Rapid Response of B-prolymphocytic leukemia (B-PLL) with VIPOR as 2nd line treatment

The Case

Mr. O is a 67 y/o man who presented to an outside primary care doctor with dyspnea on exertion and claudication. A CBC was done which reported a WBC of > 440 X 10^{-9}/L along with a HGB of 10.3 g/dL and PLT count of 55 X 10^{-9}/L. Uric acid was 10.5 mg/dL, LDH was elevated at 368 U/L, potassium was normal at 4.8 mmol/L and creatinine was normal at 0.96 mg/dL. Calcium was normal at 9.1 mg/dL. He was transferred to our hospital for further evaluation and treatment.

On exam, he had bitemporal wasting and appeared malnourished. His spleen tip was descended below his umbilicus. He lived alone and admitted to frequent alcohol use. He had been health otherwise and had not seen a doctor for more than 10 years. Review of his peripheral blood smear showed marked leukocytosis with circulating medium to large sized lymphoma cells with distinctive nucleoli. Flow cytometry revealed a monoclonal B-cell population co-expressing CD19, C20, CD22, CD11c(partial) and kappa light chains. These cells were negative for CD10, CD5, CD23. CT of the abdomen and pelvis was done which revealed marked splenomegaly, measuring 26 cm along with enlarged porta hepatis and retroperitoneal lymph nodes, measuring up to 1.8 cm. (picture 1). A bone marrow biopsy was recommended, but the patient declined and left against medical advice. He reconsidered and presented to the ER several days later and underwent a bone marrow biopsy which showed 97% involvement by B-lymphocytes which had a similar phenotype to those seen on flow cytometry. Cytogenetics were done which was complex: 43~44,X,-Y,add(2)(p11.2), der(3;8)(q10;q10), +i(3)(q10), add(4)(q11.2),add(7)(q22),-12, der(13)t(12;13)(q11.2;p11.2),-15,add(17)(p11.2),+mar[cp6]/43~44,sl, t(9;17)(p13;q24)[cp8]/46,X,-Y,add(1)(q32),add(2)(p11.2),+3, der(3;8)(q10;q10)x2, add(6)(p23), add(7)(q22),+8,+17,add(17)(p11.2)x2[cp5]/46,XY[1]. FISH was done with several probes which showed disruptions of 11q23 (ATM), 17p (TP53), 8q24 (MYC), 3q27 (BCL6), 18q21 (MALT1) and 14q32 (IGH).

He was ultimately felt by the Hematopathology department to have B-prolymphocytic leukemia based on the ICC classification with consideration for splenic B-cell lymphoma/leukemia with prominent nucleoli based on the WHO HAEM 5th edition with the caveat that in the 4th edition of the WHO HAEM, this entity would have been characterized also as B-prolymphocytic leukemia.

He was started on rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) as an inpatient with tumor lysis syndrome prophylaxis and monitoring and was discharged 4 days with allopurinol. Later. Twenty one days later as per protocol, he underwent a 2nd cycle of RCHOP. WBC on that day was also > 440. He was given the option of continuing with a 3rd cycle of RCHOP, or changing to dose-adjusted etoposide, prednisone, vincristine, Cytoxan, doxorubicin and rituximab (DA-EPOCH-R). He agreed to the latter. Twenty-one days later he was admitted for DA-

EPOCH-R. His WBC on day 1 cycle 1 was 410. He was asked to present to the outpatient clinic twice weekly for CBCs and prn transfusions as per protocol. Twenty-one days later he presents for day 1 cycle 2 or DA-EPOCH-R (dose level 2) at which time his WBC was 249. His splenomegaly had improved on exam and his weight had increased. Unfortunately, he opted to come only sporadically for his twice weekly CBCs after his 2nd cycle of DA-EPOCH-R and in follow-up, a discussion was initiated about the safety of his treatment and alternatives. Given that he lived 90 minutes away, he was offered the VIPOR combination, venetoclax, ibrutinib, prednisone, Obinutuzumab and lenalidomide[1] and once/weekly labs were negotiated.

It took approximately 4 days to have the venetoclax and ibrutinib delivered to his house. He began to immediately take the venetoclax and ibrutinib. At his one week follow-up his potassium and phosphorous were elevated with a normal creatinine despite taking allopurinol prophylaxis and he was treated in the ER with IVF. Uric acid was surprisingly normal and a repeat potassium was normal and he was sent home from the ER. What was most interesting was that his WBC had declined from 227 to 29 after just several days of ibrutinib and venetoclax, without ever starting his planned Obinutuzumab or lenalidomide.

