

Switching from ibrutinib to venetoclax in chronic lymphocytic leukemia: a management protocol based on clinical cases avoiding rapid disease progression

Cambio de ibrutinib a venetoclax en la leucemia linfocítica crónica para evitar la progresión rápida de la enfermedad: un protocolo de transición basado en casos clínicos

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Abstract

Background: Some patients with chronic lymphocytic leukemia (CLL) terminate ibrutinib treatment due to toxicity or disease progression (DP). Initiation of other treatments may be associated with a rapid DP due to ibrutinib discontinuation. **Objective:** This study aims to successfully transition patients from ibrutinib- to venetoclax-based regimens through a clinical protocol that minimizes the risk for adverse outcomes. **Methods:** Four patients with CLL who progressed and required a transition were managed using our switch protocol which consists of a 5-week period during which the dose of ibrutinib is reduced and the dose of venetoclax increased on a weekly basis. Venetoclax is initiated at 20 mg daily with a weekly escalation to a maximum of 400 mg daily and ibrutinib is decreased over a 3-week period with a definitive suspension of treatment at week 4. Patients are monitored for the risk or onset of de lisis tumoral. **Results:** All patients were successfully transitioned without rapid DP or adverse events commonly associated with ibrutinib discontinuation. **Conclusions:** A 5-week transition protocol can be successfully applied for the transition of patients with CLL requiring a switch from ibrutinib to venetoclax due to toxicity or DP.

Keywords: Ibrutinib. Venetoclax. Chronic lymphocytic leukemia. Treatment switching. Disease progression.

Resumen

Introducción: Algunos pacientes con leucemia linfocítica crónica (LLC) terminan el tratamiento con ibrutinib por toxicidad o progresión de la enfermedad (PE). El inicio de otros tratamientos puede asociarse a una rápida PE debido a la interrupción de ibrutinib. **Objetivo:** Lograr la transición de los pacientes en tratamiento con ibrutinib a regímenes basados en venetoclax mediante un protocolo que minimice el riesgo de eventos adversos. **Métodos:** 4 pacientes con LLC que progresaron y requirieron una transición fueron manejados con nuestro protocolo, que consiste en un período de 5 semanas de reducción de la dosis de ibrutinib y aumento de la de venetoclax. Venetoclax se inicia a 20 mg diarios con un aumento semanal hasta un máximo de 400 mg diarios e ibrutinib se reduce durante 3 semanas hasta la suspensión definitiva del tratamiento en la semana 4. Los pacientes son monitorizados para identificar el riesgo o la aparición de síndrome de lisis tumoral (TLS).

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Resultados: Todos los pacientes alcanzaron una transición exitosa, sin PE rápida ni eventos adversos. **Conclusiones:** El protocolo de transición de 5 semanas puede aplicarse exitosamente para los pacientes con LLC que requieren un cambio de ibrutinib a venetoclax.

Palabras clave: Ibrutinib. Venetoclax. Leucemia linfocítica crónica. Cambio de tratamiento. Progresión de la enfermedad.

Introduction

Chronic lymphocytic leukemia (CLL) is characterized by the progressive accumulation of mature lymphocytes in peripheral blood, bone marrow, and lymphatic tissues¹, with an annual incidence of 4.2/100,000 population². Its clinical course is heterogeneous, ranging from indolent, relatively stable disease, to more aggressive forms, the latter being associated with shorter life expectancy³.

Patients initiate treatment after progression to symptomatic active disease which traditionally included combination regimens of chemotherapy with an anti-CD20 monoclonal antibody such as fludarabine + cyclophosphamide + rituximab (FCR) or chlorambucil + obinutuzumab². More recently, B-cell receptor antagonists such as ibrutinib and idelalisib and BCL-2 inhibitors such as venetoclax have been added to the therapeutic arsenal, transforming the treatment landscape for patients with CLL^{4,5}.

Although ibrutinib is administered indefinitely, complete remission is rare. Despite the improved progression-free survival and overall survival associated with ibrutinib compared with traditional chemoimmunotherapeutic regimens in clinical trials setting, long-term follow-up and real-world studies have shown that a high proportion of patients withdraw from treatment (up to 30%), mainly due to toxicity or disease progression (DP)⁴. In addition, outcomes for patients with DP during ibrutinib therapy are poor⁶ and the persistence of the disease raises the possibility of the development of drug resistance⁷. Consequently, alternative treatment strategies are needed for patients requiring a switch due to toxicities or DP during ibrutinib therapy⁶. The main challenge of ibrutinib discontinuation is the possibility of rapid DP including a sudden worsening of constitutional symptoms⁴.

