

Case Report

Debulking Therapy with Obinutuzumab Is Helpful and Safe in Chronic Lymphocytic Leukemia with Extreme Hyperleukocytosis: A Case Report

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Simple Summary: Chronic lymphocytic leukemia (CLL) is the most common leukemia in Western countries, predominantly affecting individuals over 70 years old. This case highlights an elderly patient with CLL and a high tumor burden, characterized by an extremely elevated white blood cell (WBC) count (>800,000/mm³). First-line treatment with fixed-duration debulking obinutuzumab (an anti-CD20 antibody), followed by venetoclax (a BCL2 inhibitor), successfully managed the high tumor lysis syndrome (TLS) risk, leading to a drastic WBC reduction, and achieving a complete response. Initial inpatient obinutuzumab therapy for debulking, combined with venetoclax and supportive care, proved life-saving and normalized blood counts.



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Abstract: Introduction: Chronic lymphocytic leukemia (CLL) represents the most frequent leukemia in the Western world, with an incidence of 4.2/100,000/year, and is often challenging to manage, especially in patients with extremely high WBC count due to the high risk of TLS. The adequate and best treatment is an open question that should be addressed beyond the biological features of the disease in order to guarantee the best outcome. Case presentation: We present the case of an elderly patient with a high tumor burden due to an extremely high white blood cell count (above 800,000/mm³), who received fixed-duration treatment with venetoclax–obinutuzumab (BCL2 inhibitor and anti-CD20) as first-line therapy. Despite the high risk for tumor lysis syndrome, we demonstrated that with cautious management it is possible to drastically reduce the WBC count, leading to a better quality of life and also even reaching a complete response in this grouping of patients. Obinutuzumab was first administered in the inpatient setting as the initial first-line debulking therapy, using personalized low-velocity treatment which led to a sustained and prolonged white blood cell count decrease, followed by venetoclax association. Conclusions: With proper support therapy, debulking obinutuzumab followed by venetoclax represented a life-saving treatment, able to normalize the blood count and achieve a complete response in a CLL patient with an extremely high risk of TLS, avoiding losing this therapeutic option.

Keywords: chronic lymphocytic leukemia; tumor lysis syndrome; hyperleukocytosis; leukostasis; obinutuzumab–venetoclax

1. Introduction

Chronic lymphocytic leukemia (CLL) represents the most frequent leukemia in the Western world, with an incidence of 4.2/100,000/year. CLL is characterized by heterogeneous manifestations, varying from indolent to an aggressive clinical course in rare cases. Early-stage asymptomatic CLL patients do not require immediate treatment, but only a watch-and-wait strategy. Patients with advanced and/or “active” disease in terms of progressive lymphocytosis (lymphocyte count increased > 50% in 2 months or lymphocyte doubling time < 6 months), bulky lymphadenopathies, progressive marrow failure (anemia, thrombocytopenia), autoimmune disorders (including autoimmune anemia), massive splenomegaly, or the presence of constitutional symptoms, on the other hand, are considered eligible for antineoplastic treatment [1]. In recent years, the landscape of therapeutic options has widely increased, with the introduction of Bruton tyrosine kinase (BTK) inhibitors which can be used until disease progression, or fixed-duration BCL2 inhibitors in which can be used in association with anti-CD20 monoclonal antibodies, thus reserving a marginal role for chemotherapy. CLL may present with extreme hyperleukocytosis (white blood cell count, $>100 \times 10^9/L$), leading to a higher risk of leukostasis and tumor lysis syndrome [2]. Tumor lysis syndrome (TLS) is a complication characterized by the rapid breakdown (lysis) of cancer cells, leading to the release of intracellular contents such as potassium, phosphate, and nucleic acids into the bloodstream, possibly causing cardiac arrhythmias, acute kidney injury, seizures, and even death if not promptly managed [3]. TLS may occur in patients affected by hematological conditions, such as acute myeloid leukemia (AML, above all in FLT3 mutation diseases) and myeloproliferative neoplasms (MPN), deeply impacting the prognosis [4–9]. For CLL, although hyperleukocytosis requires proper care, it does not impact the final prognosis [10].

