

Case Report

Durable Disease Control by RET Inhibitor Selpercatinib in a Heavily Pre-Treated RET Fusion-Positive Papillary Thyroid Cancer

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Keywords

Selpercatinib · RET fusion · Papillary thyroid cancer · Durable disease control

Abstract

Standard treatment for unresectable papillary thyroid carcinoma (PTC) is a multi-kinase inhibitor, including lenvatinib and sorafenib. Rearranged during transfection (*RET*) fusions are found in approximately 10% of PTC. Here, we present a case of metastatic RET fusion-positive PTC with long-term disease control by selective RET inhibition. A 72-year-old woman with PTC and multiple lymph nodes and lung metastases progressed after initial lenvatinib and subsequent sorafenib treatment. Reintroduction of lenvatinib led to marked tumour shrinkage. During the rechallenge with lenvatinib, molecular screening of the tumour specimen revealed a *CCDC6-RET* gene fusion. The patient was enrolled in a phase 1/2 trial of the potent and specific RET inhibitor selpercatinib. All target and non-target lesions responded to selpercatinib in parallel with a remarkable decrease in serum thyroglobulin levels. Although a new lesion appeared in the right adrenal gland 14 months after the initiation of selpercatinib, ongoing stable disease was observed in all lesions over 28 months, including the new adrenal lesion. Adverse events included grade 3 fatigue, grade 2 anorexia, and grade 4 thrombocytopenia but were easily manageable by suspension and dose reduction of selpercatinib. Selective kinase inhibition with selpercatinib provides RET fusion-positive PTC with clinical benefits, even in patients heavily pre-treated with multi-kinase inhibitors. This case supports the importance of routine molecular profiling in patients with PTC to identify uncommon but actionable gene alterations, such as RET gene fusions.

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Introduction

The standard treatment for unresectable differentiated thyroid carcinoma (DTC) is a multi-kinase inhibitor (MKI), including lenvatinib and sorafenib, according to several clinical guidelines [1–3]. However, no standard of care has been recommended for DTC that is refractory to either targeted therapy.

Recent utilization of comprehensive molecular profiling has revealed that activation of a specific druggable driver oncogene is involved in the oncogenesis of a distinct subgroup of cancers. Of these, genetic alterations of the rearranged during transfection (RET) gene are important targets in several cancers, including thyroid cancer [4–6]. All patients with hereditary medullary thyroid cancer (MTC) had an RET germline mutation. Sporadic MTC is associated with a somatic RET mutation in approximately 40–50% of cases [7]. In contrast, RET fusions are found in fewer than 10% of DTC in non-MTCs [8, 9].

Selpercatinib (LOXO-292) is a highly selective, small-molecule RET kinase inhibitor. Recently, selpercatinib was approved for treating advanced RET-mutated MTC, advanced RET fusion-positive thyroid cancer requiring systemic therapy, and RET fusion-positive non-small cell lung cancer by the US Food and Drug Administration in 2020 and by the Pharmaceuticals and Medical Devices Agency in 2021. Herein, we report a case of RET fusion-positive heavily pre-treated papillary thyroid carcinoma (PTC) that showed durable disease control with selpercatinib in LIBRETTO-001, a phase 1–2 clinical trial [10].

Case Report

A 72-year-old woman presented with a 1-month history of hoarseness and anterior swelling of the neck since December 2015. Fine-needle aspiration cytology of the thyroid revealed PTC in January 2016. Computed tomography (CT) imaging revealed a heterogeneously enhanced thyroid tumour that constricted the trachea, multiple lymph nodes, and lung metastases. Because the tumour was deemed inoperable owing to severe invasion of the sternum manubrium, lenvatinib was immediately initiated at 24 mg/day in February 2016. Three months after lenvatinib initiation, a partial response was achieved. During the 3 years of disease control, dose reduction of lenvatinib to 4 mg every other day was required because of hypertension and proteinuria.

In February 2019, a new lesion emerged as a subcutaneous nodule on her head. Histological examination of a surgically resected specimen of this nodule revealed that the tumour was composed primarily of atypical papillary cells. Immunohistochemical staining was positive for TTF-1 and thyroglobulin (Tg), suggesting that this lesion was compatible with PTC metastasis. Simultaneously, a CT scan of the primary lesion suggested that the lesions were refractory to lenvatinib.