Data are currently scarce to determine the most appropriate strategy for patients requiring a switch from ibrutinib to venetoclax. However, Phase 2 trials have demonstrated the feasibility of administering these agents concomitantly, showing good efficacy and even eradication of residual disease^{8,9}. Given these observations, a protocol was developed for the transition of patients from ibrutinib to venetoclax through a period of concomitant treatment. Here, we present the protocol and our clinical experience of successfully transitioning four CLL patients.

Methods

After observing an abrupt DP in Patient 1 following ibrutinib discontinuation and initiation of venetoclax as in the current clinical practice, we designed a transition protocol that could be implemented in CLL to avoid such adverse events when switching from ibrutinib through a period of concomitant treatment (Fig. 1). Patients are first evaluated for their risk of developing TLS. High risk for TLS is defined as lymph node > 10 cm or lymph node > 5 cm with > 25,000 lymphocytes/mm³ or creatinine clearance < 80 mL/min. Patients at high risk for TLS are hospitalized and undergo a 48 h period of hydration with allopurinol (300 mg/24 h) before the initiation of venetoclax. Switching from ibrutinib to venetoclax is achieved over a 5-week period during which the dose of ibrutinib is reduced and the dose of venetoclax is increased on a weekly basis. Patients are monitored for the onset of TLS with a blood draw depending on the risk of TLS: at low-medium-risk patients on days 1 and 8 (both at 6-8 h post-dosing), on days 2 and 7 and weekly to week 5; at high-risk patients on days 1 and 8 (both at 4, 8, 12, and 24 h post-dosing), on days 2 and 7, and for subsequent dose increments pre-dosing and 6-8 h and 24 h post-dosing¹⁰.

A starting dose of venetoclax of 20 mg daily was selected with a weekly escalation to a maximum of 400 mg daily as described in previous clinical trials evaluating the concomitant administration of ibrutinib and venetoclax¹¹. The dose of ibrutinib was decreased over a 3-week period with a definitive suspension of treatment during the 4th week.

The effectiveness of the protocol has been assessed in four adult CLL patients requiring a switch from ibrutinib.

Results

Patient 1

Patient 1 was a 60-year-old female diagnosed with CLL in December 2012 (Binet Stage A). She had a sibling diagnosed with CLL who underwent an unrelated allogeneic transplant.

In September 2016, her CLL Binet Stage A had progressed to Stage C, with a cytogenetic study that revealed