Venetoclax (a BCL2i) has a high risk of TLS, and multiple factors, including comorbidities, influence it. Patients with a high tumor burden (e.g., lymph nodes ≥ 5 cm in diameter or an absolute lymphocyte count $\geq 25 \times 10^9/L$) are at greater risk of TLS after starting venetoclax therapy. Reduced renal function (creatinine clearance <80 mL/min) further increases this risk. A single cycle of obinutuzumab (an anti-CD20 antibody) effectively reduces TLS risk before the introduction of venetoclax, allowing the dose escalation to be safely accomplished in the outpatient setting with close monitoring regardless of TLS risk.

Eliminating the need for hospitalization during venetoclax dose escalation could improve both patient and provider convenience while reducing the overall economic burden of treatment [11].

In this case, we present an elderly CLL patient with an extremely high tumor burden (white blood count above 800,000/mm³) who received fixed-duration venetoclax–obinutuzumab combination as treatment. Debulking obinutuzumab was first administered in an inpatient setting, using a personalized low infusion velocity and reduced dosage of obinutuzumab at first due to the extremely high risk of TLS, and once a sustained and prolonged decrease in white blood cell count was obtained, treatment with venetoclax followed as per protocol.

2. Case Presentation

In May 2023, a 77-year-old male came to our attention with Rai-Binet IV C CLL, which has a high biologic risk (del 17p, TP53 mutated, IGHV unmutated). He was in

the symptomatic progression of the disease, characterized by non-tender, mobile laterocervical lymphadenopathy (~2.7 cm diameter), the spleen palpable 6 cm below the costal margin (19.4 cm diameter), and with a 8 CLL-IPI score. Laboratory findings revealed hemoglobin 9.8 g/dL, platelet count under 100,000/mm³, and a lymphocyte count rapidly increased to over 200,000/mm³, with 85% monoclonal B-cells expressing CD20+ (92.1%)/CD5+/CD23+/CD200+. In his medical history, the patient reported diabetes mellitus, hypertension, benign prostatic hyperplasia, arthritis, and previous hepatitis B exposure (HBcAb IgG positive with negative HBsAg and circulating HBV-DNA) for which the patient started prophylaxis with lamivudine 100 mg/die [12].

Notwithstanding the development of hyperleukocytosis and anemia, the patient was first enrolled to receive first-line treatment with a second-generation BTK inhibitor, acalabrutinib, but he refused lifetime treatment. The regimen ibrutinib–venetoclax was not available at that time [13], thus our treatment choice was switched to venetoclax–obinutuzumab, considering the rapid effect conferred by obinutuzumab in the reduction of lymphocyte count when administering therapy in a controlled setting. Nevertheless, the patient missed an appointment in our unit twice, delaying the start of treatment. After a few months without therapy, in August 2023, his white blood cell count reached about 800,000/mm³, and he was immediately hospitalized to receive treatment in an inpatient setting due to the high tumor burden known in this context. At admission, the complete blood count evidenced hemoglobin levels of 7.9 g/dL, white blood cell counts of 860,170/mm³ (90.2% lymphocytes), and moderate thrombocytopenia 89,000/mm³, reporting a high tumor lysis risk score based on data from the CLL14 protocol trial [14]. Laboratory TLS is commonly defined according to the Cairo–Bishop definition [15]. The patient reported a debilitating lack of energy, headaches, and drowsiness, attributable to leukostasis. At first, leukapheresis was considered for the first treatment. Still, due to the patient's poor conditions, the impossibility of inserting a proper venous catheter, and the need for prompt intervention, leukapheresis was discarded as an option.

Once admitted, the patient underwent red blood cell transfusion support, intravenous (IV) hydration (1500 mL/m², and urolithic therapy with rasburicase 7.5 mg as preparation for debulking therapy with obinutuzumab. On day 1, the patient received standard premedication with corticosteroids, antihistamines, paracetamol, and nasal O₂ cannula therapy at 4 L/min as support, given the borderline oxygen saturation (SpO₂ 93% without oxygen support). The test dose of obinutuzumab (100 mg in 100 mL of saline solution) was administered at shallow velocity (6 mL/h), compared to the standard velocity of 25 mL/h in 4 h, to prevent the onset of a life-threatening episode of TLS. Around two hours after the beginning of therapy, the patient experienced an infusion reaction with tremors, hypertension (150/80 mmHg), hyperpyrexia (38.2 °C), desaturation (SpO₂ 92% with O₂ therapy), nausea, vomiting, and the initial signs of pulmonary edema. The infusion was suspended, and the reaction was treated with hydrocortisone 200 mg IV, chlorphenamine 10 mg, paracetamol 1000 mg, ondansetron 8 mg, and furosemide 20 mg. An hour later, following complete symptom resolution, the infusion continued at 5 mL/h without other adverse events until the end of the anti-CD20 treatment. Blood serum tests showed significantly reduced leukocytes (Figure 1) and increased tumor lysis factors (creatinine, potassium, phosphatase, and lactate dehydrogenase—LDH). Despite the patient's vitals being stable, he was lethargic, although able to be woken up with sound stimuli. On day 2, the patient started obinutuzumab 900 mg in 1000 mL of saline solution with an infusion speed of 10 mL/h, progressively increasing up to 20 mL/h in the following hours. After the initial 100 mL of obinutuzumab was completed, the infusion was stopped due to the high risk of worsening the clinical TLS, based on the ongoing laboratory tests (Table 1). The white blood count was further reduced in the following days, and the kidney functionality

