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# An 81-Year-Old Man with a 6-Year History of Chronic Lymphocytic Leukemia Presenting with Disease Flare Following Ibrutinib Discontinuation

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Data Collection B  
Statistical Analysis C  
Data Interpretation D  
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**Patient:** Male, 81-year-old  
**Final Diagnosis:** Chronic lymphocytic leukemia  
**Symptoms:** Fever  
**Medication:** —  
**Clinical Procedure:** —  
**Specialty:** Hematology

**Objective:** Unusual clinical course

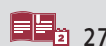
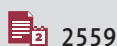
**Background:** Chronic lymphocytic leukemia (CLL) is a mature B-cell neoplasm and the most common leukemia in adults in Western countries. Novel agents, including BTK inhibitors and the BCL2 inhibitor venetoclax, have dramatically changed the treatment landscape. Moreover, a disease flare, characterized by sudden worsening of clinical symptoms, radiographic findings of rapidly worsening splenomegaly or lymphadenopathy, and laboratory changes (increased absolute lymphocyte count or lactate dehydrogenase), is a phenomenon described in up to 25% of patients with CLL after ibrutinib discontinuation. We describe a patient with CLL with disease flare after ibrutinib discontinuation due to disease progression and describe the subsequent management of venetoclax initial treatment in the course of the disease flare.

**Case Report:** We describe the case of an 81-year-old man with a 6-year history of CLL who was treated with multiple lines of therapy and developed worsening of disease-related signs and symptoms with fever, marked increase of lymphocyte count, acute worsening of renal function, and increase in lymph nodes and spleen size following cessation of targeted therapy with ibrutinib at the time of disease progression. There was subsequent overlapping of ibrutinib during the venetoclax dose escalation period to prevent disease flare recurrence.

**Conclusions:** Our report highlights the problem of disease flare after ibrutinib discontinuation in order to avoid associated patient morbidity, underscoring the importance of awareness of this phenomenon and focusing on the addition of venetoclax at time of progression in ibrutinib-treated patients, as a temporary overlap strategy, to prevent disease flare.

**Keywords:** Ibrutinib • Leukemia, Lymphocytic, Chronic, B-Cell • Symptom Flare Up • Venetoclax • Disease Progression

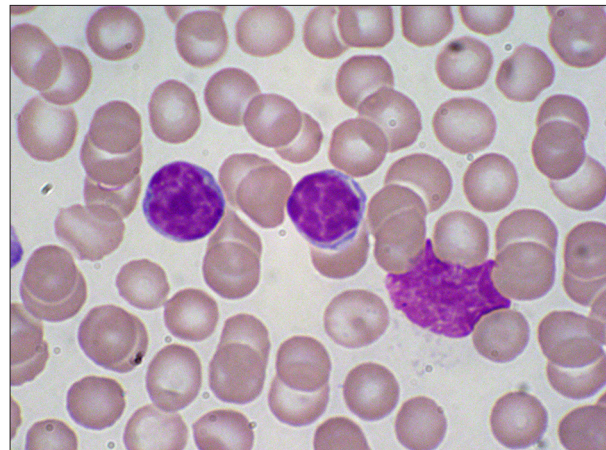
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## Background

Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma is a mature B-cell neoplasm characterized by a progressive accumulation of monoclonal B lymphocytes and is the most common leukemia in adults in Western countries, accounting for approximately 25% to 35% of all cases of leukemia in the United States [1]. In agreement with the 2018 International Workshop on CLL update of the National Cancer Institute guidelines, the diagnosis can be made when both the following criteria are met: (1) an absolute B lymphocyte count in the peripheral blood  $>5 \times 10^9/L$ , sustained for at least 3 months, with a preponderant population of morphologically mature-appearing small lymphocytes, and (2) a flow cytometry of the peripheral blood demonstrating immunoglobulin light chain restriction (kappa or lambda) and the coexpression of the surface antigen CD5 together with the B-cell antigens CD19, CD20, and CD23 [2]. The treatment of patients with CLL has undergone profound changes in the past decade [3,4]. Novel agents, including Bruton's tyrosine kinase (BTK) inhibitors (ibrutinib, acalabrutinib, zanubrutinib), the B-cell lymphoma 2 (BCL2) inhibitor venetoclax, and phosphatidylinositol 3-kinase inhibitors (idelalisib, duvelisib), have dramatically changed the chronic CLL treatment landscape. In particular, the introduction of BTK inhibitors has significantly improved the outcomes of these patients in the first-line setting [5,6] and in relapsed/refractory disease [7,8]. Despite such improvements, a very poor prognosis is reported in patients who experience disease progression on BTK inhibitors [9,10]. An attractive option in these patients is represented by the oral BCL2 inhibitor venetoclax. Venetoclax was initially approved on April 11, 2016, for the treatment of relapsed/refractory del(17p) CLL [11] and then in association with rituximab in relapsed CLL, based on the phase 3 MURANO trial, which showed an improvement in progression-free survival over chemoimmunotherapy-based therapy [12]. Subsequently, the first-line treatment with venetoclax plus obinutuzumab showed improved progression-free survival versus chemoimmunotherapy in older patients and in patients with coexisting medical conditions [13]. Venetoclax, as a single agent or associated with anti-CD20 monoclonal antibodies, is a feasible and effective treatment for CLL following progression on ibrutinib, with an overall response rate of 65% and estimated 12-month progression-free survival of 75% [14]. Moreover, data from clinical trials and real-world settings reveal, in up to 25% of cases, the rapid insurgence of disease symptoms occurring in those patients stopping ibrutinib due to disease progression [15] and in cases of temporary interruptions [16].

Therefore, this report is the case of an 81-year-old man with a 6-year history of CLL, presenting with disease flare, with worsening of disease-related signs and symptoms, including fever, marked increase of absolute lymphocyte count (ALC), acute

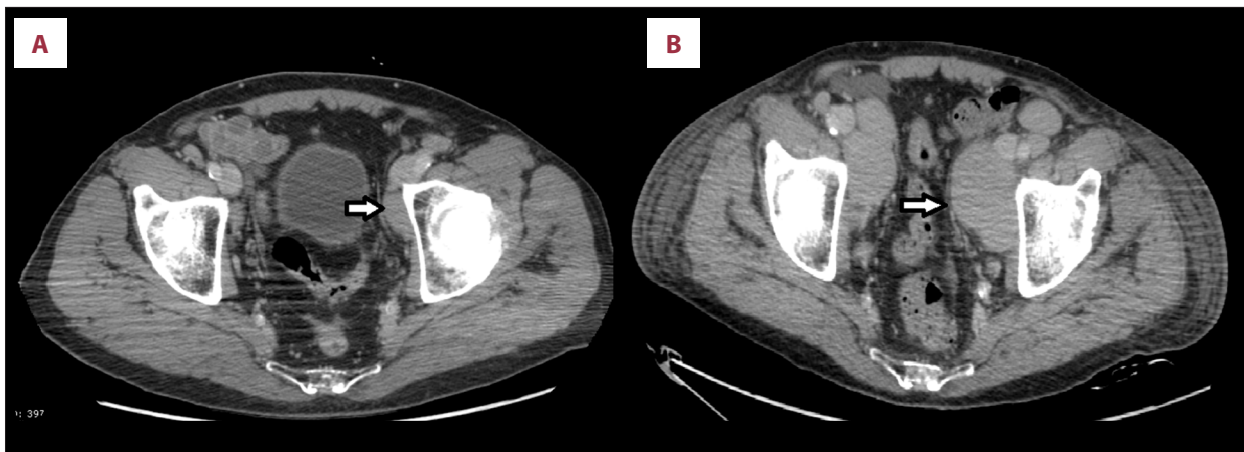


**Figure 1.** Hematoxylin & eosin-stained peripheral blood film showing the characteristically small, mature lymphocytes with a narrow border of cytoplasm and a dense nucleus lacking discernible nucleoli and having partially aggregated chromatin and Gumprecht nuclear shadows.

worsening of renal function, and enlargement of lymph nodes and spleen size. He presented following cessation of targeted therapy with ibrutinib, and the mitigation of symptoms, following the temporary reintroduction of ibrutinib, allowed an appropriate management of this condition during the initial phase of venetoclax treatment.