Although treatment was switched to sorafenib in April 2019, the tumour enlarged with increased uptake of contrast enhancement on CT in July 2019, suggesting progressive disease (PD). Because the tumours were considered refractory to standard therapy by MKIs, tumour specimens from a subcutaneous nodule on the head were subjected to the FoundationOne CDx comprehensive cancer genomic profiling test. While waiting for molecular testing results, salvage lenvatinib (8 mg/day) was rechallenged. Three months after the reintroduction of lenvatinib, marked shrinkage with decreased contrast enhancement in the primary tumour, and a decrease in serum Tg level was observed [11].

FoundationOne CDx analysis revealed that the tumour was negative for a BRAF mutation but harboured CCDC6-RET gene fusion and putatively pathogenic variants in EPHA3 (R750Q), RBM10 (E750 fs*46), and the TERT promoter (C228T; c.-124C>T). As the genomic profiling test revealed RET fusion, the patient stopped treatment with lenvatinib and provided written

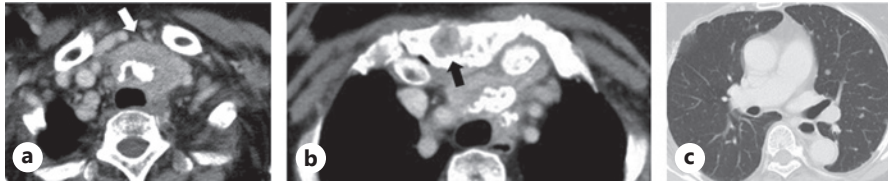


Fig. 1. Computed tomography (CT) imaging of the patient's thyroid (a), mediastinal bone lesion (b), and pulmonary lesions (c) at baseline.

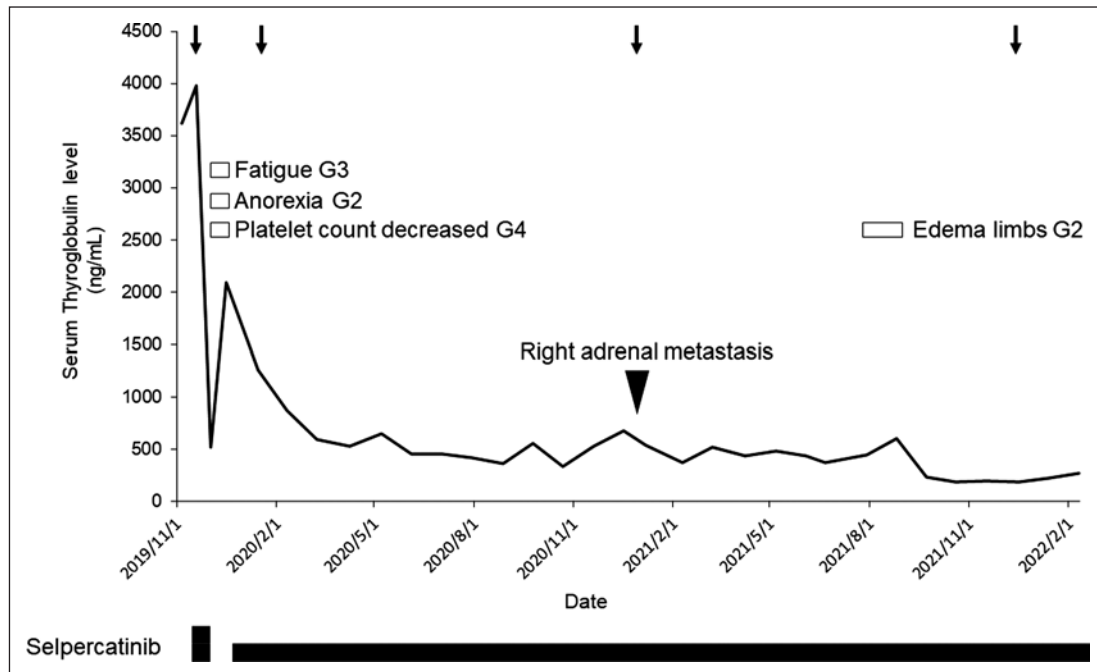


Fig. 2. Treatment course and serum thyroglobulin level. The timing of CT scan (referring to the respective panels in Fig. 1, 3–5) is shown by black arrows (baseline, week 8, week 60, and week 108, from left side).

informed consent for participation in the LOXO-RET-17001 (NCT03157128) study. Brain magnetic resonance imaging for screening showed multiple small skull metastases and a single small brain metastasis, in addition to primary (Fig. 1a), mediastinal bone (Fig. 1b), and pulmonary lesions (Fig. 1c).

