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LETTER TO THE EDITOR

Hypocalcemia induced by tyrosine kinase inhibitors: targeted treatment with 'untargeted' side effects

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Introduction

Over the last years, an increasing number of tyrosine kinase inhibitors (TKIs) targeting specific receptors have been approved for a large number of indications, in particular many cancers [1].

Their toxicity profile differs from conventional cytotoxic chemotherapeutics. Although the overall toxicity of TKIs is less life-threatening, side effects are common and not always recognized. Different classes of TKIs are associated with particular toxicities. Gastrointestinal complaints, fatigue, hair loss, skin rashes and hypertension are amongst the most prevalent side effects [2,3]. Hypocalcemia is a relatively unknown side effect of TKIs, but can occur in more than 10% of cases with a variable course. Most often, symptoms are vague and could easily be attributed to the underlying condition [2,3]. Based on the case presented here, we illustrate the risk of TKI induced hypocalcemia and discuss the importance of early and frequent monitoring of calcium levels following the start of a TKI.

Case report

A 69-year-old woman was seen in our outpatient clinic with a progressive metastatic and iodine refractory follicular thyroid carcinoma. Previously, she was treated with a total thyroidectomy followed by radioactive iodine ablation therapy, thyroid stimulating hormone (TSH) suppression therapy and external radiotherapy because of tumor invasion into cervical vertebrae. She developed postsurgical hypocalcemia due to chronic primary hypoparathyroidism (parathyroid hormone (PTH) 0.7 pmol/l) and serum calcium levels were effectively restored with oral calcium and active vitamin D (1–2 μg alfacalcidol daily). In October 2016, she started with the TKI lenvatinib, from which she rapidly experienced many side effects; including fatigue, nausea, vomiting, diarrhea and stomatitis. After 10 days, she developed a symptomatic hypocalcemia (corrected Ca^{2+} 1.85 mmol/L) with classic symptoms of neuromuscular excitability shown by muscle twitching, spasms and tingling sensations. Initially, the hypocalcemia was interpreted as a consequence of reduced absorption of calcium and vitamin D substitution therapy, given the simultaneously existing nausea and vomiting. There was no reason to doubt compliance. After prompt management with intravenous calcium her symptoms resolved and she restarted lenvatinib. However, maintaining a stable serum calcium concentration afterwards was difficult to achieve, even after the gastrointestinal complaints disappeared. Additional laboratory analysis demonstrated a normal complete blood count, normal magnesium levels (0.68, 0.64 and 0.84 mmol/l), normal phosphate levels (1.71, 1.59 and 1.81 mmol/l), and normal glucose, renal and liver function tests. In the absence of another plausible explanation (Table 1), we contributed the hypocalcemia due to the use of lenvatinib. Due to the above-mentioned adverse effects and additional episodes of gastroenteritis, lenvatinib was interrupted several times. During these short periods (on average $<$ two weeks), no alternative antitumor therapy was given. Every time the lenvatinib was reintroduced, she developed a severe symptomatic hypocalcemia (corrected Ca^{2+} 1.73, 1.75 and 1.80 mmol/l, grades 2 and 3 side effect) with in three of the four episodes typical changes on the EKG (Figure 1). However, because of frequent laboratory testing, prompt intervention was always possible and serious complications of hypocalcemia did not occur. Currently, she is on lenvatinib therapy for more than three years and is doing well with no signs of progressive disease, evaluated by computed tomography of chest and abdomen. Last evaluation was in December 2019.

Discussion

A still underestimated side effect of TKIs is hypocalcemia, which is potentially life threatening and defined as a serum calcium level, interpreted in relation to serum albumin concentration, of $<$2.10 mmol/L [4]. Hypocalcemia is associated with a spectrum of clinical manifestations, ranging from no

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Table 1. Most important causes of hypocalcemia [4].

Causes	Serum concentrations of different laboratory values			
	Parathyroid hormone	Alkaline phosphatase	Phosphate	25-Hydroxyvitamin D
Parathyroid hormone dependent[a]				
Iatrogenic hypoparathyroidism	Low	Normal	High	Normal
Autoimmune hypoparathyroidism	Low	Normal	High	Normal
Hypomagnesaemia[b]	Low (sometimes normal)	Normal	Normal	Normal or low
Parathyroid hormone independent[a]				
Vitamin D deficiency	High	Normal or high[c]	Low	Low
Vitamin D resistance	High	Normal	Normal	Normal
Parathyroid hormone resistance	High	Normal	High	Normal
Renal disease	High	Normal or high	High	Normal or low
Other				
Shifts: hyperphosphatemia, sepsis, respiratory alkalosis or tumor lysis syndrome				
Medication: bisphosphonates, cinacalcet, phenytoin or tyrosine kinase inhibitors				

