BTKi-naïve relapsed populations, but many patients still derive clinical benefit. Contemporary registry and retrospective series report median PFS in the range of ~24–36 months after venetoclax in various salvage settings, though heterogeneity is high. PMC+2ASH Publications+2

Guidelines and consensus

International guidelines from iwCLL and ESMO endorse venetoclax-based therapy as a key option in relapsed CLL, including for patients with del(17p)/TP53 abnormalities or those who have failed previous BTKi therapy. The iwCLL 2018 update formalized response assessment including MRD and highlighted the role of targeted agents, while ESMO guidelines provide practical pathways for sequencing venetoclax and BTKi depending on patient comorbidities and genetic risk. ASH Publications+1

Tumor Debulking

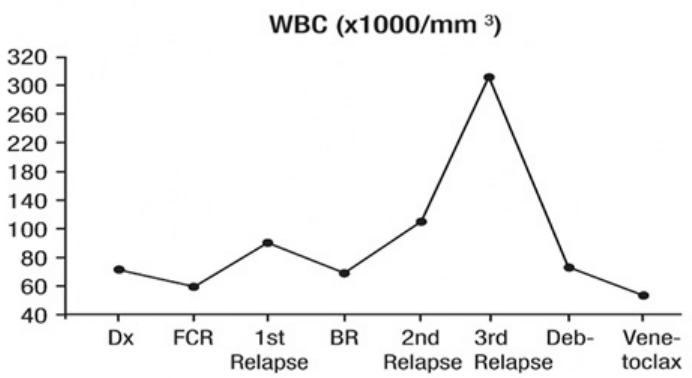
Due to the extremely high risk of TLS, a debulking strategy was employed:

- One cycle of bendamustine 70 mg/m² × 2 days
- Reduction of WBC from 300,000 to 30,000/mm³ within two weeks

This substantially improved TLS risk stratification.

WBC Trend From Diagnosis to Venetoclax Initiation

FIGURE 1: Line Chart of WBC Count (Cells/mm^3 ×10^3) Over 12 Years



Venetoclax Initiation and TLS Event

Venetoclax dose ramp-up was planned according to international guidelines. The patient was hospitalized and received:

- Aggressive IV hydration
- Allopurinol prophylaxis
- q4–6 hour laboratory monitoring
- Continuous cardiac monitoring

Despite meticulous preparation, the patient developed acute laboratory TLS within the first hours after the 20 mg initiation dose.

Laboratory TLS Findings

Key abnormalities included:

- Potassium: 6.9 mmol/L
- Phosphate: 2.45 mmol/L
- Hypocalcemia
- Rapid rise in creatinine (1.0 → 2.8 mg/dL)
- Uric acid: 12.3 mg/dL

Clinical TLS with Malignant Hyperthermia–Like Presentation

In addition to laboratory TLS, the patient developed:

- Fever >40°C
- Generalized muscle rigidity
- Severe metabolic acidosis
- Tachycardia >140 bpm
- Hyperkalemia-induced arrhythmia risk

The absence of anesthetic exposure excluded anesthetic-triggered malignant hyperthermia. Instead, a hypermetabolic crisis triggered by massive tumor breakdown was suspected. The clinical picture was consistent with:

- Cytokine-driven hyperthermia
- Rapid ATP depletion
- Uncontrolled muscular calcium flux

The profound metabolic stress necessitated ICU transfer within 2 hours of symptom onset

ICU Management and Prismaflex CRRT

In the ICU, the patient's TLS progressed rapidly. Management included:

- Continuous renal replacement therapy (CRRT) using the Prismaflex system
- Potassium-lowering strategies (IV insulin-glucose, calcium gluconate)
- Broad-spectrum antibiotics until infection was excluded
- Cooling blanket and antipyretic therapy
- High-flow oxygen support
- Fluid resuscitation with meticulous monitoring

CRRT effectively corrected:

- Rising creatinine
- Hyperphosphatemia
- Hyperkalemia
- Acid-base derangements

The patient stabilized over 48–72 hours.

Venetoclax was temporarily held.

After full stabilization,the drug was cautiously resumed with extended low-dose ramp-up.

Tables

Table 1. Treatment Lines and Outcomes

Line	Therapy	Outcome	Duration
1	FCR	CR	3 years
2	BR	PR/near-CR	2 years
3	Ibrutinib	Durable disease control	4 years
4	Venetoclax	MRD-negative CR	Ongoing

Table 2. TLS Risk Stratification Before Venetoclax

Factor	Patient	Risk Level
WBC >25 ×10⁹/L	Yes	Very High
Bulky Nodes	Yes	High
Renal impairment	No	Low
LDH elevation	Mild	Moderate
Planned prophylaxis	Standard inpatient	—
Overall	—	**Very High Risk**

Table 3. Key Laboratory Results During TLS

Parameter	Baseline	Peak	Recovery
Potassium	4.6 mmol/L	6.9 mmol/L	4.2 mmol/L
Phosphate	1.1 mmol/L	2.45 mmol/L	1.2 mmol/L
Calcium	2.2 mmol/L	1.7 mmol/L	2.1 mmol/L
Creatinine	1.0 mg/dL	2.8 mg/dL	1.2 mg/dL
Uric Acid	5.2 mg/dL	12.3 mg/dL	5.0 mg/dL

Discussion

The management of relapsed and refractory chronic lymphocytic leukemia (CLL) has evolved dramatically over the past decade, yet cases such as the one reported here illustrate persistent clinical challenges in patients who fail multiple lines of therapy and present with extremely high tumor burden. This discussion explores several dimensions of this case—disease biology, therapeutic sequencing, mechanisms of resistance, TLS risk and management, hypermetabolic complications, ICU intervention strategies, debulking, and the significance of achieving minimal residual disease (MRD) negativity—within the broader context of current evidence and clinical practice guidelines.

