Hyperkalemia in a Patient with Advanced Hepatocellular Carcinoma Probably Due to Sorafenib: Case Report

İlerlemiş Hepatoselüler Karsinomlu Hastada Muhtemelen Sorafenibe Bağlı Olan Hiperkalemi

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ABSTRACT Sorafenib is an oral tyrosine kinase inhibitor used in the treatment of metastatic hepatocellular carcinoma (HCC). Its common adverse reactions include diarrhea, hand-foot syndrome, rash, cardiac ischemia or infarction, hypertension, elevated serum lipase and hypophosphatemia. A 35-year-old male patient with unresectable HCC was treated with sorafenib for progressive disease after locoregional chemoembolization. In the second month of the sorafenib treatment, he was admitted to the emergency department with weakness and drowsiness. His serum potassium level was 8.3 mmol/ L (3.5-5.5 mmol/L) which was accompanied with mild elevations in liver enzymes. Sorafenib treatment was stopped and emergency hemodialysis was applied. His potassium level reduced to normal levels and was stabilized.

Key Words: Hepatocellular carcinoma; sorafenib; hyperkalemia

ÖZET Sorafenib metastatik hepatoselüler karsinom (HCC) tedavisinde oral yoldan kullanılan tirozin kinaz inhibitörüdür. Sık yan etkileri diyare, el-ayak sendromu, döküntü, kardiyak iskemi veya infarktüs, hipertansiyon, artmış serum lipazı ve hipofosfatemidir. Anrezektabl HCC'si olan 35 yaşındaki erkek hasta bölgesel kemoembolizasyon sonrası progresif hastalık için sorafenib ile tedavi edildi. Sorafenib tedavisinin ikinci ayında güçsüzlük ve uyuklama ile acil servise kabul edildi. Serum potasyum düzeyi karaciğer enzimlerindeki hafif yükselmelerle birlikte 8,3 mmol/L (3,5-5,5 mmol/L) idi. Sorafenib tedavisi kesildi ve acil hemodiyaliz uygulandı. Potasyum düzeyi normal aralığına döndü ve stabilleşti.

Anahtar Kelimeler: Hepatoselüler karsinom; sorafenip; hiperkalemi

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Sorafenib is an oral tyrosine kinase inhibitor used in the treatment of metastatic hepatocellular carcinoma. It is thought to block tumor growth and cell proliferation by targeting the raf-kinase, vascular endothelial growth factor receptor (VEGFR)-2, VEGFR-3 and platelet derived growth factor Beta (PDGF-β).[1,2] Sorafenib monotherapy was reported to increase progression-free and overall survival in metastatic hepatocellular carcinoma patients who were not candidates for curative surgery or transarterial chemoembolisation in multicenter and randomized phase III trials.[3,4]

Sorafenib monotherapy is usually well-tolerated in patients with metastatic hepatocellular carcinoma. Most common adverse events are diarrhea, hand-and-foot syndrome, rash, cardiac ischemia and infarct, hypertension, elevation of serum lipase levels and hypophosphatemia.[3-5]

Here, we reported a hepatocellular carcinoma patient who had hyperkalemia while on treatment with sorafenib for the treatment of progressive disease after transarterial chemoembolisation procedure.

CASE REPORT

A 35-year-old man who had a positive HBsAg (+) serology was diagnosed with unresectable hepatocellular carcinoma, intraoperatively. Progressive disease was observed after transarterial chemoembolisation, and sorafenib 400 mg twice daily was started. He was admitted to the emergency unit because of fatigue and sleepiness within the second month of sorafenib treatment and his serum potassium level was measured as 8.3 mmol/L (3.5-5.5 mmol/L). Repeated measurements confirmed the first value. Other laboratory parameters were normal except for mildly elevated transaminases. The patient did not have any other etiologic factors which can cause hyperkalemia such as renal disease, hemolysis, acidosis or prior medication use like spironolactone or angiotensin converting enzyme (ACE) inhibitors. Naranjo scale of the patient was 7. Sorafenib treatment was stopped; palliative measures including intravenous fluids with calcium gluconate and insulin in 10% dextrose were taken. A femoral venous catheter was applied for hemodialysis when serum potassium levels could not be controlled after calcium gluconate and insulin-glucose infusion. Bicarbonate hemodialysis was administered on the first and the second days of hospitalization. After one day interval, the 3rd session of hemodialysis was performed, and serum potassium level of the patient decreased to normal (4.5 mmol/L) thereafter. Serum potassium levels remained within normal limits through one week of follow up. Hyperkalemia was not seen afterwards, but we could not administer sorafenib afterwards since the patient's performance status did not improve, and he died after three months.

DISCUSSION

Hyperkalemia is an electrolyte disturbance with a high risk of cardiac mortality when serum levels increase above 5.5 mmol/L. True hyperkalemia must be differentiated from pseudo-hyperkalemia. Pseudohyperpotassemia may be seen due to blood sampling and storage procedures or to hemolysis in the test tube in severe leucocytosis (>70x10^9) and thrombocytosis (>900x10^{10}). True hyperkalemia develops in cases with excess extracellular efflux of potassium, increased potassium intake and decreased excretion. Acidosis due to acute renal failure, hyperosmolarity due to severe hyperglycemia, use of beta blockers and insulin deficiency can cause hyperkalemia by increasing the passage of extracellular potassium. Intake of potassium containing salts, mineralocorticoid deficiency (Addison syndrome, isolated aldesterone deficiency, renin deficiency, angiotensin 2 receptor blockers, angiotensin converting enzyme inhibitors and nonsteroid anti-inflammatory drugs), resistance to mineralocorticoid effect (tubulointerstitial kidney diseases, overdose use of mineralocorticoid antagonists like sprinolactone and triamterene), and severe renal insufficiency cause hyperkalemia by decreasing renal excretion.[6]

Sorafenib is metabolized primarily in liver with cytochrome P450 (CYP3A4) enzymes and uridine diphosphate glucoronyltransferase 1A9. Thus, drug interactions occur frequently. Sorafenib concentration decreases in serum with CYP3A4 inducing drugs.[7]

Blood samples of the reported patient were tested twice for exclusion of pseudohyperkalemia. Hyperkalemia was shown in both tests. He did not have thrombocytosis or leucocytosis, any clinical signs/symptoms or laboratory findings of acute or chronic renal failure. Hyperglycemia was not detected. No history of phytomedicines or use of any drugs other than sorafenib was present.

Only two cases of sorafenib-associated hyperkalemia were reported previously in the literature. Hyperkalemia were proposed to be secondary to tumor lysis syndrome in those cases.[8,9] However in this case, the size of the tumor has decreased to 75x73 mm from 98x88 mm and there were signs of tumor lysis syndrome including hypocalcemia, hyperuricemia or hyperphosphatemia.

Hyperkalemia must be treated urgently, particularly due to the effects of potassium on heart. Calcium gluconate infusion is useful for treatment. Intravenous infusion of insulin and glucose must be given in order to importing potassium into the cell cytoplasm. Insulin and albuterol have additive effects on decreasing the potassium levels.[10] Hemodialysis is an effective treatment procedure when potassium levels cannot be controlled with all these treatment modalities.

In literature, there are some case reports about adverse events due to sorafenib use, like serious left ventricle dysfunction in a patient with hepatocellular cancer, multiple eruptive keratoacanthomas in another hepatocellular cancer patient, and psoriasiform eruption in a patient with metastatic thyroid carcinoma.[11-13]

In conclusion, even if the mechanism is not clear, we suppose that hyperkalemia should be kept in mind in patients who use sorefenib.

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