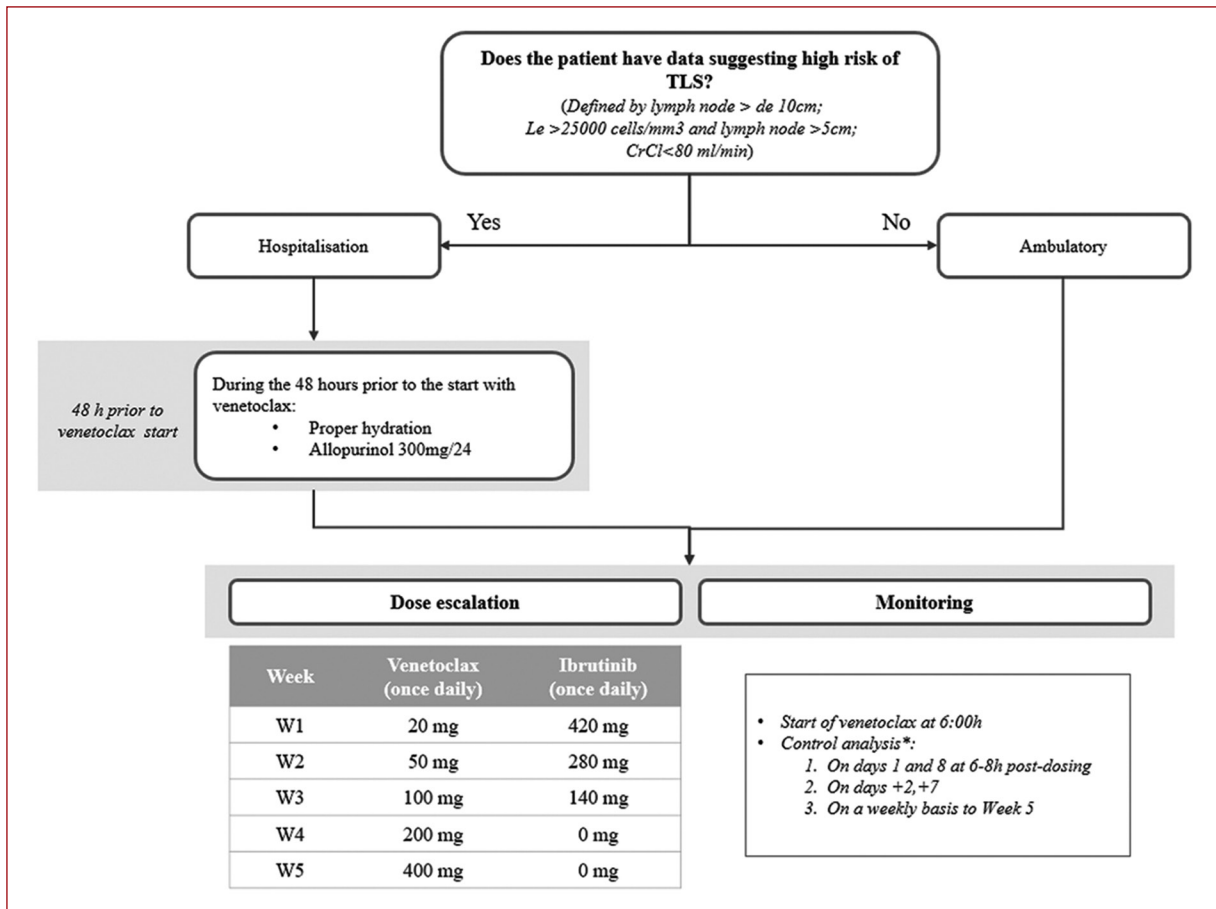


Figure 1. Protocol for the transition of patients with CLL from ibrutinib to venetoclax. *In case of high risk of TLS, control analysis should be performed on days 1 and 8 (both at 4, 8, 12, and 24 h post-dosing), on days 2 and 7, and for subsequent dose increments pre-dosing and 6-8 h and 24 h post-dosing.

that the patient had del(17p) and del(13q). Ibrutinib was started and well-tolerated, night sweats were reduced and she achieved a partial response. By October 2017, her lymphocyte count had achieved normal range ($4.3 \times 10^9/L$). DP was detected in December 2018 with a re-emergence of sweating and a lymphocyte doubling time < 6 months, requiring a switch to venetoclax.

Transition was initially performed as per clinical practice, before the protocol design. At the time of switching to venetoclax (January 2019), her lymphocyte count was $> 25 \times 10^9/mL$. The patient was assessed as intermediate risk for the emergence of TLS and was admitted to hospital for a 48 h period of hydration of allopurinol 300 mg/24 h before ibrutinib withdrawal and initiation of venetoclax 20 mg, the day after ibrutinib suspension. As no indication of TLS was detected on days 1 or 2 of venetoclax 20 mg, the patient was discharged.

On day 5 of venetoclax 20 mg, she attended the emergency room with general malaise, nausea, vomiting, and

supraclavicular adenopathies suggesting abrupt DP. She was readmitted and ibrutinib was reintroduced concomitantly with venetoclax, as defined in our transition protocol. Transition was completed in February 2019. Hematological assessments during the 5-week transition protocol are described in [table 1](#).

The patient was successfully transitioned from ibrutinib to venetoclax and remains alive following an allogeneic transplant from an unrelated donor.

Patient 2

Patient 2 was an 81-year-old woman initially diagnosed with CLL in September 2012 (Binet Stage B). She had received prior treatment for her CLL, including R-CVP (rituximab with cyclophosphamide, vincristine, and prednisone) (2013), R-bendamustine-rituximab (2015), and rituximab-4 (2016).

