CASE REPORT

Unusual increase in carcinoembryonic antigen despite response to selpercatinib in two patients with medullary thyroid cancer

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Abstract

Introduction: Serum calcitonin (CT) and carcinoembryonic antigen (CEA) are valuable tumour markers in patients with medullary thyroid carcinoma (MTC). Both markers most often evolve in parallel after treatment. Selpercatinib (LOXO-292) is a highly selective *RET* kinase inhibitor indicated in advanced *RET*-mutant MTC patients.
Cases presentation: In this study, we report two observations of *RET*-mutant progressive metastatic and symptomatic MTC patients who were treated with selpercatinib. Patient 1, a 61-year-old man, presented dyspnoea and diarrhoea at selpercatinib initiation with large neck lymph nodes and lung metastases. Patient 2, a 76-year-old man, had acute discomfort with flush and diarrhoea, with small but diffuse bone and liver disease. Both patients had an objective tumour response with rapid clinical improvement and RECIST 1.1 response (−90%) in patient 1. A rapid dramatic decrease in CT level was observed in both patients (−99% in both patients), while CEA levels gradually and sustainably increased after selpercatinib initiation (+207% at cycle 15 in patient 1 and + 835% at cycle 14 in patient 2). In both patients, ^{18}FDG PET/CT did not show any abnormal uptake that could explain the CEA increase. Colonoscopy and oesogastric fibroscopy showed colonic polyposis with mild oesophagitis and gastritis in patient 1 and were normal in patient 2.
Conclusion: These observations show an unusual and lasting increase in serum CEA in two MTC patients who exhibited an objective tumour response to selpercatinib. The mechanism behind this unexpected rise in CEA level remains unknown. The frequency of this evolving profile will be determined in further phase III studies.

Key Words

- medullary thyroid cancer
- carcinoembryonic antigen
- calcitonin

Established facts

- Serum CT and CEA are valuable tumour markers in patients with MTC, which most often decrease in parallel after the initiation of efficient treatment.
- Selpercatinib (LOXO-292) is a highly selective *RET* kinase inhibitor indicated in advanced *RET*-mutant MTC patients.

Novel insights

- An unusual and lasting increase in serum CEA, together with a dramatic decrease of CT, may be observed in MTC patients who show an objective tumour response to selpercatinib.

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Introduction

Serum tumour markers are important tools in the management of patients with medullary thyroid carcinoma (MTC) (1). Serum calcitonin (CT) and carcinoembryonic antigen (CEA) are produced by neoplastic C-cells, and their serum concentrations are generally related to tumour burden (2). Nevertheless, while CT is relatively specific for MTC, CEA is not. Other malignant tumours such as colon, rectum or lung carcinomas, and other benign conditions can also lead to increased CEA levels, including smoking, infections, inflammatory bowel disease, pancreatitis, and cirrhosis of the liver. A mild increase in CEA is also observed in benign tumours in the same organs, in which a more pronounced increased level of CEA indicates cancer. After initial surgery of MTC, CT and, to a lesser extent, CEA are useful for the diagnosis of residual disease. Given the longer half-life of CEA compared to CT, it is necessary to wait longer after surgery to measure CEA compared with CT. In patients with persistent disease, serial measurements of CT and CEA during follow-up allow their doubling time (DT) to be determined and help predict tumour progression and survival (2, 3). Both markers are related to tumour burden and they often evolve in parallel with similar DT, but in some patients, serum CEA can increase while CT does not, suggesting dedifferentiation and aggressive outcome (4).

Selpercatinib (LOXO-292) is a novel, highly selective, small-molecule *RET* kinase inhibitor which recently proved as highly efficient and well-tolerated in phase 1–2 trial including *RET*-mutant MTC patients. The tumour response rate according to RECIST 1.1 was 69% in the 55 patients who had previously received vandetanib, cabozantinib, or both and 73% in the 88 patients who had not. The percentages of biochemical response were 91% (95% CI, 80–97) with respect to CT level and 66% (95% CI, 52–79) for CEA level (5).

