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CASE REPORT

Acute severe hypocalcaemia after initiation of a selective RET-inhibitor in medullary thyroid cancer

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Abstract

Medullary thyroid cancer (MTC) is a rare subtype of thyroid cancer originating from parafollicular C-cells of the thyroid. Tyrosine kinase inhibitors are used to treat patients with advanced MTC. Selpercatinib is a highly selective RET inhibitor used in the treatment of advanced RET-mutated MTC, having shown higher potency and fewer side effects compared to multikinase inhibitors in clinical trials. As a relatively new drug, its toxicity profile continues to be characterised. This report describes a case of severe acute hypocalcaemia in a 64-year-old male with advanced MTC treated with selpercatinib. The patient, who had stable hypoparathyroidism, experienced acute hypocalcaemia (corrected calcium 1.4 mmol/L) 2 weeks after initiating selpercatinib, requiring hospitalisation for calcium supplementation and monitoring. Selpercatinib was temporarily withheld and later reintroduced at a lower dose, successfully preventing recurrence of hypocalcaemia. Investigations excluded other common or important causes of hypocalcaemia, which led us to conclude that this could be a drug-related adverse event. This case highlights the need for careful monitoring of electrolyte disturbances in patients on selpercatinib, particularly those with pre-existing hypoparathyroidism. Although rare, the development of hypocalcaemia with RET inhibitors may necessitate dose interruptions and adjustments. Our experience has also illustrated that re-challenge with selpercatinib is feasible with appropriate management strategies.

Keywords: medullary thyroid cancer; RET-inhibitor; hypocalcaemia; tyrosine kinase inhibitor

Introduction

Medullary thyroid cancer (MTC) is a rare subtype of thyroid cancer, accounting for 1–2% thyroid cancers. It originates from parafollicular C-cells of the thyroid gland. For patients with advanced disease requiring systemic therapy, the mainstay of therapy is tyrosine kinase inhibitors (TKIs), such as multikinase inhibitors (MKIs), e.g. vandetanib and cabozantinib, or more recently selective RET inhibitors such as selpercatinib or pralsetinib.

The LIBRETTO-001 and -531 trials introduced selpercatinib into the treatment paradigm of advanced MTC (Wirth *et al.* 2020, Hadoux *et al.* 2023). Selpercatinib is a highly selective RET inhibitor, which demonstrates higher potency and a more favourable side-effect profile compared to MKIs. LIBRETTO-001 was a phase 1/2 basket trial, which enrolled 143 patients with *RET*-altered MTC; 88 of whom received selpercatinib as first-line systemic therapy, and 55 received prior treatment with vandetanib and/or cabozantinib (Wirth *et al.* 2020). In the previously treated group, selpercatinib achieved an objective response rate (ORR) of 69% (95% CI, 55–81), and

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at 1 year 86% responses (95% CI, 67–95) were ongoing, and 82% (95% CI, 69–90) of patients were progression-free. In the treatment-naïve group, ORR was 73% (95% CI, 62–82), and at 1 year 91% responses (95% CI, 72–97) were ongoing, and 9% (95% CI, 82–97) remained progression-free.

The follow-up LIBRETTO-531 phase 3 randomised controlled trial investigated selpercatinib in advanced *RET*-mutant MTC and reported an overall response rate of 69.4% (95% CI: 62.4, 75.8) in the selpercatinib group compared to 38.8% (95% CI: 29.1, 49.2) in the control group, who received either cabozantinib or vandetanib (odds ratio 3.7, 95% CI, 2.2, 6.3; $P < 0.0001$) (Hadoux *et al.* 2023). Importantly, at a median follow-up of 15 months, overall survival was better with selpercatinib (HR: 0.374, 95% CI: 0.147, 0.949).

As selpercatinib only entered clinical use in the past few years, data on its toxicities are still being generated. The most common adverse events reported in the studies are hypertension, diarrhoea, elevated liver enzymes, dry mouth and fatigue. Acute severe hypocalcaemia is relatively uncommon and rarely attributed to selpercatinib. None of the seven cases of grade 3–4 hypocalcaemia in LIBRETTO-001 was attributed to selpercatinib. In LIBRETTO-531, two cases of grade 3–4 hypocalcaemia were noted in the selpercatinib group, fewer than the seven in the control group.

