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A case of hypocalcemia, hypophosphatemia, and hypomagnesemia in association with Venetoclax

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ABSTRACT

Venetoclax is a drug commonly associated with tumor lysis syndrome (TLS) and electrolyte imbalances. However, its effects on electrolyte metabolism are not limited to TLS. We present a patient with relapsed chronic lymphocytic leukemia who experienced electrolyte imbalances as grade 2 hypocalcemia, hypophosphatemia, and hypomagnesemia during the venetoclax escalation period, independent of TLS or renal or gastrointestinal loss. The patient was successfully managed with close electrolyte monitoring and appropriate electrolyte replacement without discontinuing venetoclax. There is limited data on electrolyte imbalances associated with venetoclax other than TLS. Studies show the incidence and severity of electrolyte imbalances, but managing these adverse events is not clear enough. Therefore, we would like to share our approach and experience with a patient who developed venetoclax-induced hypocalcaemia, hypophosphatemia and hypomagnesaemia.

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Case Report

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INTRODUCTION

Venetoclax is an orally administered second-generation BH3 mimetic drug. This drug highly selectively inhibits B-cell leukemia/lymphoma-2 (BCL-2) protein, one of the most important anti-apoptotic proteins. In chronic lymphocytic leukemia (CLL), increased expression of bcl-2 causes cell survival advantages and chemoresistance, which have been proved.[1] Venetoclax plays a role in CLL through caspase activation and cell death. It was approved in relapsed/refractory CLL with 17p deletion in 2016 and independent from 17p status in 2018 by the Food and Drug Administration. Tumor lysis syndrome (TLS) has been reported as a notable adverse event, and a 5-week dose escalation schedule, risk stratification prophylaxis, and monitoring for prevention and prevention of TLS are recommended in clinical practice. However, limited studies and case reports of electrolyte imbalances associated with venetoclax exist.[2,3] Therefore, we would like to present the management of a case of hypocalcemia, hypophosphatemia, and hypomagnesemia during venetoclax escalation in relapsed CLL.

CASE REPORT

A 74-year-old patient was diagnosed with relapsed CLL four years after his initial diagnosis. In his medical history, he was diagnosed with CLL in 2019 and achieved remission status after 6 cycles of rituximab and bendamustine chemotherapy. In the relapsed state, the disease was considered to need treatment due to the high leucocyte doubling ratio. Venetoclax monotherapy was selected as a

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second-line option for the patient. A five-week dose escalation schedule was established, starting with 20 mg of venetoclax daily for the first week after hospital admission. The patient was closely monitored for TLS during the first week due to the high lymphocyte count and the risk of venetoclax-related adverse events. Hydration with 0.9% isotonic NaCl and allopurinol 300 mg/daily were administered according to daily follow-up and monitoring of renal function tests and electrolytes. The patient completed the first week without complications and was discharged. The dose-escalation schedule was continued as outpatient treatment with weekly follow-up. On the day of discharge, which was the 7th day of venetoclax treatment, the laboratory findings were lymphocyte count 9,710/mm3, glomerular filtration rate (GFR) 60.4 mL/min/1.73 m2, sodium (Na) 138 mmol/L, potassium (K) 5.1 mmol/L, corrected calcium (Ca) 8.8 mg/dL, and magnesium (Mg) 1,6 mg/dL.