In February 2021, selpercatinib (Retsevmo®) was approved in Europe as monotherapy for the treatment of patients with advanced *RET*-mutant MTC who require systemic therapy following first-line treatment with cabozantinib and/or vandetanib. Since 2019, selpercatinib has been available in France as part of a compassionate protocol by Loxo/Eli Lilly company and has a temporary authorization for nominative use granted by the National Agency for the Safety of Drugs and Health Products (in French, ANSM). Patients eligible for compassionate use of selpercatinib must have progressed on or have been intolerant to standard therapy such as vandetanib, cabozantinib, or both, or have contraindications for these drugs, and not be eligible for therapeutic trials. Two *RET*-mutant MTC patients were treated by selpercatinib in this setting. They exhibited a rapid clinical and radiological response, with an expected dramatic decrease in serum CT levels but a progressive and unusual increase in serum CEA was not explained by the detection of another cancer or by the onset of any benign disorder known to increase CEA levels. These two observations underline the need to carefully analyse the evolution of both serum CT and CEA levels after selpercatinib treatment in addition to imaging.

Case reports

Case report 1

A 61-year-old man was diagnosed with MTC in April 2017 due to dysphonia. He underwent a total thyroidectomy with neck central and lateral lymph node dissection showing a 55-mm MTC with 12 metastatic lymph nodes (pT3N1b). Postoperative CEA level was 95 µg/L. He was then referred to the department of nuclear medicine and endocrine oncology (Gustave Roussy, Villejuif, France). Vandetanib was initiated in January 2018 for progressive lung metastases but was withdrawn in April 2018 for progressive disease. Chemotherapy with dacarbazine and fluorouracil was given from June to September 2018. Somatic *RET* analysis showed a *RET* M918T mutation. Pralsetinib was initiated in November 2018 in the framework of a trial with a tumour response as early as January 2019 but was withdrawn because of grade IV toxicity with peritonitis and pneumoperitoneum due to diverticulitis. Under pralsetinib, CT levels dropped from 406 to 18 ng/L and CEA levels from 279 to 92 µg/L (shown in Fig. 1). After abdominal surgery performed in March 2019 and clinical recovery, the patient presented dyspnoea and diarrhoea and showed progressive disease in the neck lymph nodes and lung metastases. After obtaining authorization from Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM) and the agreement of Loxo/Eli Lilly, selpercatinib 160 mg BID was initiated on 28 August 2019. Before treatment initiation, ECOG score status was 2, and hematologic, hepatic, and renal functions were normal. Pre-treatment CT level was 1080 ng/L (N < 10; ECL, Cobas 6000, Roche) and CEA 165 µg/L (n < 7; ECL, Cobas 6000, Roche). A clinical response was observed from day 14 of the first cycle of treatment (C1), with a decrease in dyspnoea and diarrhoea and in the size of the palpable lymph nodes. At cycle 2, CT scan showed a RECIST 1.1 tumour response (−39%) associated with a dramatic decrease in CT level to 27 ng/L and a stable CEA level at 149 µg/L. The patient remained on this

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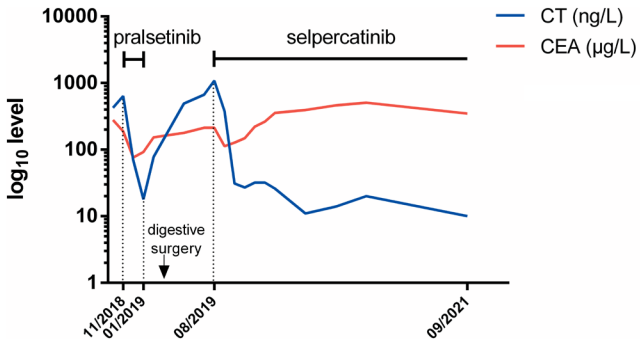

Figure 1
Outcome of logarithmic values of serum calcitonin (CT) and carcinoembryonic antigen (CEA) before and after treatment with pralsetinib and then with selpercatinib in patient 1.