Table 1. Clinical cases of patients' series 1, 2, 3, and 4

Clinical case	Disease progression immediately before the onset of venetoclax		Protocol application									
			Hematological analyses				Hematological analyses				Weekly monitoring	
	Date	Stage and symptoms	Hematological analyses		Day + 1	Day + 2	Day + 7	Day + 8	Week 2 Venetoclax 50 mg + ibrutinib 280 mg	Week 3 Venetoclax 100 mg + ibrutinib 140 mg	Week 4 Venetoclax 200 mg + ibrutinib suspension	Week 5 Venetoclax 400 mg ^b
Patient 1*	September 2016	Binet stage C Progression CLL-IPI 10 (non-mut, p53 85%, TP53 mut ex 8)	Hb g/dL	13.7	13.0	12.3	12.7	13.1	12.8	14.2	13.5	
			Leu/L	5.2 × 10 ⁹	57.7 × 10 ⁹	76 × 10 ⁹	26.1 × 10 ⁹	14.1 × 10 ⁹	3.8 × 10 ⁹	5.8 × 10 ⁹	6.5 × 10 ⁹	
			Lym/L	50.8 × 10 ⁹	52.5 × 10 ⁹	71.9 × 10 ⁹	23.5 × 10 ⁹	1.9 × 10 ⁹	1.3 × 10 ⁹	2.1 × 10 ⁹	1.8 × 10 ⁹	
			Neu/L	3.5 × 10 ⁹	4.6 × 10 ⁹	2.6 × 10 ⁹	1.8 × 10 ⁹	1.9 × 10 ⁹	1.3 × 10 ⁹	2.8 × 10 ⁹	3.5 × 10 ⁹	
			Plt/L	85 × 10 ⁹	103 × 10 ⁹	85 × 10 ⁹	82 × 10 ⁹	97 × 10 ⁹	11 × 10 ⁹	10.3 × 10 ⁹	10.2 × 10 ⁹	
			LDH U/L	336	1214	1093	348	315	220	216	390	
Patient 2	June 2019	Binet Stage B. asymptomatic (no-mutated TP53; no-mutated IGHV; FISH: mutation of ATM)	Hb g/dL	13.6	13.3	12.9	13.2	13.0	12.9	12.8	13.3	
			Leu/L	28.8 × 10 ⁹	29.8 × 10 ⁹	21.8 × 10 ⁹	20.2 × 10 ⁹	14.6 × 10 ⁹	9 × 10 ⁹	5.3 × 10 ⁹	5.5 × 10 ⁹	
			Lym/L	25 × 10 ⁹	26.4 × 10 ⁹	18.3 × 10 ⁹	16.4 × 10 ⁹	11.4 × 10 ⁹	6.4 × 10 ⁹	2.7 × 10 ⁹	2.7 × 10 ⁹	
			Neu/L	3.3 × 10 ⁹	2.9 × 10 ⁹	2.9 × 10 ⁹	2.9 × 10 ⁹	2.6 × 10 ⁹	2.1 × 10 ⁹	1.8 × 10 ⁹	2.2 × 10 ⁹	
			Plt/L	108 × 10 ⁹	111 × 10 ⁹	94 × 10 ⁹	120 × 10 ⁹	108 × 10 ⁹	120 × 10 ⁹	119 × 10 ⁹	132 × 10 ⁹	
			LDH U/L	208	331	NC	328	NC	285	163	184	
Patient 3**	August 2019	Stage: Rai II/ Binet B-no mutated IGHV; FISH: mutation of ATM; mutated TP53 (VAF 17%)	Hb g/dL	14.4	14.0	12.9	14.5	14.5	13.7	13.8	13.8	
			Leu/L	11.2 × 10 ⁹	8.2 × 10 ⁹	6.2 × 10 ⁹	5 × 10 ⁹	50 × 10 ⁹	3.8 × 10 ⁹	3.3 × 10 ⁹	2.6 × 10 ⁹	
			Lym/L	7.81 × 10 ⁹	5.99 × 10 ⁹	3.82 × 10 ⁹	2.79 × 10 ⁹	2.9 × 10 ⁹	1.96 × 10 ⁹	1.63 × 10 ⁹	1.16 × 10 ⁹	
			Neu/L	2.73 × 10 ⁹	1.84 × 10 ⁹	1.93 × 10 ⁹	1.61 × 10 ⁹	1.7 × 10 ⁹	1.27 × 10 ⁹	1.28 × 10 ⁹	1.02 × 10 ⁹	
			Plt/L	146 × 10 ⁹	218 × 10 ⁹	192 × 10 ⁹	222 × 10 ⁹	230 × 10 ⁹	214 × 10 ⁹	212 × 10 ⁹	203 × 10 ⁹	
			LDH U/L	260 (Vn <250)	NC	NC	NC	NC	NC	139	127	
Patient 4	September 2020	Stage Rai II/ Binet A, with an IPI score 4	Hb g/dL	12.8	10.8	10.3	10.4	11.3	11.2	11.8	9.5	
			Leu/L	258.2 × 10 ⁹	191.9 × 10 ⁹	184.8 × 10 ⁹	128.2 × 10 ⁹	87.9 × 10 ⁹	55.3 × 10 ⁹	40.1 × 10 ⁹	19.8 × 10 ⁹	