[a]Measurement of the parathyroid hormone (PTH) is crucial in the differential diagnosis of hypocalcemia. When parathyroid function is intact, PTH should be elevated as a normal response of serum calcium levels. In case of a problem within the parathyroid glands, the parathyroid glands will not have enough function to allow the PTH to rise sufficiently and therefore the PTH is low. Normal PTH levels in this context should also be considered as 'abnormal'. A high concentration of PTH by normal kidney function usually means a vitamin D deficiency. A low concentration of PTH usually indicates primary hypoparathyroidism. The most common cause of primary hypoparathyroidism is (para)thyroid surgery.
[b]Magnesium is important for the synthesis and distribution of PTH. Low serum magnesium levels inhibits the secretion of PTH.
[c]In case of osteomalacia due to vitamin D deficiency.

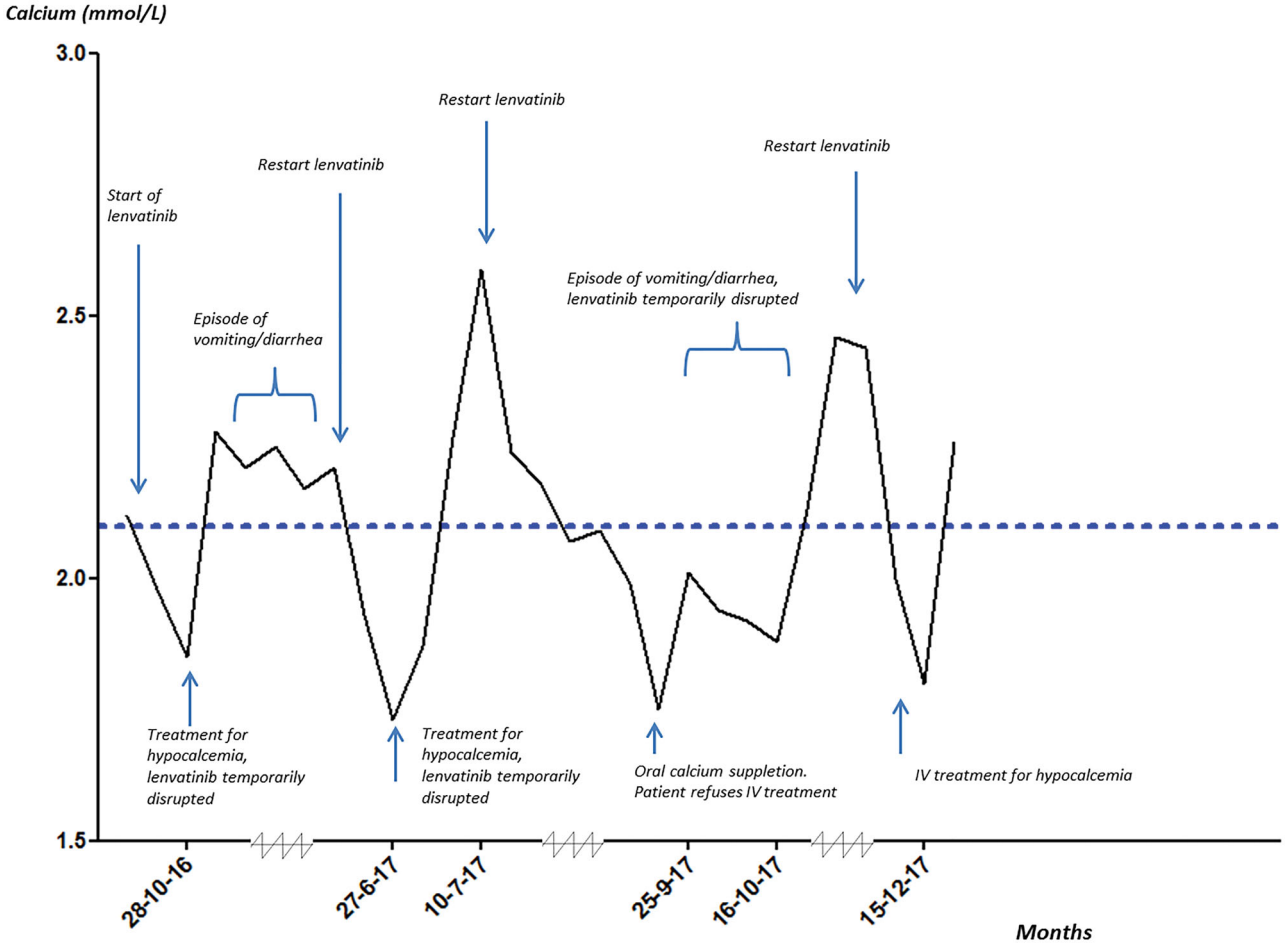

Figure 1. For albumin corrected serum calcium levels (mmol/L) and corresponding treatment for hypocalcemia after start and stop of the tyrosine kinase inhibitor (TKI) lenvatinib in our patient. The lower limit of normal (2.10 mmol/L) is presented as a blue dotted line. IV: intravenous therapy.