## Case Report

An 81-year-old male patient was incidentally diagnosed with CLL in April 2015 after a routine examination. Blood tests revealed isolated lymphocytosis with a white blood cell count of  $12.70 \times 10^9/L$  (reference range,  $4-10.90 \times 10^9/L$ ), ALC of  $7.24 \times 10^9/L$  (reference range,  $1-4.50 \times 10^9/L$ ), platelet count of  $225 \times 10^9/L$  (reference range,  $150-450 \times 10^9/L$ ), and hemoglobin count of 12.5 g/dL (reference range, 13.5-17.5 g/dL). Peripheral blood film examination revealed typical small, mature-appearing lymphocytes with a darkly stained nucleus, partially aggregated chromatin, indiscernible nucleoli, a narrow rim of slightly basophilic cytoplasm, and Gumprecht nuclear shadows (Figure 1). Flow cytometry was consistent with a classic CLL immunophenotype, identifying a CD5+, CD19+, CD23+, CD20low, and slg-lambda low B-cell clone. Immunoglobulin variable heavy-chain sequence analysis showed an unmutated status (rate of homology 100%). Interphase fluorescence in situ hybridization revealed the absence of 13q-, +12, 11q, and 17p- cytogenetic abnormalities. Computed tomography (CT) showed only enlarged axillary lymph nodes (max  $24 \times 10$  mm), and stage Binet A and stage Rai I were assessed. In May 2017, a preoperative examination for carotid artery stenting revealed severe thrombocytopenia ( $6 \times 10^9/L$ ) associated with an elevated



**Figure 2.** Computed tomography (CT) images of the abdomen. (A) Axial image showing abdominal lymphadenopathy (white arrow) after 6 months of ibrutinib treatment (in May 2019). (B) Axial CT image showing marked lymphadenopathy enlargement after ibrutinib suspension (white arrow).

lymphocyte count (ALC  $80.38 \times 10^9/L$ ) and low hemoglobin count (10.0 g/dL), indicating stage Binet C and stage Rai IV. A bone marrow examination was compatible with immune thrombocytopenia secondary to CLL; therefore, prednisone 1 mg/kg and immune globulin 0.4 g/kg of body weight intravenously for up to 5 days was started, obtaining a complete platelet count normalization. Due to relapse of immune thrombocytopenia in July 2017, he started a first-line CLL-specific disease treatment with chlorambucil plus rituximab (chlorambucil 8 mg/m<sup>2</sup>/day for 7 days every 28 days, rituximab 375 mg/m<sup>2</sup> on day 1 from the third cycle, and then 500 mg/m<sup>2</sup> thereafter from cycles 4 to 8, every 28 days for 8 cycles), as previously described [17], with the achievement of a partial response [2]. The patient's disease progressed early after the end of treatment. A few months later, blood examinations documented increased lymphocytosis (ALC  $41.36 \times 10^9/L$ ), with normal hemoglobin and platelets counts, while a CT scan revealed multiple superior and sub-diaphragmatic lymphadenopathies (max 5.5×4.3 cm) and splenomegaly (about 16 cm in length). Interphase fluorescence in situ hybridization revealed the appearance of 17p deletion. In view of the disease progression, 10 months after the end of treatment, he started second-line therapy with ibrutinib 420 mg per day, obtaining a rapid good response with partial regression of lymphadenopathies. Also, after an initial increase of lymphocyte count, as expected, he obtained a progressive reduction in lymphocyte count. After 6 months, blood tests revealed an ALC of  $20.89 \times 10^9/L$ , hemoglobin count of 11.0 g/dL, and platelet count of  $159 \times 10^9/L$ , while a radiologic scan documented a significant reduction of all previously reported lymphadenopathy and normalization in spleen size, consistent with a good partial response [2]. Ibrutinib therapy was taken continuously without substantial adverse events. On month+12 of treatment, the patient temporarily held ibrutinib in view of an elective inguinal hernia surgery. The last bio-humoral evaluation prior to ibrutinib