(Continues)

Table 1. Clinical cases of patients' series 1, 2, 3, and 4 (*continued*)

Clinical case	Disease progression immediately before the onset of venetoclax			Protocol application								
	Date	Stage and symptoms	Hematological analyses	Hematological analyses								
				Day + 1	Day + 2	Day + 7	Day + 8	Week 1 Venetoclax 20 mg + Ibrutinib 420 mg	Week 2 Venetoclax 50 mg + Ibrutinib 280 mg	Week 3 Venetoclax 100 mg + Ibrutinib 140 mg	Week 4 Venetoclax 200 mg + Ibrutinib suspension	Week 5 Venetoclax 400 mg ^b
	(no-mutated TP53; FISH: mutation of ATM; chromosome 12 trisomy in 12% of the cells)	Lym/L	246.8 × 10 ⁹	184.8 × 10 ⁹	176.7 × 10 ⁹	123.7 × 10 ⁹	84.2 × 10 ⁹	52.2 × 10 ⁹	37.3 × 10 ⁹	9.2 × 10 ⁹		
			Neu/L	5.8 × 10 ⁹	3.7 × 10 ⁹	4.3 × 10 ⁹	2.7 × 10 ⁹	2.7 × 10 ⁹	2.3 × 10 ⁹	2.1 × 10 ⁹	1.5 × 10 ⁹	
			Plt/L	111 × 10 ⁹	94 × 10 ⁹	70 × 10 ⁹	65 × 10 ⁹	68 × 10 ⁹	72 × 10 ⁹	84 × 10 ⁹	59 × 10 ⁹	
			LDH U/L	961	811	696	643	590	916	1114	1471	

Hb: hemoglobin; IU: international unit; LDH: lactate dehydrogenase; Leu: leukocytes; Lym: lymphocytes; Plt: platelets. *Patient 1: symptoms of DP required a switch to venetoclax, which was initially performed as per clinical practice, before the protocol design and required reintroduction of ibrutinib due to abrupt DP. After ibrutinib reintroduction, transition protocol was initiated. **Patient 3: ibrutinib dose reduction period was extended as the patient had a high tumor burden, and risk for TLS and DP remained high. Ibrutinib 280 mg was maintained during week 4, and ibrutinib suspension was achieved during week 5.

This patient was assessed as high risk for the emergence of TLS and was admitted to hospital for a 48 h period of hydration of allopurinol before initiation of the transition and she remained in hospital during 3 days. The transition protocol was initiated in June 2019 and the patient remains on venetoclax with well-controlled CLL (Table 1).

Patient 3

Patient 3 was a 49-year-old man diagnosed with CLL in 2004 (Stage Rai 0, Binet A). He had received multiple prior treatment for CLL including fludarabine (2007), rituximab (2008), rituximab + cyclophosphamide (2010), rituximab + fludarabine (2012), FCR (2012), rituximab + chlorambucil (2015), and bendamustine (2016). He was initiated on ibrutinib in 2016 with DP prompting a need for a transition to venetoclax in August 2019. At this time, clinical stage was Rai II, Binet B. He presented with lymph node growth at all areas up to 4 × 6 cm, unmutated IGHV, 11q deletion, and mutated TP53 (VAF 17%).

The patient was assessed as high risk for the emergence of TLS and was admitted to hospital for a 48 h period of hydration of allopurinol before initiation of the transition protocol in September 2019 remaining in hospital during 3 days. A 4-week reduction of ibrutinib was employed for this patient with three capsules at week 1, two capsules at weeks 2 and 3, and one capsule at week 4, and definitive suspension of ibrutinib at week 5. The decision to extend the dose reduction period for ibrutinib was taken as the patient had a high tumor burden and so remained at increased risk for TLS and for DP on ibrutinib withdrawal. The transition protocol was initiated in September 2019 and with current complete clinical remission on venetoclax (Table 1).