test, electrolytes, LDH, C-reactive protein (PCR), and procalcitonin (PCT) improved. During the following days, the patient received support and transfusion therapy, with worsening of the coagulation tests (INR, APTT) leading to the patient receiving 3 units of fresh frozen plasma. On the 8th day from the start of obinutuzumab treatment, considering the stability of the WBC count (107,000/mm³) and increase in platelets (51,000/mm³), obinutuzumab was again administered, giving the first scheduled 500 mg IV in 500 mL of saline solution, starting with slightly higher infusion velocity (20 mL/h), reaching up to 60 mL/h, without any adverse events or alterations of the parameters of tumor lysis syndrome. Once the WBC count reached 29,000/mm³ (N: 5408/mm³; L: 23,049/mm³), the patient was dismissed to continue therapy on a day hospital regimen. He started venetoclax ramp-up on cycle 1 day 22, presenting a WBC count of 3590/mm³ (N: 1848/mm³; L: 1558/mm³). In the following months, the patient continued obinutuzumab–venetoclax treatment as per the therapeutic protocol without any complications. He completed the cycles of obinutuzumab and venetoclax, maintaining a complete response over a year and a half after the beginning of the therapy, presenting Hb 14 gr/dL, PLTs 167,000/mm³, WBC 3,900/mm³, N 2250/mm³, L 1000/mm³, normal spleen size (14.9 cm diameter), and absence of lymphadenopathy.

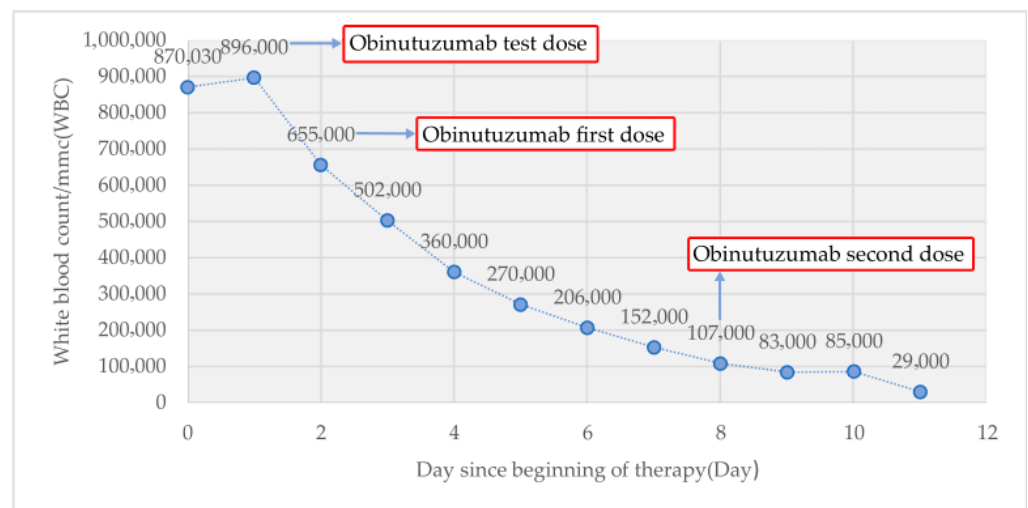


Figure 1. Trend of white blood cell/mm³ (WBC) count during debulking therapy with obinutuzumab.

