CASE REPORT

Introduction

Hypocalcemia is a known side effect of regorafenib, however, the mechanism is poorly understood. Regorafenib is a new tyrosine kinase inhibitor approved by the US Food and Drug Administration (FDA) for treatment of metastatic colorectal cancer. This report describes a case of profound hypocalcemia potentially related to the use of regorafenib in a patient with metastatic colon cancer. The etiology of hypocalcemia is not clearly published in the English literature. This case illustrated the importance of monitoring calcium and phosphate levels in patients who are on a tyrosine kinase inhibitor to avoid potential lethal toxicity.

Case Report

A 65-year-old woman with a history of hypertension, diabetes, and metastatic colon cancer presented with progressive weakness, fatigue, and postictal symptoms at an oncology clinic. She had profound hypocalcemia (corrected Ca 5.5 mg/dl, baseline of 8.3 mg/dl) and was admitted to the hospital (see Figure 1 for lab results). She recently had been started on regorafenib approximately 15 days prior to presentation. Her parathyroid hormone (PTH) level was elevated at 541 pg/ml (reference 10-65 pg/ml) and her phosphorus level was 4.5 mg/dl. Her 25-hydroxy vitamin D level was low at 4 ng/ml (reference 30-80ng/ml). Urine studies showed a random urine calcium less than 2 mg/dl/24-hour. There was normal urinary excretion of phosphate, sodium, potassium, and cyclic adenosine monophosphate (AMP). Her admission echocardiogram revealed a prolonged QTc of 487 msec.

On admission, regorafenib was discontinued and the patient was admitted to the telemetry unit. Her hypocalcemia was managed with intravenous calcium infusion to maintain serum calcium above 6 mg/dl. She required approximately 22 g of calcium gluconate infusion over the first four days of hospitalization. On day 5 of admission, ergocalciferol as well as calcitriol was initiated, and she was transitioned from parenteral calcium to oral calcium citrate as her serum calcium levels improved. On day 10, her calcium levels stabilized close to baseline and she was discharged on calcium citrate 3800 mg TID AC, ergocalciferol 50,000u q48h, and calcitriol 2 mcg PO TID. Follow-up laboratory studies demonstrated stability of her calcium and phosphorus levels.

Discussion

Regorafenib is a multi-kinase inhibitor that targets kinases involved with tumor angiogenesis and oncogenesis. It may cross-react with other receptors involved in both calcium and phosphate homeostasis. We hypothesized that the degree of profound hypocalcemia in our patient may have been due to severe vitamin D deficiency and possible PTH resistance type 2.
Proposed mechanisms of action for regorafenib included: 1) increased metabolism of vitamin D in the liver by inducing P 450 enzyme activity or inhibiting hydroxylation of vitamin D to 25-hydroxy vitamin D or 2) induction of PTH resistance type 2 in which there is a defect downstream on the PTH receptor pathway allowing normal levels of urinary cyclic AMP but low calcium and Vitamin D levels. Profound hypocalcemia can have very serious clinical consequences. This case suggested that serum calcium levels should be monitored closely among patients receiving tyrosine kinase inhibitor to avoid potential lethal toxicity.

References

Keywords: regorafenib, tyrosine kinase inhibitor, hypocalcemia, colon cancer, chemotherapy