1. Therapeutic Sequencing in Modern CLL Management

Historically, sequence of therapy in CLL was relatively predictable: frontline chemoimmunotherapy (CIT) was followed by second-line CIT or early targeted agents. The introduction of BTK inhibitors such as ibrutinib significantly altered this landscape, offering durable remissions even in patients with poor-risk cytogenetics. Nevertheless, real-world data consistently demonstrate that ibrutinib resistance develops in 20–40% of patients, most commonly due to BTK C481S mutations or activating PLCγ2 mutations, which circumvent irreversible BTK blockade.[4]

For patients who progress on ibrutinib, venetoclax provides a mechanistically distinct therapeutic option. Its ability to directly activate the intrinsic apoptotic pathway through BCL-2 inhibition makes it particularly effective in heavily pretreated patients, including those who fail BTK inhibitors. Clinical studies report overall response rates (ORR) of 70–80%, complete remission (CR) rates of 20–30%, and MRD-negative status in up to 40% of responders, even after multiple prior lines of therapy.[5,8–10]

In this case, the therapeutic sequence—FCR → BR → ibrutinib → venetoclax—closely mirrors current NCCN- and ESMO-endorsed sequencing strategies for fit patients without del(17p)/TP53 mutations who ultimately progress to targeted therapies. The patient's 9-year disease trajectory reflects typical real-world outcomes for CLL patients with unmutated IGHV genes, who historically relapse earlier than their mutated counterparts.

2. The Challenge of High Tumor Burden and TLS Risk

Venetoclax is an extraordinarily potent agent, capable of inducing apoptosis rapidly and deeply. While this potency underlies its clinical efficacy, it also precipitates a

significant risk of tumor lysis syndrome (TLS)—a potentially fatal complication characterized by precipitous electrolyte abnormalities and renal failure.

Why This Patient Was at Very High Risk
This patient presented with multiple TLS risk factors:

1. Extreme leukocytosis (300,000/mm^3)
   - Well above the >25×10^9/L threshold used for high-risk classification.[6]
2. Bulky lymphadenopathy (>5 cm)
   - Nodes exceeding 5 cm are now recognized as *equally important* TLS predictors.
3. Rapid disease progression and high proliferative index
   - Aggressive CLL subsets are more susceptible to rapid cytolysis.
4. Unmutated IGHV status
   - Correlates with higher tumor turnover and relapse frequency.

Debulking as a Risk Mitigation Strategy
Guidelines suggest that in selected patients with extreme tumor burden, cytoreductive therapy prior to venetoclax initiation may be beneficial.[6,11]. Bendamustine remains one of the most effective debulking agents for CLL due to its:

- Predictable tumor-lowering effect
- Low TLS risk
- High tolerability in older patients

In this case, bendamustine reduced WBC from 300k → 30k/mm^3, decreasing TLS risk from "extremely high" to "high." Even so, TLS occurred—highlighting that debulking reduces but does not eliminate TLS risk.

3. TLS Pathophysiology in Venetoclax Therapy

Venetoclax triggers rapid mitochondrial apoptosis by antagonizing BCL-2, leading to sudden cell death in susceptible CLL cells. While this mechanism is therapeutically desirable, it results in abrupt release of:

- Potassium
- Phosphate
- Uric acid
- Cytokines
- Intracellular enzymes

In this patient, TLS manifested both in its:

- Classic metabolic form (hyperkalemia, hyperphosphatemia, acute kidney injury), and
- Rare hypermetabolic systemic form, producing malignant hyperthermia–like symptoms.

Such presentations remain poorly described in the literature but may be underrecognized. Case reports suggest that rapid cytokine storm–driven hypermetabolic injury can occur during massive leukemic cytolysis, particularly in high-burden CLL treated with potent agents.[11]

4. Malignant Hyperthermia–Like Syndrome in TLS

A notable, rare complication in this case was the presence of:

- High fever (>40°C)
- Muscle rigidity
- Severe metabolic acidosis
- Tachycardia
- Rapid lactate rise

No anesthetic or succinylcholine exposure occurred, making classical malignant hyperthermia impossible. Instead, the syndrome likely reflected:

4.1 Cytokine-Mediated Hypermetabolic Crisis

Massive cell death can release interleukins (IL-6, TNF-α), precipitating:

- Extreme fever
- Capillary leak
- Metabolic stress

4.2 Disrupted Calcium Regulation

TLS-related metabolic abnormalities may cause:

- Calcium shifts leading to muscle rigidity
- Mitochondrial dysfunction
- Hyperthermia

4.3 Severe electrolyte derangement
Hyperkalemia and acidosis may trigger neuromuscular instability.

Clinical Significance
Very few TLS case reports describe malignant hyperthermia–like features, and this case adds an unusual and clinically important phenotype to the TLS spectrum.