treatment with excellent tolerance. Further follow-up showed the pursuit of the tumour response with the best tumour response of −90% obtained at C10 in June 2020 (shown in Fig. 2). At the same time, CT level was 11 ng/L (−99%/baseline) with a further increase in CEA level to 463 µg/L (+180%). No other tumour was visible on the CT scan from neck to pelvis. ^{18}FDG PET/CT did not show any abnormal uptake that could explain the increase in CEA level. Liver enzymes remained normal during follow-up in this patient who did not have alcohol abuse. Colonoscopy and oesogastric fibroscopy revealed the presence of colonic polyposis corresponding to low-grade dysplastic tubular adenoma on pathology and mild esophagitis and gastritis in September 2020. No other cause of the increase in CEA level was observed. The CEA peak was reached at C15 (+207%). At the last follow-up in September 2021 (C25), the CEA level was 349 µg/L and CT 10 ng/L while the morphological response was maintained.

Case report 2

A 76-year-old man was referred in May 2016 to the department of nuclear medicine and thyroid unit (Centre François Baclesse, Caen, France) for postsurgical management of MTC. The patient had undergone total thyroidectomy in April 2016 for a multinodular goitre without prior CT or CEA measurement. Pathology demonstrated a bilateral MTC classified as pT1bNXM0. No genomic *RET* mutation was found, but this sporadic tumour was shown to present a somatic *RET* mutation, namely C630R (FoundationOne™, NGS). On 31 May 2016, postsurgical CT level was 196 ng/L (n < 9.5; ECL, Cobas 6000, Roche) and CEA level 11.5 µg/L (n < 4.7; ECL, Cobas 6000, Roche). In January 2017, CT level had increased to 399 ng/L, while CEA level remained subnormal at 6.1 µg/L. At this time, MRI detected 2-cm liver lesions and a small bone lesion of the pelvis. Given the absence of symptoms and low tumour burden, active surveillance was advised. In June 2017, CT and CEA levels were 1097 ng/L and 9.5 µg/L, respectively, and MRI detected new small pelvic bone lesions, so treatment with denosumab was initiated. The symptoms were slowly but gradually enriched with the onset of acute discomfort including back pain, flush, and bowel urgency. The diarrhoea became more frequent at about three stools per day in June 2019. At this time, MRI showed progressive bone disease on the spine and pelvis without dangerous lesions and relatively stable small (<1 cm) liver lesions.

After multidisciplinary staff and oncogeriatric advice, vandetanib 300 mg/day was initiated on 8 August 2019.