Recognition of hypocalcaemia is crucial due to its potentially life-threatening manifestations. Symptoms of hypocalcaemia include seizures, neuromuscular excitability (Trousseau's and Chvostek's signs), tetany, paraesthesia, psychosis and QTc interval prolongation (Hall *et al.* 2022, Anderson *et al.* 2024).

In this case report, we describe a case of acute severe hypocalcaemia in a patient with advanced MTC initiated on selpercatinib on a background of stable hypoparathyroidism. This would be classified as a grade 4 adverse effect, as defined by the Common Terminology Criteria for Adverse Events, version 5.0 (Table 1) (Common Terminology Criteria for Adverse Events CTCAE v5.0 2021 2021).

Table 1 Hypocalcaemia adverse event grades according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE).

Grades	Corrected calcium concentration (mmol/L or mg/dL)
1	2.0–2.1 (8.0 – LLN)
2	1.75 to <2.0 (7.0 to <8.0)
3	1.5 to <1.75 (6.0 to <7.0)
4	<1.5 (<6.0)
5	Death as a result of hypocalcaemia

Abbreviations: LLN, lower limit of normal.

Case description

In 2018, a 64-year-old male presenting with diarrhoea and a neck mass was diagnosed with sporadic MTC (T4 N1b M0) with a somatic Met918Thr *RET* mutation. The disease involved the tracheal wall and oesophagus. He developed hypoparathyroidism post-surgery and was established on 1-alfacalcidol 1 microgram (mcg) once daily (OD) since 2019. He also had type 2 diabetes mellitus, managed on dapagliflozin 10 milligram (mg) OD. Other concomitant medications included atorvastatin 20 mg OD, ramipril 2.5 mg OD and levothyroxine 175 mcg OD, and there were no concerns regarding compliance to medication.

In 2023, his calcitonin had risen to 12,220 pmol/L, associated with recurrent severe diarrhoea, voice hoarseness and stridor. Computed tomography showed a residual tumour invading the wall of the trachea and oesophagus, nodal disease in the mediastinum and multiple lung nodules. He was then referred to our centre for further management. The multidisciplinary team recommended commencing systemic therapy and favoured a selective RET inhibitor as a first-line option, given the risk of catastrophic fistulation of the trachea or oesophagus with potent vascular endothelial growth factor inhibitors such as cabozantinib or vandetanib. At the time, selpercatinib was not funded in the first-line setting, so it was successfully applied for through a named-patient programme.

After receiving approval from both the drug company and the local drugs and therapeutic committee, selpercatinib was initiated at a reduced dose of 120 mg twice daily. This cautious approach was taken in view of potential rapid tumour shrinkage and consequent fistulation.

Immediately before starting selpercatinib, the patient's corrected calcium was 2.02 mmol/L (normal range 2.1–2.5 mmol/L), with a phosphate of 1.34 mmol/L, within the target range for hypoparathyroidism (Bollerslev *et al.* 2015). This calcium level was consistent with historical corrected calcium levels of 2.02 mmol/L and parathyroid hormone (PTH) of 1.9 pmol/L (NR 0.8–5.7) before he was referred to our centre in 2023. The patient had been on a stable dose of 1 mcg of 1-alfacalcidol OD. His baseline serum magnesium levels of 0.78 mmol/L (NR 0.7–1) and thyroid function were within the normal range. The patient tolerated treatment well in the first 2 weeks and saw rapid clinical benefit, notably significant improvement and resolution of diarrhoea.

However, after 2 weeks of treatment, his corrected calcium had fallen to 1.4 mmol/L, which was associated with a raised phosphate of 2.22 mmol/L. PTH was 2.1 pmol/L (NR 0.8–5.7), and vitamin D was 65 nmol/L. 1,25-Dihydroxyvitamin D was 135 pmol/L (NR 43–144). Electrocardiogram showed a QTc interval of 489 ms. The patient reported tingling sensations in his hands in the preceding 24 h as the only symptom.