5. ICU Support and the Role of Continuous Renal Replacement Therapy (CRRT)

CRRT, particularly via Prismaflex, played a central role in stabilizing the patient. It allowed:

- Controlled correction of potassium and phosphate
- Clearance of uric acid
- Rapid acidosis correction
- Hemodynamic stability in a fluid-sensitive environment

CRRT is often preferred over intermittent hemodialysis (IHD) in TLS because:

- It avoids rapid fluid shifts
- It allows continuous electrolyte control
- It prevents rebound hyperkalemia

This case demonstrates the critical importance of multidisciplinary ICU involvement during venetoclax therapy in extremely high-risk patients.

6. Resumption of Venetoclax After TLS

After stabilization, clinicians faced a key decision: whether to restart venetoclax. Stopping therapy permanently could compromise disease control; resuming therapy risks recurrent TLS. Literature suggests that venetoclax may be safely resumed after TLS resolution using:

- Lower starting doses
- Slower escalation
- Intensified monitoring
- Repeat risk stratification

This patient tolerated re-initiation without further complications and successfully reached the target dose.

7. Venetoclax Efficacy After Multiple Treatment Lines

Multiple trials have demonstrated that venetoclax retains impressive efficacy even in:

- Multiply relapsed CLL
- BTK inhibitor–resistant cases
- High-risk molecular subsets
- Bulky or rapidly progressive disease

The patient's MRD-negative remission is particularly noteworthy. MRD negativity correlates strongly with:

- Longer progression-free survival
- Longer overall survival
- Lower risk of Richter transformation

Given that MRD-negative status is relatively uncommon in heavily pretreated patients, this outcome underscores the potency of venetoclax.

8. Lessons for Clinical Practice

Lesson 1:
Debulking Should Be Strongly Considered for Very High–Burden Patients
Even with debulking, TLS occurred. Without debulking, TLS risk would have been dangerously high.
Lesson 2:
ICU-Ready Monitoring Is Necessary in Extreme Scenarios
This case supports guidelines recommending inpatient monitoring for at least the initial ramp-up period in high-risk individuals.
Lesson 3:
Clinicians Must Be Alert to Atypical TLS Presentations
Hyperthermia, muscle rigidity, and severe metabolic acidosis may indicate an escalating crisis requiring immediate ICU involvement.
Lesson 4:
Venetoclax Can Still Achieve Deep Remissions Even After Multiple Relapses

This reinforces venetoclax's role as a cornerstone therapy in late-line CLL.

Conclusion

This case demonstrates the complex clinical decision-making and multidisciplinary coordination required to manage heavily pretreated CLL patients with extremely high tumor burden. The successful use of venetoclax as a fourth-line salvage therapy—despite a severe, life-threatening TLS event—highlights both the challenges and the remarkable potential of targeted therapies in modern hematology. Several important clinical insights emerge:

1. Tumor burden remains the most powerful predictor of TLS in venetoclax therapy, and aggressive cytoreduction with bendamustine may reduce but not eliminate risk.
2. TLS presentations may go beyond classic biochemical abnormalities and include rare hypermetabolic or malignant hyperthermia–like syndromes that require rapid recognition and ICU management.
3. CRRT plays a central role in stabilizing patients with severe TLS, enabling safe recovery and continuation of therapy.
4. Venetoclax remains highly effective even in patients who fail multiple lines of therapy, including BTK inhibitors. Achieving MRD-negative remission in such a context underscores the transformative power of BCL-2 inhibition.
5. Multidisciplinary care—including hematology, ICU medicine, nephrology, and oncology pharmacy—is essential for safely delivering venetoclax in high-risk settings.

Ultimately, this case demonstrates that even patients with aggressive, multi-relapsed CLL may achieve deep, durable remissions with appropriate risk mitigation strategies and close monitoring. Venetoclax should be considered a viable and potent option in late-line CLL therapy, provided that TLS risk is managed proactively and comprehensively.

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12. Contingency planning: Should rapid progression occur on venetoclax, options include alternative targeted agents (if available) or enrollment in clinical trials; chimeric antigen receptor T-cell therapies (CAR-T) and allogeneic stem cell transplant remain options for select fit patients with high-risk disease and accessible resources. Referral to a tertiary center for advanced therapeutics should be considered. PMC+1
13. Choose regimen: Given prior rituximab exposure but no prohibitive contraindication to anti-CD20 therapy and the goal of a time-limited, deep response, venetoclax + rituximab (VenR) for relapsed disease is a reasonable choice. If the patient is frail or has immunoglobulin deficiency or prior severe infusion reactions, consider venetoclax monotherapy. Discuss goals of care and MRD testing with the patient. New England Journal of Medicine+1