Mediterranean Journal of Hematology and Infectious Diseases

Scientific Letters

A Case of Multiple Myeloma in a Patient in Treatment for Chronic Lymphocytic Leukemia

Keywords: Multiple myeloma; Chronic lymphocytic leukemia; Concomitant treatment; BELLINI trial.

Published: May 01, 2025 **Received: February 18, 2025** **Accepted: April 12, 2025**

Citation: Biglietto M., Coppetelli U., Fiori L., Gherardini M., Maglione R., Pulsoni A., Romeo A.A. A case of multiple myeloma in a patient in treatment for chronic lymphocytic leukemia. Mediterr J Hematol Infect Dis 2025, 17(1): e2025033, DOI: http://dx.doi.org/10.4084/MJHID.2025.033

To the editor.

We describe the case of a 58-year-old male patient diagnosed with Chronic Lymphocytic Leukemia (CLL) and Multiple Myeloma (MM), respectively, in 2016 and 2022. Characteristics of both diseases are summarized in **Table 1**. After 5 years of watching and waiting for CLL, in April 2021, investigations were conducted due to night sweats, lymphadenopathy, and progressive lymphocytosis (77620/mmc), revealing splenomegaly (LD = 18 cm) and enlarged supra- and sub-diaphragmatic lymph nodes on CT (ranging from 28x17 to 32x61 mm, with a 15 cm abdominal lymph node conglobate) and PET-CT scans (SUVmax 8.1). To exclude Richter's syndrome, a lymph node biopsy confirming CLL and a bone marrow biopsy were performed, confirming the diagnosis of CLL and revealing 10% of clonal plasma cells in the absence of SLIM-CRAB criteria, namely a Smouldering MM (SMM). Interphase FISH and NGS on peripheral blood lymphocytes showed unmutated-IGHV, absence of del17p, wt-TP53, and cr12 trisomy. Meeting treatment criteria for CLL, Acalabrutinib was started in November 2021, after initial debulking with Chlorambucil and prednisone for 7 days. This old therapy regimen was adopted as a bridge to Acalabrutinib while waiting for the drug to become available at the hospital pharmacy, in

Table 1. Characteristics of CLL and MM.

Disease	CLL	IgG kappa MM
Year of diagnosis	2016	2022
Immunophenotype at diagnosis	CD5+ CD19+ CD20+ CD23+ CD200+ FMC7+ Kappa+ CD10-	CD38+ CD138+ Cyclin D1+ Kappa+ CD56-
Blood count at diagnosis	Hb: 11.1 g/dl WBC: 37710/mmc N: 3800/mmc L: 27950/mmc M: 5730/mmc Plts: 114000/mmc	Hb: 14.2 g/dl WBC: 15440/mmc N: 3720/mmc L: 9870/mmc M: 1630/mmc Plts: 210000/mmc
Blood smear at diagnosis	Compatible with CLL[§] Absence of plasma cells	Compatible with CLL[§] Absence of plasma cells
FISH/Sequencing before treatment start*	Unmutated IGHV wt-TP53 Absence of del17p	t(11;14) 1q21 amplification
Staging at diagnosis	Rai I/Binet A	ISS III R2-ISS III IMPeTUS BM3, F1, L4 [9]

CLL: Chronic Lymphocytic Leukemia, MM: Multiple Myeloma, Hb: Hemoglobin, WBC: White Blood Count, N: Neutrophils, L: Lymphocytes, M: Monocytes, Plts: Platelets, wt: wild type.
[§]Small lymphocytes with clumped chromatin and scant cytoplasm.
*On peripheral lymphocytes for CLL and on medullary plasma cells for MM.

Table 2. Adjusted Ven-Vd

Cycle	Venetoclax	Bortezomib (1.3 mg/m^2)	Dexamethasone 20 mg
Cycle 1 **28-day cycle***	**Ramp up-phase**: 20 mg/day (Week 1) 50 mg/day (Week 2) 100 mg/day (Week 3) 200 mg/day (Week 4)	Days 1, 4, 8, 11	Days 1, 2, 4, 5, 8, 9, 11, 12
Cycles 2-8 **21-day cycles**	400 mg/day	Days 1, 4, 8, 11	Days 1, 2, 4, 5, 8, 9, 11, 12
Cycles ≥ 9 **35-day cycles**	400 mg/day	Days, 1, 8, 15, 22	Days 1, 2, 8, 9, 15, 16, 22, 33