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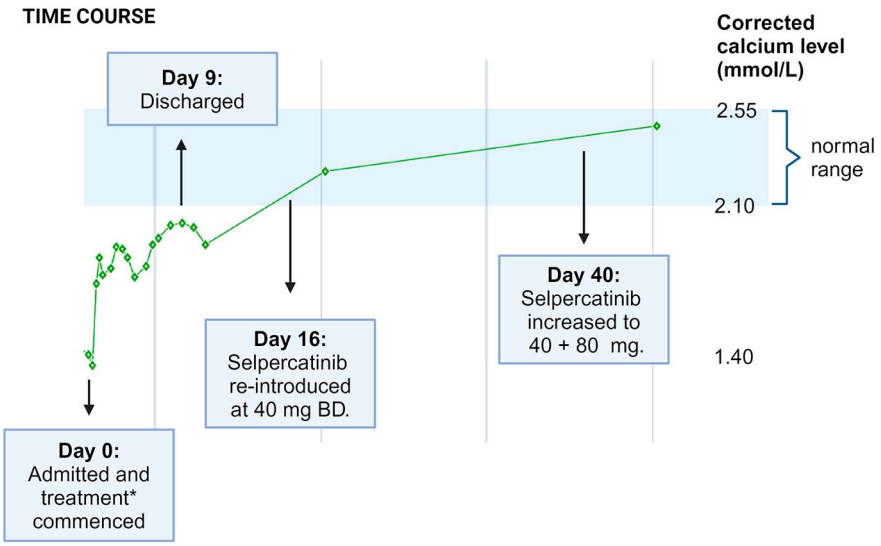

Figure 1

Time course of events following detection of hypocalcaemia.

Tests for bone resorption were grossly normal, with C-terminal telopeptide of type 1 collagen (CTX) of 0.51 mcg/L (NR 0.1–0.5) and procollagen type 1 N-terminal propeptide (P1NP) of 64 mcg/L (NR 20–76). 24 h urine calcium was 1.8 mmol/L.

Management

The patient was admitted immediately and commenced on an intravenous calcium infusion with cardiac monitoring. Due to the profundity of hypocalcaemia, selpercatinib was temporarily withheld on admission. The 1-alfacalcidol dose was increased to 1 microgram twice daily (BD), and he was commenced on oral calcium carbonate 4.5 g three times a day. His corrected calcium improved after 24 h to 1.86 mmol/L, and phosphate fell to 1.8 mmol/L. In the following 2 days, his corrected calcium levels fluctuated between 1.77 and 1.91 mmol/L, with further intravenous therapy. As his calcium levels remained below target and he continued to require intravenous calcium, 1-alfacalcidol was increased to 1.5 micrograms twice daily. When this did not have the desired effect of increasing and sustaining the calcium levels, it was then changed to calcitriol 2 micrograms OD in case the mechanism was inhibition of 25-hydroxylation of vitamin D. These measures improved and maintained the calcium levels at 2.0 mmol/L without intravenous calcium infusions.

He was discharged from hospital after 9 days with his calcium levels monitored twice a week as an outpatient (Fig. 1).

His calcium levels gradually improved and normalised a week later. Selpercatinib was cautiously reintroduced at 40 mg twice daily after 16 days. Once his calcium levels reached 2.5 mmol/L, calcium supplements were gradually weaned off, and his calcitriol dose reduced to 1 microgram daily, with his serum calcium remaining in the normal range. The dose of selpercatinib was gradually increased with close monitoring of his calcium levels.

Since recommencement of selpercatinib, no recurrences of hypocalcaemia have been observed, which is approximately 3 months at the time of writing this report, despite taking a similar dose of vitamin D analogue compared to before the initiation of treatment. His disease continues to respond to selpercatinib with a RECIST partial response.

Discussion

Hypocalcaemia is a relatively common adverse event in patients with MTC treated with TKIs, although reported rates are lower in highly selective RET inhibitors, likely reflecting post-operative hypoparathyroidism in a number of patients following thyroidectomy.

In the LIBRETTO-001 phase 1–2 trial, which investigated selpercatinib in MTC with or without prior treatment with cabozantinib or vandetanib, Wirth *et al.* reported that 3% patients developed grade 1 or 2 hypocalcaemia as an adverse effect attributed to selpercatinib, with no identification of grade 3 or 4 hypocalcaemia attributable to the treatment (Wirth *et al.* 2020).

In the LIBRETTO-531 phase 3 trial, in which 193 MTC patients received selpercatinib versus 98 patients in the control group who received either cabozantinib or vandetanib, 20 (10.4%) patients in the selpercatinib group experienced hypocalcaemia, with just two (1%) patients developing grade ≥3 (Hadoux *et al.* 2023). Hypocalcaemia was also observed in the control group, with 25 (25.8%) of patients having developed any grade and seven (2.2%) ≥ grade 3. The EXAM phase 3 trial investigating cabozantinib in MTC reported

Table 2 Important causes of hypocalcaemia.