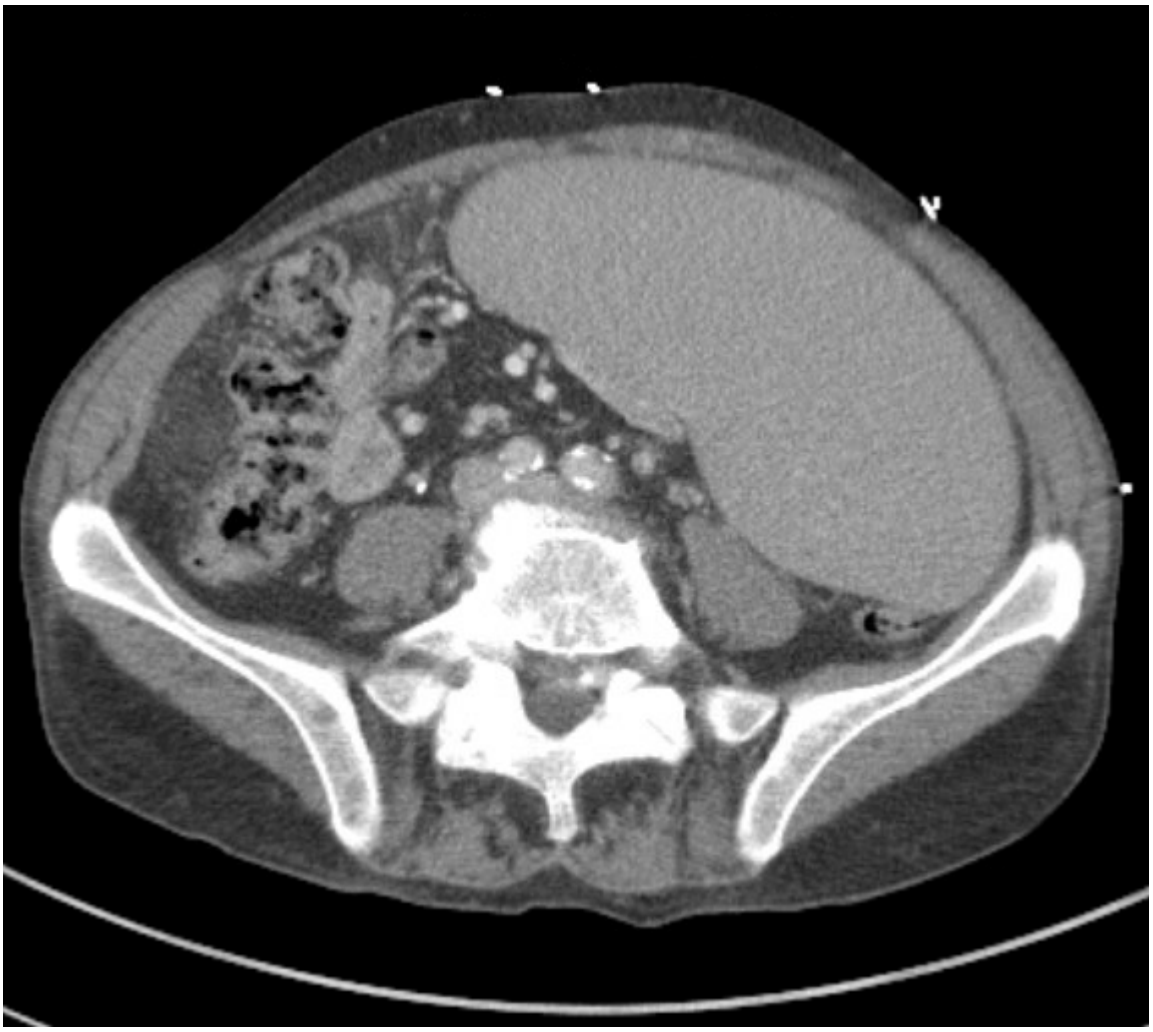
Discussion

B-Prolymphocytic leukemia is a rare disease. Its diagnosis requires > 55 percent of the circulating cells in the peripheral blood to be prolymphocytes. These cells normally contain prominent nucleoli. Multiple genetic derangement are common in this disorder and there is no standard of care given limited prospective trials.[2]

The VIPOR regimen was developed by Christopher Melani and colleagues at the National Institute of Health (NIH) lymphoma service and was initially studies in a phase I trial in patients with relapsed/refractory B-cell lymphoma.[1] In that trial, multiple lymphoma types were enrolled including germinal center- B GCB) type and non-GCB type diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), marginal zone lymphoma (MZL) and high grade B-cell lymphoma (HGBCL). The tumor reduction rate was impressive at 90%.

More recently this regimen has been studied in a phase IB trial in R/R DLBCL with an overall response rate of 54% and a complete response rate of 38% with manageable toxicity. [3]

As we learn more about the genetic drivers of B-cell lymphoma, more treatments are tailored and developed for subtypes. The VIPOR regimen aims to target multiple pathways simultaneously in an effort to exploit dependencies. This strategy has paid off for our patient despite not being exposed yet to the lenalidomide portion of his treatment.



Picture 1

Date	12/4/2024	12/11/2024	1/3/2025	1/25/2025	2/15/2025	3/25/2025	4/1/2025
Event	Diagnosis	D1C1 RCHOP	D1C2 RCHOP	D1C1 DA-EPOCH-R	D1C2 DA-EPOCH-R	VIPOR ordered	D3C1 VIPOR
WBC	>440	>440	>440	410	249	227	**29**

Table 1

[1] Melani, C. Phase I Study of VIPOR (Venetoclax, Ibrutinib, Prednisone, Obinutuzumab, and Lenalidomide) in Relapsed/Refractory B-cell Lymphoma: Safety, Efficacy and Molecular Analysis.
[2] Collignon, Aude. Prolymphocytic Leukemia: New Insignts into Diagnosis and Treatment Curr Oncol Rep 2017;19(29):1-11
[3] Melani, C. Combination Targeted Therapy in Relapsed Diffuse Large B-cell Lymphoma NEJM 2024;390:2143-2155