The second week of treatment with 50 mg venetoclax daily and the third week of treatment with 100 mg venetoclax daily have been completed. However, at the end of the 200 mg daily dose on day 28 of venetoclax, the patient complained of abdominal pain, nausea, and loss of appetite. Laboratory findings showed that corrected Ca 7.9 mg/dL and phosphorus (P) 1.3 mg/dL while serum Na, K, chloride, creatinine, albumin, alkaline phosphatase, vitamin D and intact parathormone levels and GFR values were normal. Hypocalcemia and hypophosphatemia were graded as grade 2 according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, oral calcium-vitamin D3 supplementation was administered, and the venetoclax dose was maintained at 200 mg daily. After one week, the patient's discomfort subsided, and the results of laboratory tests were as follows: corrected Ca 9.9 mg/dL, P 2.0 mg/dL, and Mg 1.4 mg/dL. The results of the 24-hour urine test (2000 mL volume) for renal electrolyte loss were as follows: Ca 32 mg/day (100-300), P 15 mg/day (400-1300), and total protein 94 mg/day (0-140). There was no evidence of renal electrolyte or protein loss within the normal range of 24-hour urine test results. Grade 2 electrolyte imbalance was treated with oral calcium-vitamin D3 (1,000 mg/880 IU) effervescent twice a day, and magnesium oxide (365 mg) effervescent once-a-day replacement and venetoclax was continued at 200 mg daily. One week later, the patient's symptoms disappeared, and the laboratory abnormalities were reversed with oral replacement. The dose of venetoclax was increased to 300 mg daily after three weeks of constant dosing, and the oral replacements were discontinued. The electrolyte imbalance did not recur at follow-up, and venetoclax was increased to 400 mg daily. The patient has been receiving venetoclax 400 mg daily for two months without any complications, and the response was also achieved concerning CLL. The graphs of the electrolyte values were shown in Figure 1 (A, B, and C).

DISCUSSION

There is limited data on electrolyte imbalance with venetoclax other than in the context of TLS. Concerning clinical trials, in the single-arm Phase 2 study of venetoclax monotherapy in CLL (clinical trial number: NCT 02141282), preliminary results showed that 11% of patients experienced treatment-emergent grade 3/4 hypophosphatemia. The final results of this study reported non-serious decreased appetite, hypocalcemia, hypomagnesemia, and hypophosphatemia at 11%, 25%, 22%, and 19.7%, respectively.[4,5] In the venetoclax monotherapy study in 350 patients with CLL, hypocalcemia of any grade was reported in 12% of patients, and 95% of adverse events occurred during dose escalation.[6] In the other clinical trial of venetoclax monotherapy, grade 1-3 treatment-emergent adverse events were hypophosphatemia in 3% and hypocalcemia in 5%.[7] In terms of case reports, Lubbe et al.2 presented a patient with venetoclax-induced hypophosphatemia, hypocalcemia, and hypomagnesemia, as well as severe hypokalemia due to a possible effect on the proximal and distal convoluted tubule. However, this patient was taking concomitant medication for diabetes, hypertension, systemic sclerosis, and Sjogren's syndrome in addition to venetoclax, and the chemotherapy protocol used was R-CHOP (rituximab, vincristine, doxorubicin, cyclophosphamide, prednisolone) for non-Hodgkin's lymphoma. The authors attributed the pathogenesis of electrolyte disturbances to the localization of bcl-2, the outer membrane of mitochondria, and the high proportion of mitochondria in the proximal and distal convoluted tubules.[8]

In our patient, venetoclax monotherapy was associated with grade 2 hypocalcemia, hypophosphatemia, and hypomagnesemia. There was no evidence of renal tubular electrolyte loss in