Low PTH (Del Rio *et al.* 2019, Bilezikia 2020)	High PTH (Kooh *et al.* 1975, Palumbo *et al.* 2021)	Other (Pepe *et al.* 2020, Schaefer *et al.* 2020)
Postsurgical hypoparathyroidism	Vitamin D deficiency	Pseudohypocalcaemia
Autoimmune	Chronic kidney disease	Acid–base imbalances
Abnormal parathyroid gland development	Pseudohypoparathyroidism	Pancreatitis
Parathyroid gland destruction		Hypo/hypermagnesaemia
		Drugs

a hypocalcaemia rate of 23.8% with 10.7% grade ≥3 (Schlumberger *et al.* 2017).

Phase 3 trials have reported moderate rates of hypocalcaemia in other TKIs used to treat differentiated thyroid cancer, specifically 12.6% on lenvatinib with 5% grade ≥3 (Schlumberger *et al.* 2015) and 35.7% on sorafenib with 10.2% grade ≥3 (Brose *et al.* 2014). Rates of hypocalcaemia with TKI treatment in thyroid cancer seem to be higher compared to other tumour types, pointing towards the predisposing role of post-surgical hypoparathyroidism. A real-world study that included 25 patients with advanced thyroid cancer treated with lenvatinib showed a 24% incidence of hypocalcaemia (De Leo *et al.* 2023), with cases attributed to both PTH-dependent and PTH-independent mechanisms.

In general, hypocalcaemia can be divided into PTH and non-PTH-mediated aetiologies, with post-surgical hypoparathyroidism being the most common cause (Table 2) (Pepe *et al.* 2020). A number of hormones, proteins and serum electrolytes, including PTH, 1,25(OH)-vitamin D, calcitonin, calcium-sensing receptor, serum calcium and phosphorus, play a role in maintaining calcium homeostasis.

In this case, the timing of the development of hypocalcaemia and the lack of an alternative explanation led us to conclude that selpercatinib was the most likely cause of hypocalcaemia.

The pathophysiological mechanism underlying RET inhibitor-induced hypocalcaemia has not been defined. There is evidence to suggest direct effects of KIs via platelet-derived growth factor receptor-mediated activity in osteoblasts and osteoclasts (Berman *et al.* 2006). Deficiencies in calcium or vitamin D may also occur from liver dysfunction, malabsorption or tumour lysis syndrome, resulting in the binding of calcium with excess phosphorus (Lodish 2013, Matuszkiewicz-Rowinska & Malyszko 2020), and notably, we observed an increase in phosphate at the time of the initial presentation, but no other features of tumour lysis syndrome were observed.

Notably, our patient displayed partial hypoparathyroidism, with a detectable but inappropriately normal PTH with low calcium a year before starting selpercatinib. PTH was unchanged when presenting with acute severe hypocalcaemia, suggesting suppression of PTH release was not the explanation. It is striking that the hypocalcaemia occurred with resolution of the diarrhoea, so it is hard to explain these changes due to malabsorption.

A peculiarity of this case was that we observed an improvement in our patient's calcium levels on switching 1-alfacalcidol to calcitriol, which was done initially in case the mechanism was inhibition of 25-alpha-hydroxylation. However, as the normal level of 1,25(OH)-vitamin D excludes inhibition of 25-alpha-hydroxylation as a cause, meaning the improvement in calcium levels observed after this switch may have been coincidental.

Furthermore, we did not observe any change in bone markers to suggest an alteration in bone turnover. Thus, the mechanism of this acute severe hypocalcaemia following selpercatinib initiation in a patient with prior well-controlled post-operative hypoparathyroidism remains unknown.

Conclusion

This case highlights the importance of vigilance in electrolyte disturbances in patients treated with selpercatinib, the immediate and short to medium-term management of hypocalcaemia in this context and that a re-challenge of selpercatinib can be achieved safely.

Declaration of interest

Kee Howe Wong – advisory work for Eli Lilly.

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Patient consent

Patient written consent to submit the case report for publication was obtained. Eli Lilly's permission to publish was obtained as the patient received the drug on a compassionate access programme.

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