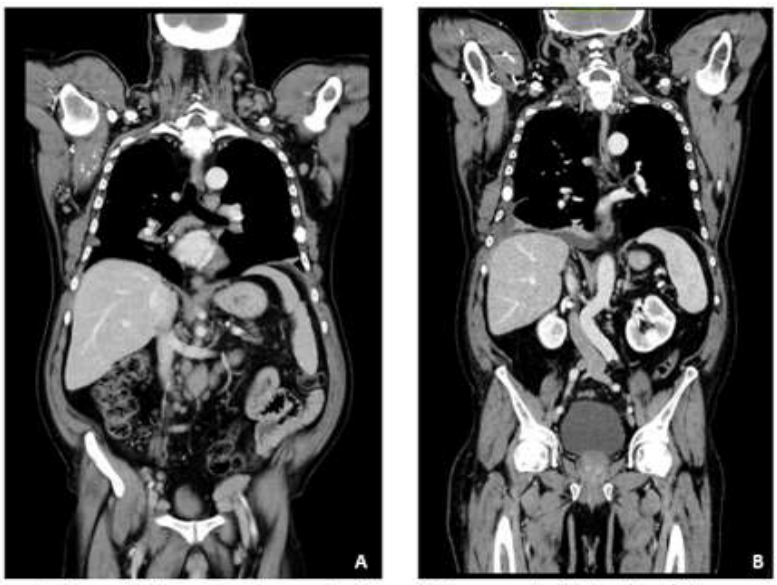
*In the original protocol, Venetoclax was administered at 800 mg/day, and there was no ramp-up. In addition, the first cycle lasted 21 days.

view of the high burden of the disease. In February 2022, In May 2022, osteolytic lesions and spleen enlargement were reported. Interphase FISH analysis on clonal medullary plasma cells showed t(11;14) and 1q21 amplification. Meeting treatment criteria for MM, considering the patient transplant ineligible for comorbidities (Chronic Obstructive Pulmonary Disease, Pickwick syndrome, Congestive Heart Failure, Hypertension), treatment until progression with Venetoclax-Bortezomib-Dexamethasone (Ven-Vd) regimen, on the basis of the phase III BELLINI trial,[1] was started. Vd was administered as per the trial schedule, while Ven as prescribed for CLL, starting with 20 mg/day for 7 days, then increasing to 50 mg, 100 mg, 200 mg, and 400 mg per day for 7 days each, reaching a final dosage of 400 mg/day (**Table 2**). After 8 cycles, complete response (CR) for MM and Partial Response (PR) for CLL were reported (**Figure 1**). After 15 cycles, with sustained CR for MM, Bortezomib was withheld for grade 3 peripheral neuropathy. In December 2024, the patient died due to a rapid relapse of MM and concomitant pneumonia in the intensive care unit, retaining the CLL response.

Synchronous and sequential diagnosis of MM and CLL/SLL is a rare event, with a few cases reported in the literature. Multiple studies were conducted in an attempt to prove a clonal relationship between the two diseases. However, different reports suggest that there may not be any clonal relationship between their cells of origin.[2-6] Nevertheless, we can hypothesize that some genes may have pleiotropic effects, and certain biological pathways may affect their mutual development due to the enrichment of B cell regulatory elements.[7-8]

The largest experience in the management of concomitant MM and CLL is reported by Ailawadhi S. et al.[8] From their experience, out of 10735 patients diagnosed with MM between 2000 and 2015, 28 (0.26%) also developed CLL: 15 before the diagnosis of MM, 11

Figure 1. CLL response post-VIII Ven-Vd.



A: Coronal CT scan pre-therapy. **B:** Coronal CT scan post-eight cycles of therapy.

simultaneously, and 2 after. None of them needed specific treatment for CLL, which resulted in responding to anti-myeloma treatment, and their prognosis was not statistically different from patients affected by MM only (58 vs 84 months, p = 0.198). Of note, in their experience, in 14 patients, MM and CLL were restricted to the same light chain. However, they did not attempt to identify a common origin cell or a clonal relationship. No prognostic differences were noted between patients with both diseases, regardless of whether they were restricted to the same light chain or not.

Our experience shows an optimal response for MM and CLL, both with a BELLINI trial-like therapy.[1] The reason for choosing this treatment regimen is the better results observed in relapsed/refractory MM (RRMM) carrying the t(11;14) (PFS 36.8 vs 23.4 months). The Venetoclax maximum dose was reduced (400 mg/day vs 800 mg/day), and a CLL-like ramp-up was performed in our case because of the high risk of hematological and infectious adverse events. In October 2023, we had to withhold Bortezomib for grade 3 peripheral neuropathy, and MM relapsed 14 months later, while CLL response had been retained.

We can conclude that, as already described, MM seems to be the main determinant of survival of this rare subgroup of patients. Ven-Vd could be a promising regimen in this setting. However, more data regarding safety and effectiveness are required.

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Competing interests: The authors declare no conflict of Interest.

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