Table 1. Hemoglobin (HB, normal range 14–18 gr/dL), platelets (PLT, normal range 150,000–450,000/mm³), serum creatinine (Cr, normal range 0.84–1.21 mg/dL), uric acid (normal range 3.4–7.0 mg/dL), serum potassium (K⁺, normal range 3.5–5.1 mmol/L), serum calcium (Ca⁺, normal range 8.5–10.2 mg/dL), serum phosphate (P⁻, normal range 2.5–4.5 gr/dL), and lactate dehydrogenase (LDH, normal range 120–250 U/L) during debulking therapy with obinutuzumab.

Days from the Start of Cycle	Hb (g/dL)	PLT (/mmc)	Cr (mg/dL)	Uric Acid (mg/dL)	K ⁺ (mmol/L)	Ca ⁺ (mg/dL)	P ⁻ (mg/dL)	LDH (U/L)
−1	7.9	105,000	1.14	8	4.3	9.7	4.3	518
0	8.8	60,000	1.3	<1.5	6	9.1	6.3	520
1	8.4	46,000	1.8	1.8	5.8	8.3	5.8	2131
2	8.5	36,000	1.77	1.7	5.5	7.7	6.2	1405
3	8.6	29,000	1.44	1.6	5	7.4	5.6	867
4	8.3	26,000	1.16	1.7	4.7	7.4	5.5	852
5	8.5	30,000	0.97	<1.5	4.7	7.5	5.4	832

Table 1. *Cont.*

Days from the Start of Cycle	Hb (g/dL)	PLT (/mmc)	Cr (mg/dL)	Uric Acid (mg/dL)	K ⁺ (mmol/L)	Ca ⁺ (mg/dL)	P- (mg/dL)	LDH (U/L)
6	8.06	30,000	0.76	<1.5	4.6	7.7	4.4	500
7	7.35	28,000	0.71	<1.5	4.1	7.9	2.9	332
8	7.49	37,000	0.64	<1.5	4.4	8.2	2.8	313
9	8.1	51,000	0.65	<1.5	4.2	7.9	2.8	292
10	8.46	51,000	0.69	<1.5	4.2	8.3	2.8	264

3. Discussion

Hyperleukocytosis is a condition characterized by an abnormally elevated number of white blood cells in the bloodstream, typically defined as a count exceeding 100,000 cells per microliter [16]. It may represent a significant risk of complications, such as leukostasis, where the increased viscosity of the blood can lead to blockages in small blood vessels, impairing blood flow and potentially causing tissue damage or organ dysfunction, such as respiratory, neurological, or renal compromise [17,18]. Hyperleukocytosis is quite frequent with CLL, but it rarely causes leukostasis, due to the small size of mature lymphocytes and their features [19]. Given that cases of leukostasis in CLL are rare in the literature, guidelines are not fully established. Leukostasis may exacerbate disease complications and require prompt medical intervention, including leukapheresis to reduce the white blood cell count and alleviate symptoms rapidly. Leukocytapheresis, often referred to as leukapheresis, is a therapeutic procedure to reduce the number of white blood cells in the bloodstream. During leukapheresis, blood is withdrawn from the patient and passed through a specialized machine that separates the white blood cells from the other blood components and selectively removes them. In contrast, the remaining blood components are returned to the patient's circulation. By effectively lowering the number of circulating leukocytes, leukapheresis can help alleviate symptoms and reduce the risk of complications associated with leukostasis, considering that a single leukapheresis session can reduce the WBC count by 20–50% [20]. Although used in clinical practice, there is no solid evidence for using leukapheresis for leukostasis in CLL since it does not impact the production of leukemic cells in the bone marrow, its effects are temporary, and WBC counts can rapidly rebound after the procedure. While leukapheresis has been shown to improve pulmonary and central nervous system symptoms, its overall impact on patient outcomes and survival remains uncertain. Current evidence suggests that leukapheresis does not provide a mortality benefit despite its common use in managing leukostasis [17,21].