symptoms to severe complaints [4]. Signs of neuromuscular excitability, like muscle twitching, spasm, tingling and numbness are classical, but the development of symptoms depends on both the absolute concentration of calcium and how rapidly serum levels decline. Low serum calcium levels are most often caused by disorders of parathyroid hormone (PTH) or vitamin D. Nevertheless, the detection of hypocalcemia implicates a broad differential diagnosis (Table 1).

Although TKI induced hypocalcemia is not a well-known prominent class-specific side effect, it was frequently (up to 36%) observed in clinical studies and – in the post-marketing use of various TKIs [2,3,5–8] (Figure 2, Table 2). Usually, this

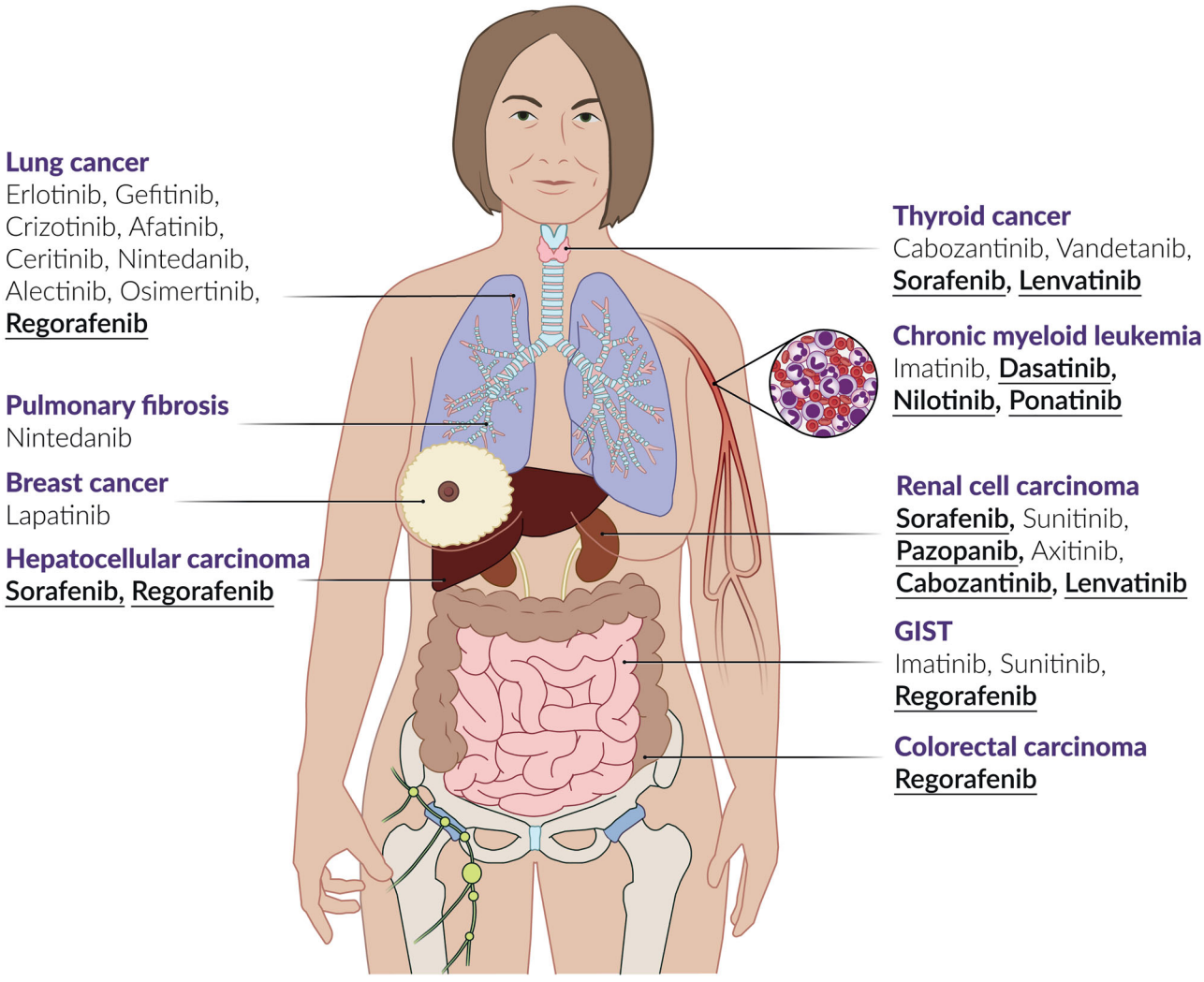

Figure 2. Overview of receptor tyrosine kinase inhibitors and their tested field of application. Bold and underlined receptor tyrosine kinase inhibitors (TKIs): TKIs in which hypocalcemia is reported as a side effect in >10% of cases. GIST: gastrointestinal stromal tumor.