suspension showed an ALC of  $14.91 \times 10^9/L$ , hemoglobin count of 11.0 g/dL, with normal values in platelet count, lactate dehydrogenase (LDH), and renal function. Clinically small, sub-centimetric lymph nodes in axillary and inguinal sites were noted. Seven days after ibrutinib suspension, the patient developed fever up to 38.5 °C, associated with deep asthenia. For this reason, the surgery program was delayed. Concurrently, with the febrile episode, laboratory testing revealed a marked increase of ALC ( $61.10 \times 10^9/L$ ) and LDH levels (1300 U/L; reference range, 230-460 U/L) and a decrease in platelet count ( $129 \times 10^9/L$ ). An objective increase of inguinal lymph nodes size was also observed. Neither clear clinical signs nor organ specific symptoms of infection were identified. Ibrutinib was then reintroduced after 13 days, and a rapid good response was obtained again. After 18 months of ibrutinib therapy, examinations started to document a slight progressive lymphocytosis (ALC  $40.90 \times 10^9/L$ ), associated with a moderate decrease in hemoglobin count (10.3 g/dL). Clinically, a slight enlargement of lymph nodes of all the surface stations was documented (diameter max 3 cm in right axilla), ibrutinib was discontinued after a total of 19 months of treatment, and radiological restaging examinations were planned. After about 3 days, the patient was admitted to the hospital for an acute febrile episode, with a body temperature up to 39.0°C. Laboratory tests documented a marked increase of lymphocyte count (ALC  $128 \times 10^9/L$ ), drop in hemoglobin (8.9 g/dL) and platelet count ( $115 \times 10^9/L$ ), worsening of renal function (serum creatinine 1.61 mg/dL; reference range, 0.50-1.40 mg/dL), and elevated C-reactive protein (12 mg/dL; reference range, 0-0.7 mg/dL) and LDH levels (1515 U/L). A whole-body CT scan documented considerable lymph node increase of almost all superficial and deep stations (max 6.2×4.4 cm in abdomen) and increase of spleen size (15 cm bipolar diameter length) (Figure 2). Empirical antibiotic therapy with piperacillin/tazobactam was administered, even though no pathogens were identified from either blood

or urine cultures. After excluding infectious etiologies, in the suspicion of a disease rebound as related to the abrupt ibrutinib discontinuation, full-dose ibrutinib (420 mg/day) was resumed after 12 days. Even though the clinical regression of superficial nodes was just partial, the patient experienced a significant improvement in general condition, without fever recurrence. Despite this, the lymphocyte count continued to increase, although less rapidly ( $257 \times 10^9/L$  after 6 days from ibrutinib reintroduction vs  $227 \times 10^9/L$  prior to the start of ibrutinib). One week later, in view of the ongoing disease progression, presence of del(17p) deletion, and the proven efficacy of venetoclax in ibrutinib-treated patients [11,14], venetoclax as a subsequent therapy was added. The dosage was started at 20 mg per day and then administered according to a 5-week schedule of a gradual dosage increase (ramp-up) from 20 mg per day to 400 mg per day, holding the ibrutinib full dosage. After 5 weeks, once the target dose of 400 mg per day was reached, ibrutinib was permanently discontinued, without any additional disease flares, and rituximab  $375 \text{ mg/m}^2$  of body surface for the first dose and  $500 \text{ mg/m}^2$  thereafter for cycles 2 to 6 was administered, according to the MURANO trial [12]. After 6 months of treatment, examinations showed a good partial response. The CT scan showed a substantial complete regression of all previously reported lymphadenopathies (except for  $18 \times 10 \text{ mm}$  in the left inguinal region) and normalization of spleen size (10 cm in length), while laboratory examinations showed an ALC of  $0.4 \times 10^9/L$ , with normal values in platelet count and LDH and normal renal function. At the latest available follow-up, 13 months after the start of third-line treatment, the patient was still in a good partial response and was continuing venetoclax treatment.

## Discussion

Our report highlights the issue of disease flare after ibrutinib discontinuation and the appropriate management of this acute, symptomatic condition, in particular when a switch to a venetoclax-based treatment is indicated, including an initial 5-week dose-ramping period.

The outcomes of patients with chronic lymphocytic leukemia have dramatically improved with the introduction of novel agents like BTK and BCL2 inhibitors. Ibrutinib is a very effective therapy, demonstrating durable response in the relapsed/refractory setting [7,8], and subsequently becoming the standard-of-care treatment in the frontline setting in high-risk patients [5]. However, the various adverse effects, both hematological and non-hematological, including bleeding, are frequently responsible for dose modifications or treatment interruptions [18,19]. Data from long-term follow-up of pivotal studies [9,10,20] and real-world evidence [21] suggest that intolerance rather than progression is the most common reason