Moreover, assessing the complications associated with central catheter insertion and the risk of catheter-related infections should be thoroughly evaluated before starting leukapheresis. In our case, leukapheresis was initially considered an option for treatment. Still, due to the patient's poor condition and the time needed to implant a proper venous catheter for leukapheresis, we aimed to rapidly treat the patient with a debulking therapy that could promptly decrease the white blood count. TLS plays a pivotal role in the management of CLL as well, and several evaluations and strategies have been developed to overcome it, especially in the settings of new immunotherapies. Its management varies significantly depending on the therapy used, given the different risks associated with each treatment. Traditional chemotherapy agents pose a relatively low risk of TLS in CLL due to the disease's typically slower progression, and few cases are reported [22]; however, newer targeted therapies may increase TLS risk due to their potent action on malignant

cells. Venetoclax is associated with a high TLS risk because of its rapid and effective action in reducing tumor burden, especially in patients with a high leukemic cell count or bulky disease [23], although with the experience acquired with these new drugs the acute events of TLS are relatively rare; in a large real-life cohort of patient treated with venetoclax, only seven patients developed laboratory TLS, and none developed clinical TLS [24]. Preventive measures are therefore tailored to the therapy type: with venetoclax, a carefully controlled dose ramp-up, rigorous hydration, and prophylactic medications like allopurinol or rasburicase are often recommended. Continuous monitoring of blood chemistry, especially during the initial phases of treatment, is essential for early detection and management of electrolyte imbalances, ensuring safe and effective therapy for patients at risk of TLS.

To reduce tumor burden before starting target therapy, debulking therapy represents a well-established practice. Common approaches to debulking include the use of low-dose chemotherapy, such as bendamustine [25], or monoclonal antibodies, such as rituximab or obinutuzumab, which can effectively decrease lymphocyte counts and spleen size, improving the safety and efficacy of subsequent treatments and allowing for better control of the disease with reduced toxicity [26].

BTK inhibitors may represent an option for first-line therapy, given the high-risk molecular profile in our case; however, they can lead to initial transient leukocytosis [27], potentially increasing the risk of leukostasis. Although outdated, chemoimmunotherapy (with agents such as chlorambucil, fludarabine, or bendamustine) [28] could be used as a first-line approach for debulking. Nevertheless, the presence of a TP53 mutation is associated with resistance to chemoimmunotherapy. Other Bcl-2 inhibitors (e.g., navitoclax, BCL201, lisaftoclax, sonrotoclax) are still undergoing clinical trials and are not yet available in clinical practice [29–32]. Regarding anti-CD20 drugs, the only options available in Italy are obinutuzumab and rituximab, with the latter being prescribable only as a second-line treatment. Considering all these factors, the obinutuzumab–venetoclax regimen was considered the most effective and appropriate therapy to reduce the disease burden rapidly. Although the use of obinutuzumab–venetoclax in our setting was aimed to rapidly treat our high-risk patient, combining obinutuzumab–venetoclax with BTK inhibitors could be helpful in this setting. Recent studies have demonstrated that the combination of acalabrutinib, venetoclax, and obinutuzumab significantly improves outcomes in patients with high-risk CLL, reducing the risk of disease progression or death by 58% compared to standard chemoimmunotherapy, with a median follow-up of 41 months [33]. Additionally, the phase II VIS trial is evaluating the efficacy of venetoclax and obinutuzumab as a first-line treatment, followed by venetoclax alone or in combination with zanubrutinib for patients exhibiting minimal residual disease. These findings suggest that incorporating obinutuzumab and venetoclax into treatment regimens offers a promising approach for managing high-risk CLL [34–37]. On the other hand, the type of therapy must be appropriate to the patient's comorbidities, considering the immunosuppressed condition, with a high risk of infection or poor immune response common in hematological conditions [38–43].

To date, little data have been reported for patients with WBC higher than 7–800,000/mm³ at the start of treatment, and the choice between BCL2 and BTK inhibitors is largely debated. Our experience demonstrated that the venetoclax–obinutuzumab association represented a valid opportunity to promptly treat the hyperleukocytotic CLL patient, aiming for a tailored velocity of obinutuzumab infusion with proper support therapy.

4. Conclusions

Managing hyperleukocytosis in CLL requires a structured decision-making approach that balances disease control with the risk TLS. Therapy selection should consider tumor burden, renal function, and overall patient fitness. For patients at a high risk of TLS (e.g.,

those with bulky lymphadenopathy or impaired renal function), careful risk stratification and prophylactic measures such as hydration and uric acid-lowering agents (e.g., allopurinol or rasburicase) are essential. As demonstrated in this case report, with proper supportive therapy, personalized velocity infusion, and controlled management, fixed-duration venetoclax–obinutuzumab represented a life-saving treatment associated with favorable outcomes.

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