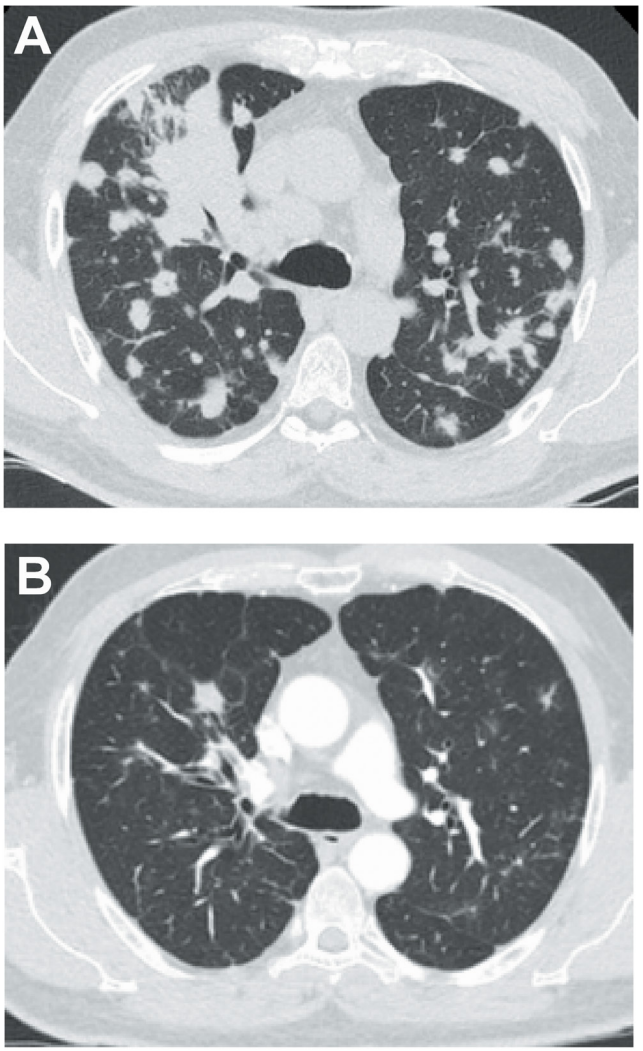

Figure 2
Outcome of lung metastases after selpercatinib in patient 1. Compared to pre-treatment CT scan in August 2019 (A), CT performed in June 2020 (B) showed the best tumour response of −90% according to RECIST.

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Just before initiation, CT and CEA levels were 25,251 ng/L and 72.4 µg/L, respectively, with a CT doubling time estimated at 6 months (shown in Fig. 3). Although the disease was considered clinically, biologically, and radiologically stable, CT scan performed on 2 January 2020 demonstrated the presence of a small digestive perforation in the caecum anterior to a diverticulum responsible for a fistula in the bladder (pneumaturia). Vandetanib was immediately withdrawn. As the perforation did not resolve spontaneously, the patient was operated on 13 March 2020 (laparotomy with caecum ablation and sigmoid resection with colorectal anastomosis and resection of bladder spot). The postsurgical period was uneventful.

At the end of April 2020, the digestive perforation was clinically resolved with the absence of deep abscess or colo-bladder fistula on CT scan. Hematologic, hepatic, and renal functions were normal with an ECOG 1 status. After obtaining authorization from the ANSM and the agreement of Loxo/Eli Lilly, selpercatinib 160 mg BID was initiated on 8 May 2020. Pre-treatment CT level was 48,965 ng/L and CEA was 142 µg/L. On 12 May 2020, the patient reported that the acute discomfort and diarrhoea had abated rapidly and completely. Furthermore, CT level dramatically decreased to 3725 ng/L on 19 May 2020 and to a nadir of 85 ng/L (−99%/baseline) at C14 in July 2021. At the same time, CEA level rose to 156 µg/L on May 19 and reached a peak of 1328 µg/L (+835%) at C14 (shown in Fig. 3). RECIST criteria could not be applied for tumour evaluation. Nevertheless, CT scan and MRI showed that unmeasurable diffuse bone lesions and infracentimetric liver lesions were stable. Tolerance was excellent except for a moderate increase in creatinine level (grade 1) and liver enzymes (grade 1) at C2 (aspartate aminotransferase (and alanine aminotransferase 2.5 × upper normal limit with normal alkaline phosphatase) that spontaneously resolved at C4. The patient did not have excessive alcohol consumption. An ^{18}FDG PET/CT scan in September 2020 did not show any hypermetabolic lesion in the digestive tract or lungs that could explain the CEA increase. Colonoscopy and oesogastric fibroscopy were normal in October 2020. At the last follow-up visit (C16, September 2021), the clinical response was maintained with a CEA level at 1076 µg/L and CT at 111 ng/L.

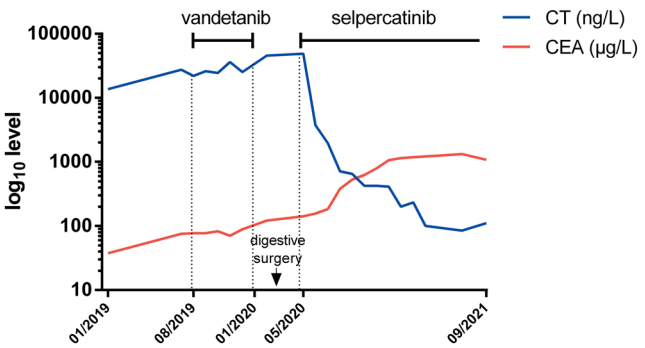

Figure 3
Outcome of logarithmic values of serum calcitonin (CT) and carcinoembryonic antigen (CEA) before and after treatment with vandetanib and then with selpercatinib in patient 2.