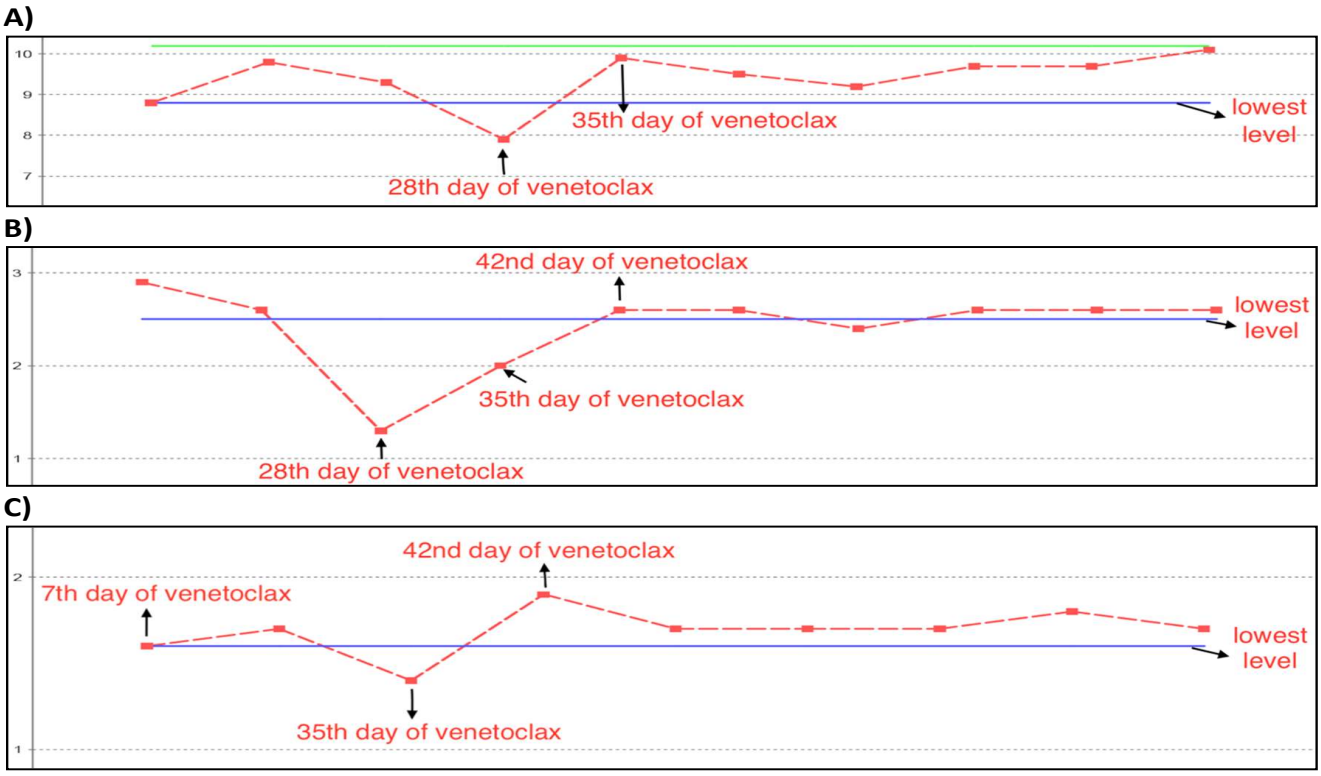

Figure 1. Graphs of calcium, phosphorus, and magnesium values A) Timeline of serum calcium level B) Timeline of serum phosphorus level C) Timeline of serum magnesium level.

the accompanying blood electrolyte levels or the 24-hour urine tests. The patient did not describe nausea, vomiting, or diarrhea as evidence of gastrointestinal loss. We cannot explain the pathogenesis of the electrolyte deficiency in our patients. However, we recommend close electrolyte monitoring, controlled dose escalation, and replacement of the deficient electrolyte while escalating the dose of venetoclax.

CONCLUSIONS

Herein, we reported a patient with non-severe electrolyte imbalance who was successfully treated with oral replacement without discontinuing venetoclax. More data in the literature on the pathogenesis of electrolyte disturbances other than TLS needs to be provided, and the reported data on the rate and degree of electrolyte imbalance should change. The purpose of this case report is to demonstrate that electrolyte levels can be affected by venetoclax, especially during dose escalation, without evidence of gastrointestinal or renal loss, and such a problem can be managed with a close monitoring and replacement approach. Further studies are needed to elucidate the mechanism of electrolyte disturbances with venetoclax.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Consent

Informed consent was obtained from the patient.

Authors' Contribution

Study Conception: TAK; Study Design: TAK; Literature Review: TAK; Critical Review: TAK; Data Collection and/or Processing: TAK; Analysis and/or Data Interpretation: TAK; Manuscript preparing: TAK.

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