Table 2. Relevant phase 3, randomized, double-blind, placebo-controlled trials with the TKIs lenvatinib and sorafenib regarding hypocalcemia.

References	*N*	TKI	TDD	Cancer	Occurrence of hypocalcemia (%)	Grade ≥3 (%)	Required dose adjustments or disruption (%)
Schlumberger et al. [3]	261	Lenvatinib	24 mg	DTC	12.6	5.0	1.5
Kudo et al. [5]	478	Lenvatinib	8–12 mg	HCC	1.1	0.4	0.2
Escudier et al. [6]	451	Sorafenib	800 mg	RCC	12.0	2.2	NA
Llovet et al. [7]	297	Sorafenib	800 mg	HCC	26.5	2.2	NA
Brose et al. [2]	207	Sorafenib	800 mg	DTC	35.7	10.2	NA
Worden et al. [8]							

DTC: differentiated thyroid carcinoma; HCC: hepatocellular carcinoma; RCC: renal cell carcinoma; NA: not assessed; TDD: total daily dose; TKI: tyrosine kinase inhibitor.

concerned a grades 1 and 2 hypocalcemia (corrected serum Ca^{2+} >1.75 mmol/L). Severe hypocalcemia (grade ≥3; Ca^{2+} <1.75 mmol/L) was reported in 0.4–5.0% and 2.2–10.2% for lenvatinib and sorafenib, respectively [2,3,5–8]. Hypocalcemia occurred more often and more severely in patients with thyroid carcinoma (especially with concomitant primary hypoparathyroidism) compared to patients treated for renal cell- and hepatocellular carcinoma [2,3,5–8]. The lack of sufficient autoregulation for retaining calcium homeostasis could be an explanation. However, a few cases of severe TKI induced hypocalcemia in tumors other than thyroid cancer and in absence of a parathyroid disorder are described in literature [9,10].

TKI induced hypocalcemia can occur at any time during treatment, but it is usually observed four weeks after treatment with sorafenib and 11–28 weeks after treatment with lenvatinib [3]. Of note, our patient already developed severe hypocalcemia two weeks following the start of lenvatinib (Figure 1). The pathophysiological mechanism underlying TKI induced hypocalcemia is not known. Interference of TKIs with intracellular processes that directly or indirectly affect effectors of the calcium homeostasis is suggested to be responsible. Recently, alteration of bone metabolism due to TKI affected kinase expression on osteoblast and osteoclast activity has been described [11]. Furthermore, hypocalcemia can occur due to calcium- or vitamin D deficiency as a

consequence of: (1) reduced liver metabolism in case of liver metastasis or cirrhosis, (2) calcium binding to excess phosphorus in case of TKI induced tumor lysis syndrome or (3) malabsorption due to frequently reported TKI side effects such as vomiting and diarrhea [9].

Our case illustrates that a normal serum calcium level or a stable calcium substitution therapy prior to therapy does not protect against the occurrence of TKI induced hypocalcemia. Hypocalcemia due to TKIs can often be corrected with oral calcium and dose adjustments. Discontinuation of the TKI is usually not necessary [3]. However, it is important to be aware of situations that can induce fluctuations in calcium homeostasis, such as vomiting or diarrhea. In such a case or in case of severe hypocalcemia (grade $\geq$3), temporary interruption of the TKI can be necessary, similar to our case. To the best of our knowledge, permanent discontinuation of lenvatinib due to severe hypocalcemia (grade 4) was only reported in one patient [3].

In an era in which targeted therapies – such as TKIs – are increasingly used, awareness of – most often easily treatable – side effects is crucial in preventing serious complications and maintaining patients' quality of life.

Summary

Hypocalcemia is a not well-known side effect of TKIs, but occurs in up to 10% of the patients with a variable course. Most often, symptoms are vague and could easily be attributed to the underlying condition. A normal serum calcium prior to TKI therapy does not preclude development of hypocalcemia. With timely diagnosis, it can be well corrected with oral supplementation. Early and frequent monitoring of calcium levels following the start of a TKI is mandatory, with special attention to patients who have primary hypoparathyroidism.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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