She received the recommended phase 2 dose of 160 mg selpercatinib orally twice-daily in November 2019. Figure 2 shows the treatment course and the serum Tg levels (Fig. 2). Although no serious adverse events were observed, the patient developed grade 3 fatigue, grade 2 anorexia, and grade 4 thrombocytopenia on day 16 of cycle 1, which required a blood transfusion and suspension of selpercatinib. A reduced dose of selpercatinib (80 mg orally twice daily) was administered from cycle 2. Serum Tg levels decreased remarkably, although transient rebound was observed following the interruption of selpercatinib in cycle 1. CT scan after the first 8 weeks of treatment showed a 24.6% decrease in the sum of the measurable lesions according to Response Evaluation Criteria in Solid Tumours version 1.1 (Fig. 3a, b). Multiple pulmonary metastases had almost completely disappeared by week 8 (Fig. 3c). Durable disease control has been achieved in all target and non-target lesions, in parallel with a stable Tg level.



Fig. 3. CT imaging of the patient's thyroid (**a**), mediastinal bone lesion (**b**), and pulmonary lesions (**c**) at week 8 of selpercatinib therapy showing tumour shrinkage.

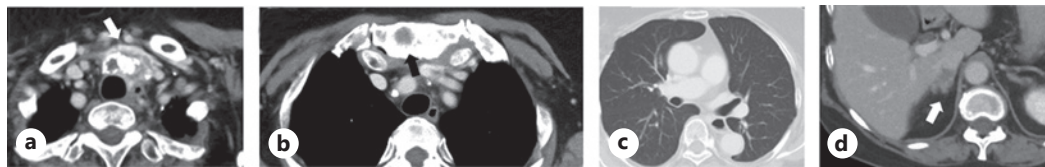


Fig. 4. CT imaging of the patient's thyroid (**a**), mediastinal bone lesion (**b**), and pulmonary lesions (**c**) at week 60 of selpercatinib therapy showing stable disease. A new lesion in right adrenal metastasis appeared at week 60 (**d**).

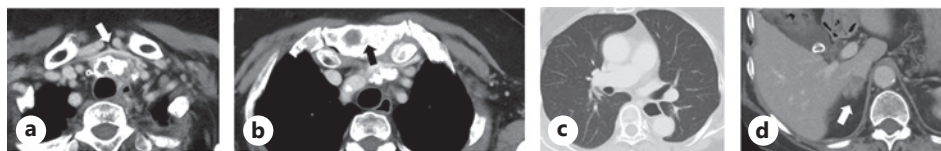


Fig. 5. CT imaging of the patient's thyroid (**a**), mediastinal bone lesion (**b**), and pulmonary lesions (**c**) at week 108 of selpercatinib therapy showing stable disease. A new lesion in right adrenal metastasis was stable (**d**).

In January 2021, a CT scan detected a metastatic lesion in the right adrenal gland (Fig. 4d, Fig. 2), although other lesions remained stable (Fig. 4a–c). According to the Response Evaluation Criteria in Solid Tumours version 1.1, the appearance of new lesions was defined as PD. Because she was clinically stable and the study protocol permitted the continuation of the same treatment beyond PD, we decided to continue selpercatinib.

She tolerated 80 mg selpercatinib orally twice-daily as of April 2022. All treatment-related adverse events were grade 2 oedema, grade 1 rash, dysgeusia, and palmar-plantar erythrodysesthesia syndrome according to the Common Terminology Criteria for Adverse Events version 5. The latest CT scans after 28 months of treatment revealed ongoing stable disease in all lesions, including new adrenal lesions (Fig. 5a–c, d).

Discussion

We report the case of an adult patient with PTC harbouring a *CCDC6-RET* gene fusion who responded to selpercatinib and achieved durable disease control for over 2 years. This case is of significance because a highly selective RET inhibitor as the 4th line regimen has been clinically beneficial despite a prior treatment history of multiple MKIs of lenvatinib and sorafenib.

RET gene fusions are not common and present in 10–20% of PTCs [9, 12] and 6% of poorly differentiated thyroid cancers [13]. Although the incidence of RET gene fusions is

higher in younger versus older patients with PTC and in those with a history of radiation exposure [14–16], this 72-year-old patient without prior radioactive iodine ablation had RET gene fusion in the PTC cells of a subcutaneous metastasis at the time of disease progression on the 1st line lenvatinib. Importantly, RET fusion proteins are oncogenic drivers in a subset of patients with PTC [17, 18], and RET fusion-positive PTC confers an aggressive phenotype [19]. In contrast, no *BRAF* mutation was detected in this case. Activating somatic alterations in the mitogen-activated protein kinase (MAPK) signalling pathway, including point mutations in *BRAF* and *RAS*, are almost always mutually exclusive with those in *RET* and *NTRK1* tyrosine kinases [9, 20]. Furthermore, a point mutation in the TERT promoter identified in this patient was associated with disease aggressiveness and poor prognosis in PTCs [21, 22]. Therefore, our molecular data, together with disease control by the selective RET inhibitor, suggest that this patient's PTC is at least partially driven by the identified CCDC6-RET gene fusion as well as by TERT mutation.

