Exceptional Case

Electrolyte disorders secondary to venetoclax

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ABSTRACT

Emerging cancer drugs introduce new forms of nephrotoxicity that may also present as electrolyte disorders. Here, we report a patient with non-Hodgkin lymphoma who developed severe hypokalaemia with concurrent hypophosphataemia, hypocalcaemia and hypomagnesaemia secondary to venetoclax. Although electrolyte disorders have been reported during treatment with venetoclax, these were ascribed to tumour lysis prophylaxis. Based on the temporal relationship and urinary studies, we show that venetoclax can cause these electrolyte disorders, likely through an effect on the proximal and distal convoluted tubule. In patients treated with venetoclax, we recommend close monitoring of electrolytes and avoiding co-medication that can contribute to electrolyte disorders.

Keywords: BCL-2, hypokalaemia, nephrotoxicity, non-Hodgkin lymphoma

BACKGROUND

Venetoclax is a selective inhibitor of B-cell lymphoma-2 (BCL-2) and is approved for treatment of chronic lymphocytic leukaemia [1]. Although electrolyte disorders have been observed during treatment with venetoclax, these were ascribed to concomitant therapy for tumour lysis prophylaxis [2]. Here, we report a patient with non-Hodgkin lymphoma who developed severe hypokalaemia with concurrent hypophosphataemia, hypocalcaemia and hypomagnesaemia in the setting of venetoclax and chemotherapy.

CASE REPORT

The patient was a 67-year-old female with a history of Type 2 diabetes, hypertension, systemic sclerosis and Sjögren syndrome for which she used metformin, lisinopril, long-acting insulin, a statin and acetylsalicylic acid. During outpatient controls, she had normal kidney function, electrolytes and acid–base parameters. She presented with lymphadenopathy and was diagnosed with Epstein–Barr virus-positive diffuse large B-cell lymphoma. She was referred for treatment in a Phase IB/II, open-label study with venetoclax [3].

One day prior to chemotherapy, she received prophylactic allopurinol (300 mg for 10 days). Treatment started with rituximab (510 mg), vincristine (1.9 mg), doxorubicin (68 mg), cyclophosphamide [1020 mg, all intravenous (i.v.) on Day 0] and prednisolone (100 mg, orally on Days 0–4) (R-CHOP). One day after chemotherapy (Day 1), she received pegfilgrastim (6 mg). Venetoclax (800 mg/day orally) was started on Day 3. On Day 6, she developed febrile neutropenia due to pneumonia, for which meropenem and normal saline were started. On Day 7, a routine laboratory test revealed severe hypokalaemia (serum potassium 1.9 mmol/L), hypocalcaemia and hypophosphataemia. These laboratory values were confirmed by subsequent measurements to exclude a technical error. The majority of the electrolyte disorders were characterized by increased urinary excretion. During hypokalaemia, spot urine potassium was 30 mmol/L and the transtubular potassium gradient (TTKG) 11.3. The fractional excretions of phosphate (46%) and...
magnesium (6.3%) were increased. In contrast, hypocalcaemia was accompanied by hypocalciuria (urine calcium/creatinine 0.07 mmol/mmol) with low 25-hydroxyvitamin D (27 nmol/L). Other laboratory results showed new-onset proteinuria (1.5 g/day) with elevated β2-microglobulin excretion (18 mg/day) and high sodium chloride excretion (237 and 252 mmol/day, respectively). Acid–base balance remained normal.

Although the patient had no symptoms, the electrocardiogram showed premature atrial contractions, flattened T-waves and a U-wave configuration in V1. I.v. supplementation of potassium, phosphate, magnesium and calcium was started (Figure 1). Because venetoclax was considered as the offending drug, it was discontinued prematurely on Day 7. Electrolytes remained normal after discontinuation of i.v. supplementation. No other explanations for the electrolyte disorders were identified. Chemotherapy was continued 1 month later (R-CHOP without venetoclax).

**DISCUSSION**

This is the first report to link venetoclax more directly to the development of severe electrolyte disorders. According to the Naranjo scale, this adverse drug reaction was classified as ‘probable’ [4]. Although electrolyte disorders during treatment with venetoclax were ascribed to concomitant therapy for tumour lysis prophylaxis [2], allopurinol has not been associated with the electrolyte disorders observed in this case. In previous reports, hypokalaemia occurred in 25–40% of cases, but no urinary studies were reported [2, 3]. Hypokalaemia, hypophosphataemia and hypomagnesaemia in this patient were accompanied by increased urinary losses, suggesting renal tubular toxicity of venetoclax. In contrast, hypocalcaemia was caused by reduced calcium absorption possibly due to gastrointestinal toxicity. Venetoclax can cause gastrointestinal toxicity, although doxorubicin and vincristine can also cause this. Hyperparathyroidism secondary to hypocalcaemia likely contributed to hypophosphataemia. A notable aspect of this case is the selectivity of the renal tubular toxicity. BCL-2 localizes to the outer membrane of mitochondria. In the kidney, both the proximal tubule and the distal convoluted tubule are the nephron segments with high mitochondrial density. Indeed, the observed renal tubular disorders suggest impairment of these segments. Renal hypokalaemia, hypophosphataemia and tubular proteinuria are consistent with the proximal tubular defect, although there was no full-blown Fanconi syndrome. The combination of hypokalaemia and hypomagnesaemia suggests involvement of the distal convoluted tubule. Lesions in the proximal and distal convoluted tubule often cause hypokalaemia because they increase distal delivery of sodium and activate the renin–angiotensin system. Although we did not measure renin and aldosterone, the patient did have a high TTKG and evidence for salt loss. In BCL-2-deficient mice, electrolytes were not measured, but these mice did display a renal phenotype with cyst formation in the proximal and distal tubules, and renal failure [5].

In summary, we report a patient who developed severe renal electrolyte disorders after treatment with venetoclax. In patients treated with venetoclax, we recommend close monitoring of electrolytes and avoiding co-medication that can contribute to electrolyte disorders, especially diuretics and laxatives.

**PATIENT CONSENT**

Informed consent was obtained to publish this case.
CONFLICT OF INTEREST STATEMENT

Dr. Lugtenburg received honoraria for advisory board meetings and research funding from Roche. All authors declare that they have no conflict of interest and that the results have not been published previously in whole or part.

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