for ibrutinib discontinuation. After 6 years of follow-up for patients treated in the RESONATE trial, 16% had discontinued ibrutinib because of an adverse event [8]. A retrospective real-life study reports that 41% of 621 primarily relapsed patients discontinued the drug, and almost half discontinued because of toxicity [21]. Consequently, the discontinuation of ibrutinib is an event that clinicians frequently encounter in clinical practice. Rapid CLL signs and symptoms of progression following ibrutinib discontinuation have been recognized. Hampel et al defined a rapid progression of disease after stopping ibrutinib as the presence of at least 2 among the following 3 characteristics: (a) clinical symptoms (consisting of any of the following: fever, worsening fatigue, lymph node enlargement-related symptoms, or malaise); (b) examination and/or radiographic findings of rapidly worsening splenomegaly or lymphadenopathy; and (c) laboratory changes (increasing ALC or increasing LDH) obtained within 4 weeks after ibrutinib discontinuation [15]. In particular, they reported a cohort of 202 patients who received ibrutinib outside of the context of a clinical trial at the Mayo Clinic over a 4-year period in which 52 patients discontinued ibrutinib, 56% for toxicity and 32% for disease progression. Rapid progression of disease within 4 weeks after discontinuation was observed in 25% of patients, mostly in those stopping ibrutinib for disease progression, rather than toxicity [15]. The same authors highlight how similar flares in disease signs or symptoms can occur in up to 25% of patients during ibrutinib temporary discontinuation [16]. This phenomenon has also been observed with the temporary suspension of ibrutinib therapy in patients with Waldenstrom macroglobulinemia, and is substantially managed by restarting ibrutinib treatment [22,23]. In our case, the patient experienced a sudden worsening of disease-related signs and symptoms and changes in radiologic and laboratory examinations quickly after ibrutinib discontinuation due to rapid progressive disease, according to the definition provided by Hampel [15]. Also, the febrile episode experienced by our patient in conjunction with the transient ibrutinib suspension should be considered a disease flare reaction due to ibrutinib discontinuation, which, in this case, was managed with the simple reintroduction of ibrutinib.

The best approach in managing the treatment of patients experiencing rapid progression of disease after ibrutinib discontinuation remains undefined. Reintroduction of ibrutinib is a temporary option that has demonstrated efficacy in patients with CLL or Waldenstrom macroglobulinemia who develop withdrawal-related symptoms [16,23], although in the setting of a temporary hold rather than at time of progression. Moreover, this approach would remain problematic in patients with a strong contraindication (ie, active bleeding). Another proactive approach, which may represent a very feasible strategy, was proposed by Maddocks et al and consists of the continuation of ibrutinib at disease progression to avert sharp worsening of disease manifestations until the next therapy plan is in place

or in combination with additional treatment in the setting of rapid progression or transformed disease [10]. Because venetoclax is an effective treatment in CLL following progression on ibrutinib [14], the overlapping of ibrutinib during the dose escalation period, until receiving a fully therapeutic dosage, as in our case, may be proposed. Hampel et al, from the Mayo Clinic, identified 18 patients in which venetoclax was added as subsequent treatment in patients progressing on ibrutinib monotherapy, holding ibrutinib to prevent disease flare [24]. All patients started venetoclax according to the weekly ramp-up per the package insert. Ibrutinib was then discontinued in 10 patients (median overlap of 2 months, range 0-14 months), mainly as planned once the venetoclax target dose was reached. Of note, 4 patients tapered ibrutinib over 2 to 8 weeks, 2 of whom received corticosteroids (prednisone 60 mg daily for 1 week, followed by a taper). Among the patients who finally discontinued ibrutinib, only 1 experienced a flare [24]. The feasibility of this combination has been confirmed by data from phase II trials, in which safety and efficacy of the combination of ibrutinib and venetoclax co-administration in the first-line and relapsed/refractory setting were explored. No substantial additional adverse events were reported concerning combination therapy in published data on either drug alone [25,26]. Lastly, another feasible approach, especially in patients with either rapidly progressive disease or high tumor burden, is to perform an accelerated ramp-up dosing schedule to 400 mg per

day by week 3, as proposed by Jones et al in a phase II trial of venetoclax for patients with disease progression after ibrutinib [14]. This strategy has proven to be safe and effective also in real-world settings [27].

## Conclusions

Awareness among clinicians of the phenomenon in CLL of disease flare after ibrutinib discontinuation and during a transitory period of treatment discontinuation is critical and would avoid associated morbidity. The issue of mitigating disease progression and CLL flare could be crucial in the case of occurrence of ibrutinib resistance concomitant with the need to switch to subsequent line therapy. When venetoclax therapy is considered, holding ibrutinib until the full target dose of venetoclax is reached is an adequate and safe approach. In the absence of consensus recommendations, the best management of disease flare after ibrutinib discontinuation remains to be defined.

## Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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