The safety and efficacy of selpercatinib have been evaluated in RET-altered thyroid cancers using LIBRETTO-001 [10]. However, the majority of patients with thyroid cancer enrolled in Libretto-001 had RET-mutant MTC, with the objective response rate of approximately 70%, regardless of the number of previous MKI therapies received. Previous case reports on selpercatinib in thyroid cancers have mainly focused on MTCs [23–26] and ATC [27]. Although selpercatinib activity was also observed in patients with RET fusion-positive thyroid cancer with other histology in LIBRETTO-001, the sample size of each histology is small, and precise information on the efficacy of selpercatinib for PTC is still limited [10].

In the present case, selpercatinib treatment was maintained after a new adrenal metastasis was noted, as adverse events were minimal and other lesions in the thyroid, mediastinal bone, skull, and lung could be controlled by selpercatinib. Accordingly, selpercatinib treatment beyond PD lasted for more than 14 months. Brain metastasis is also durably controlled, which is consistent with a report on the activity of selpercatinib in patients with metastasis in the central nervous system [23].

Treatment options are limited for patients with DTC who develop resistance or intolerance to sorafenib and lenvatinib. First, rechallenge with initially administered MKIs may be efficacious after a drug holiday or intervening therapy, as has been reported for thyroid cancer [11, 28, 29] or gastrointestinal stromal tumours [30]. Indeed, this patient experienced re-sensitization by rechallenged lenvatinib after a 7-month interval between the interruption of initial lenvatinib and its reintroduction. Recently, cabozantinib has shown clinical benefits in patients who have been previously treated with lenvatinib, sorafenib, or both [31]. Cabozantinib is an inhibitor of several tyrosine kinases that mediate tumour growth and angiogenesis in DTC, including VEGFR2, AXL, MET, and RET [32]. Third, the implementation of molecular screening for either somatic *RET* mutation or RET fusion may be recommended to identify patients who may benefit from RET inhibitors, even non-MTC patients.

A question is raised on whether multi-kinase inhibition or selective kinase inhibition should be performed in the frontline in patients with RET driver genes. To date, there is little insight into the optimal treatment sequence for patients with RET fusion-positive PTC. For instance, upfront tyrosine kinase inhibitors targeting specific driver genes are the standard of care in non-small cell lung cancer with EGFR mutations or ALK/ROS1 fusion [33]. Furthermore, while the tumours in this case were not refractory to rechallenged lenvatinib, selpercatinib showed a clinical benefit. These findings may support the use of upfront selective RET inhibitors prior to MKIs. Because RET fusion proteins are key targetable oncogenic drivers in a part of PTCs, RET screening should be performed as early as possible to initiate upfront selective kinase inhibition by selpercatinib. Acquired resistance to RET inhibitors may be overcome by subsequent salvage MKIs. On the other hand, upfront MKIs can act against different

and broad pathways, although multi-targeted therapy against RET-altered cancers may lead to off-target toxicity despite limited clinical efficacy.

Conclusion

In conclusion, durable disease control was achieved with selpercatinib in patients with PTC harbouring a CCDC6-RET gene fusion who were heavily pre-treated with lenvatinib and sorafenib. Because selective kinase inhibition with selpercatinib provides RET fusion-positive PTC with clinical benefits, routine clinical detection of somatic RET alterations may be highly recommended. Further discussion of the optimal sequences of MKIs and selective RET inhibitors is required.

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Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

Dr. Yokota serves an advisory role in Merck Biopharma, MSD, and Rakuten Medical; has received lecture fees from Merck Biopharma, Ono Pharmaceutical Co., Ltd., Bristol-Myers Squibb, AstraZeneca, Chugai, MSD, and Eisai; and has received grants from AstraZeneca, Chugai Pharma, Syneos Health, Lilly, Incyte, Novartis, and GlaxoSmithKline.

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Author Contributions

Tomoya Yokota collected data, wrote the manuscript, designed the figures, and reviewed the manuscript.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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