Discussion

An unusual increase in serum CEA level occurred in two sporadic *RET*-mutated MTC patients who presented an objective tumour response to selpercatinib. In both cases, the CEA increase contrasted with the rapid dramatic decrease in CT level and rapid clinical improvement. While this response was confirmed by RECIST 1.1 evaluation in patient 1 (−90%), no such evaluation was possible in patient 2 owing to small and diffuse bone and liver lesions. To our knowledge, this uncommon evolving profile of the two tumour markers has not been reported so far, either after selpercatinib or other anti-tumoural treatments.

The increase in CEA levels after selpercatinib was not related to the occurrence of another malignant tumour that would have secreted CEA. In both cases, digestive (colon and stomach) carcinomas were ruled out by endoscopic investigations, and the ^{18}FDG-PET/CT did not show any hypermetabolic lesions, particularly in the lungs, which would have suggested another primary tumour. Furthermore, it was not linked to liver toxicity or excessive alcohol consumption.

In the report of the phase 1–2 study (5), Supplementary Figs 5 and 6 showed that 7 out of 53 patients experienced a CEA increase compared with 2 out of 54 patients who had increased CT after selpercatinib. However, neither individual values of CT and CEA were available for each patient nor their correlation with outcome. Hence, it is not possible to know whether the profile of both tumour markers observed in that cohort of patients evolved similarly.

What could the mechanisms be behind this apparently paradoxical rise in CEA level? One hypothesis could be cell lysis with the progressive release of cell components. The release of CEA expressed on the surface of the membranes might be greater than that of CT, which is located mainly inside the neoplastic cell. Serial measurements of a cell lysis marker such as cytokeratin could throw light on this issue. However, the CEA level gradually increased even after patient 1 reached a 90% tumour response, which

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argues against this hypothesis. Another hypothesis is that selpercatinib selects neoplastic MTC cells expressing CEA with a longer half-life of CEA in comparison to CT, but this does not seem to apply to patients with persistent tumour response. Immunohistochemical studies on tumour biopsy before and after selpercatinib, as well as *in vitro* studies on MTC models, might be informative. Interestingly, a transient increase in CEA level, known as CEA surge, has been observed in metastatic colorectal cancer patients treated with chemotherapy, particularly those receiving leucovorin–fluorouracil–oxaliplatin regimens (FOLFOX), and is often associated with a clinical benefit (6, 7). A putative explanation is an increase in CEA expression in response to interferon-alpha and -gamma and interleukin-6. However, it should be noted that CEA surges after FOLFOX lasted a maximum of 4 months, while the CEA increase in the cases presented here was observed for more than a year. Another hypothesis is that non-specific rises in CEA level related to benign digestive morbidities occurred in both patients. Indeed, patient 1 experienced peritonitis due to diverticulitis treated by surgery and had benign disorders that could be associated to mild elevations in CEA, while patient 2 had colic perforation and surgery, respectively, 7 and 2 months before starting selpercatinib. The relatively long half-life of CEA could explain the delay in timing between any type of abdominal injury and when serum CEA rises. However, it is difficult to imagine a continuing rise in CEA more than a year after digestive surgery as in patient 2, who had no digestive symptomatology. In addition, CEA levels generally return to normal in patients operated on for localized colon cancer and do not continue to increase after this procedure.

In conclusion, clinicians should be aware that CEA levels can increase in some patients after successful treatment of *RET*-mutant MTC patients with selpercatinib. The frequency of this evolving profile will be determined in further phase III studies. This might lead to limiting the biological follow-up of patients with selpercatinib to the measurement of CT levels only.

Declaration of interest

Stéphane Bardet has participated to scientific advisory boards organized by Eisai and Eli Lilly and Sophie Leboulleux to scientific advisory boards by Eisai, Eli Lilly and Bayer. Renaud Ciappuccini and Livia Lamartina have no conflicts of interest to declare.

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Statement of ethics

Written informed consent was obtained from the patients for publication of this case report and any accompanying images.

Author contribution statement

Stéphane Bardet and Sophie Leboulleux collected data and wrote the manuscript. Renaud Ciappuccini designed the figures and reviewed the manuscript. Livia Lamartina contributed to data collection and reviewed the manuscript.

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