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SORAFENIB MAY INDUCE HYPOPHOSPHATEMIA THROUGH A FIBROBLAST GROWTH FACTOR-23 (FGF23)-INDEPENDENT MECHANISM

E. Bellini^{1,2}, A. Pia^{1,3}, M.P. Brizzi^{1,2}, M. Tampellini², M. Torta^{1,2}, M. Terzolo^{1,3}, L. Dogliotti^{1,2} and A. Berruti^{2,*}

Author Affiliations

1Department of Clinical and Biological Sciences

2Department of Medical Oncology and

3Department of Internal Medicine, University of Turin, San Luigi Gonzaga Hospital, Orbassano, Italy

*[✉](E-mail: alfredo.berruti@gmail.com)

Sorafenib, a drug approved for the treatment of advanced renal cancer, inhibits RAF/MAPK pathway, vascular endothelial receptor-2 and -3, platelet-derived growth factor receptor-2 and -3, and c-Kit [1].

Hypophosphatemia is a common side-effect, occurring in ~45% of patients [2]. This metabolic derangement is mostly asymptomatic, but the mechanisms involved are unclear [2].

The physiological balance of phosphate is maintained by the coordinated interactions of the small intestine, bone, parathyroid gland and kidneys [3] (Figure 1).

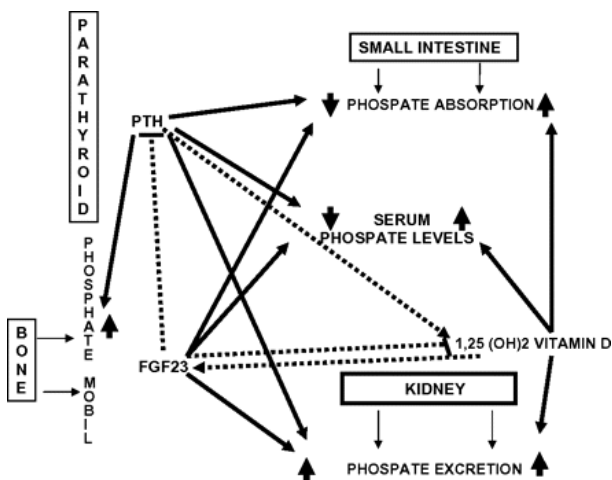


Figure 1. The physiological homeostasis of phosphate is maintained through the complex interactions among, calcitriol [1,25(OH)₂ vitamin D] and FGF23. Calcitriol increases the serum phosphate levels, while

both PTH and FGF23 decrease the circulating levels of this anion. FGF23 can inhibit PTH synthesis from parathyroid and calcitriol synthesis in the kidney. PTH, parathyroid hormone; FGF23, fibroblast growth factor-23.

A major breakthrough in understanding the regulation of phosphate homeostasis was accomplished by the identification of serum fibroblast growth factor-23 (FGF23), a bone-derived hormone able to cause hypophosphatemia by increasing the urinary excretion and decreasing the intestinal absorption of phosphates [4].

A 64-year-old male with metastatic kidney cancer received sorafenib (400 mg b.i.d. orally) till progression for a total of 11 months. No major toxic effects were recorded and particularly no diarrhea or mucositis was observed. Serum FGF23 together with serum calcium, phosphorus, parathyroid hormone (PTH), 1,25(OH)₂ vitamin D, alkaline phosphatase, C-telopeptide of type I collagen (CTX), urinary calcium and phosphorus were measured at baseline condition and every month during the first 5 months. Renal and hepatic functions were within normality throughout the study. The patient who had normal baseline serum phosphorus levels developed hypophosphatemia after 1 month that persisted for two additional months and was associated with a decrease in serum calcium, urinary calcium and phosphate (Table 1). Serum PTH increased, while serum 1,25(OH)₂ vitamin D and serum FGF23 decreased. Serum CTX also decreased, but serum alkaline phosphatase did not change (Table 1).

Table 1 Variation in time of phosphate regulation hormones during Sorafenib administration

	FGF23 ^a , pg/ml	Vitamin D, ng/ml ^b	CTX, ng/l (0.0–1)	ALP, U/l (30– 120)	PTH, pg/ml (10–65)	Ca, mmol/l ^c (2.1–2.55)	Ca tot U 24 H, mmol/24 h (2.5– 7.5)	P, mg/dl (2.5–4.8)	Phosph U 24 H, mg/24 h (400– 1300)
Baseline	4.9	22	0.49	65	30	2.67	1.25	4.1	977
First month	4.5	19	0.26	90	104	2.4	0.22	2.7	787
Second month	3.8	15		88	110	2.3	0.2	2.5	738
Third month	3.1	13	0.17	92	162	2.3	0.2	2.6	642
Vitamin D administration									
Fourth month	7.75	21	0.25	81	81	2.43	0.5	3.0	797
Fifth month	10.2	23	0.42	96	57	2.53	0.9	3.4	853

Reference range enclosed in parenthesis.

FGF23 normal values are not available, so only the trend of this hormone serum levels can be considered.

Normal vitamin D ≥30 ng/ml; insufficiency 10–29 ng/ml; deficiency <10 ng/ml.

Albumin-corrected serum calcium.

FGF23, serum fibroblast growth factor-23; CTX, C-telopeptide of type I collagen; ALP, serum alkaline phosphatase; PTH, serum parathyroid hormone; Ca, serum calcium; Ca tot U 24 H, 24-h urinary calcium; P, serum phosphate; Phosph U 24 H, 24-h urinary phosphate.

Due to the severe hypovitaminosis D attained in the first 3 months, a single i.m. dose of cholecalciferol (300 000 U) was administered. In the subsequent 2 months, serum phosphate returned to normal, calcium and vitamin D slightly increased, PTH consistently decreased and FGF23 increased. Also, serum CTX levels increased, while serum alkaline phosphatase did not change (Table 1).

The decrease in urinary phosphate and calcium levels over time and the decreasing trend of FGF23 levels suggest that drug-induced hypophosphatemia in this patient was sustained by a low intestinal phosphate absorption and/or low bone phosphate release, while FGF23 was not contributory. Sorafenib inhibited the osteoclast activity as documented by the decrease of serum CTX. The reduction in serum vitamin D levels and the normalization of phosphate levels after vitamin D supplementation suggest a predominant role of this hormone in this metabolic disorder. The mechanism by which sorafenib can cause hypovitaminosis D is unclear and deserves to be confirmed in a prospective study. Concomitant malabsorption can be conceivably excluded since no diarrhea was recorded.

Prolonged hypovitaminosis D and hyperparathyroidism lead to osteomalacia, asthenia, and increased risk for cardiovascular disease [5]. These effects could negatively impact on long-term sorafenib tolerability. Moreover, since vitamin D has antiproliferative activities, hypovitaminosis D can also potentially influence the drug efficacy [5]. Further studies are warranted to confirm the results of this paper, assess the prognostic significance of hypophosphatemia and define its appropriate treatment.

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