Patient 4

Patient 4 was a 77-year-old man initially diagnosed with CLL (Stage Rai 0/Binet A). He had received FCR (2010) and was initiated on ibrutinib on 2016. DP requiring a switch to venetoclax was detected on September 2020, classified as Stage Rai II/Binet A, with unmutated IGHV and TP53, 10% of cells with chromosome 12 trisomy, and loss of a copy of the ATM gene.

Patient 4 was assessed as high risk for the emergence of TLS and was admitted to hospital for a 48 h period of hydration of allopurinol before initiation of the transition. In this case, the transition protocol was initiated in September 2020 to switch into the Murano

regimen (venetoclax + rituximab). One week after reaching full dose of venetoclax, rituximab was added to the treatment regimen. The patient remains alive on venetoclax + rituximab combination with well-controlled CLL (Table 1).

Discussion

A protocol was developed for the safe and effective transition of patients with CLL requiring a switch from ibrutinib to venetoclax regimens due to toxicity or DP. Application of our transition protocol in four patients requiring a switch from ibrutinib to venetoclax has confirmed the feasibility of this approach. All four patients were successfully transitioned without rapid progression of CLL or adverse outcomes commonly associated with ibrutinib discontinuation and without TLS emergence. During the short period of concomitant therapy, the regimen was well tolerated by all four patients as was venetoclax once monotherapy had been achieved.

The absence of marked hematological and extrahe-matological toxicity during the period of drug overlap is consistent with the ibrutinib/venetoclax combination clinical trials where no translation into an increased incidence of toxicity was detected^{12,13}. In fact, prior ibrutinib leads to a decrease in the risk of TLS in patients at high risk at baseline¹³.

Experience with the four patients presented here highlight the flexibility of the approach, which can be adapted to the individual clinical situation with the possibility of extending the ibrutinib dose reduction period for patients with a high tumor burden, as for Patient 3, minimizing the risk for an aggressive rebound or the emergence of TLS, and also the possibility of implementing the transition protocol to other treatment regimens based on venetoclax as was successfully achieved in Patient 4, for whom rituximab was added to venetoclax after protocol completion.

The present protocol proposes the hospitalization of patients at high risk of TLS for hydration and administration of allopurinol during the 48 h before the start with venetoclax as described in the venetoclax product information sheet¹⁰. However, for patients at medium risk, the prophylaxis could be performed on an outpatient basis to reduce health-care resource use, costs, and improve the patient's quality of life, which again reflects the flexibility our protocol¹⁰. In this case, hospitalization was proposed for all patients to increase this novel protocol's safety as it had not been previously defined.

Within the scope of these clinical cases, TP53 mutation status was described in all patients, with Patients

2 and 4 having unmutated TP53 at the time of DP. Therefore, the cases described cannot establish a clear causal relationship between TP53 mutation and the rapid DP. Despite it being described that TP53 loss predisposes patients to relapse, some studies have identified that clone size of TP53 loss may diminish during DP while mutant BTK clone expands¹⁴. In our clinical cases, no determination of BTK or PLCG2 resistance mutations through a molecular analysis of CLL cells was performed. However, a recent case report of patients transitioned from ibrutinib to venetoclax over a period of a 2-week treatment overlap identified two different transition patterns after ibrutinib interruption. A high burden of BTK and PLCG2 mutations was found only in patients with a favorable transition pattern while the majority of CLL cells of the patient with rapid DP after the transition did not harbor BTK or PLCG2 mutations and likely progressed through resistance mechanisms not involving the BTK signaling pathway. Hence, they suggest that removing BTK inhibition might be particularly harmful if CLL cells are progressing through mechanisms external to the BTK axis¹⁵. Without this being the scope of our work, this suggests that further investigating the role of these resistance mechanisms could help tailor the transition strategy.

Given the current lack of information to guide the management of patients who interrupt treatment with ibrutinib, the successful outcomes of patients who underwent this transition protocol showed that this new tool may help improve their management, significantly reducing the risk of aggressive relapse of the disease. For the purposes of the current case series, we have focused on switching to venetoclax as this agent is considered an option for patients whose disease progresses during ibrutinib therapy, especially in patients with del(17p) or TP53 mutation^{1,2,16}. The protocol may be applicable for patients requiring a switch from other B-cell receptor antagonists such as idelalisib or acal-abrutinib to venetoclax.

Conclusions

We developed and demonstrated the clinical utility of a management protocol for the transition of CLL patients requiring a switch from ibrutinib to venetoclax due to toxicity or DP.

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Conflict of interests

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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