Sustained Response with Dose Reduced Selpercatinib in a Pediatric Patient with Metastatic NCOA4-RET Fusion Papillary Thyroid Carcinoma

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Abstract

Understanding the molecular landscape of papillary thyroid carcinoma (PTC), the most common thyroid cancer in children, creates additional therapeutic approaches. *RET* gene rearrangements are observed in pediatric PTC and selective inhibition of RET is now possible with specific tyrosine kinase inhibitors designed to target diverse *RET*-activating mutations. We present a 13-year-old female with radioactive iodine-refractory metastatic PTC, found to harbor a *NCOA4-RET* fusion, who responded to treatment with selpercatinib with elimination of supplemental oxygen need, marked reduction in pulmonary nodules and mediastinal lymphadenopathy, and substantial improvement in thyroglobulin levels. Response was maintained despite 2 dose reductions for possibly-related weight gain.

Introduction

Papillary thyroid carcinoma (PTC) is the most common type of differentiated thyroid cancer (DTC) in children and adolescents, accounting for approximately 90% of thyroid cancers in pediatric patients.[1] Unlike adults, pediatric patients with PTC often present with advanced, metastatic disease but tend to favorably respond to total thyroidectomy with lymph node dissection followed by radioactive iodine (RAI) therapy.[2] For the subset of patients who become refractory to RAI treatment or have RAI non-avid disease, molecularly targeted kinase inhibitors may provide a medical therapeutic option.[1] Furthermore, children with metastatic or relapsed/refractory PTC frequently harbor clinically relevant genomic alterations, with *RET* fusions most commonly observed.[1,3,4] A review of approximately 2000 pediatric patients with PTC revealed *RET* fusions in 25-30% of sporadic cases (range 14-55%).[1]

Selpercatinib (LOXO-292) is a first-in-class, highly selective, ATP-competitive, small-molecule RET kinase inhibitor. In LIBRETTO-001, a phase 1/2 clinical trial evaluating selpercatinib in *RET* -mutant medullary thyroid cancer and *RET* fusion-positive thyroid cancer, 79% of 19 adult patients with *RET* fusion-positive previously treated thyroid cancer had an objective response with activity seen across histologic subtypes, with durable antitumor activity.[5] In May 2020, the Food and Drug Administration granted accelerated approval to selpercatinib for patients [?]12 years of age with advanced or metastatic *RET*fusion-positive thyroid cancer who require systemic therapy and are RAI-refractory when RAI is appropriate.[6] Data for selpercatinib use in pediatrics is less robust, but shows promising activity in cases of medullary thyroid cancer,[7,8] *CCDC6-RET* fusion positive PTC[4] and soft tissue sarcoma,[7] with preliminary safety and efficacy seen in pediatric patients with *RET* -altered solid tumors enrolled on LIBERTTO-121.[9] Here we report the

sustained response to selpercatinib, despite 2 dose reductions, in a 13-year-old patient with metastatic PTC harboring a somatic *NCOA4-RET* fusion.

Methods and Case Description

A 9-year-old former 33-week female triplet presented with exercise-induced dyspnea and intermittent oral cyanosis when chest x-ray revealed innumerable pulmonary nodules thought to be consistent with miliary tuberculosis or granulomatous disease. At age 11 she was evaluated for a right-sided neck mass; ultrasound showed a 2.7x1.7x2.9 cm hypervascular lesion at the carotid bifurcation. Magnetic resonance imaging was attempted, but due to hypoxemia, study was aborted and she was hospitalized for further evaluation and respiratory support. Chest computed tomography demonstrated diffuse sub-centimeter nodules with mediastinal and cervical lymphadenopathy. Rheumatologic and infectious work-ups were unrevealing. She underwent thoracoscopic lung biopsy where pathology confirmed metastatic PTC. Total thyroidectomy and lymph node dissection was performed showing classic subtype, with final tumor-node-metastasis staging of T1bN1bM1. Post-surgical thyroglobulin (Tg) level was 2850 ng/mL; antithyrogloblulin antibody was elevated at 46 IUnits/mL (normal <1.8 IUnits/mL).

The patient then started RAI treatment, receiving an initial dose of 20 mCi, which was initially complicated by radiation pneumonitis requiring hospitalization and steroid therapy. The next dose was reduced to 10mCi without recurrent symptoms of radiation pneumonitis. Subsequent doses were slowly increased and well-tolerated. She received a cumulative 280 millicuries from 7 treatments over 29 months. Post-treatment total body iodine scans performed 3-5 days after RAI administration continued to show stable, diffuse increased uptake throughout her lungs and thyroid stimulating hormone (TSH)-suppressed Tg level remained persistently elevated at 810 ng/mL, anti-Tg antibody was 8.1 IUnits/mL. She continued to require 3 liters of oxygen via nasal cannula and endorsed dyspnea with exertion. Somatic genetic testing was pursued using TEMPUS (Chicago, IL) and revealed a *NCOA4-RET* fusion.

The patient began oral selpercatinib 120 mg twice daily (BID) at the age of 13 years, following weight-based dosing guidelines (120 mg BID for weight <50 kg and 160 mg BID for weight ≥50 kg). Within 1 week, we noted an increase in oxygen saturation levels to [?]98% off supplementation while active in clinic. After two 28-day cycles imaging showed improving partially calcified mediastinal lymphadenopathy with marked improvement in innumerable pulmonary metastases (Fig.1). Tg level decreased to 143 ng/mL with anti-thyroglobulin antibody of 16 IUnits/mL (Fig. 2). Dosing was subsequently increased to 160 mg BID due to weight gain. The patient slowly trialed off of oxygen support, and after 4 cycles of therapy, she was off of supplemental oxygen and cleared by pulmonology for exercise.

Overall selpercatinib has been well tolerated; however, the patient continued to gain weight above her expected baseline and underwent a dose reduction to 120 mg BID after 9 cycles of therapy for possibly-related grade 3 weight gain. The patient noted a decrease in her appetite after the reduction but continued to endorse poor food choices and limited activity. Dose reduction again occurred after 18 cycles of therapy to 80 mg BID. She otherwise continued on levothyroxine for appropriate TSH suppression to <0.1 mcIUnit/mL.

The patient remains on selpercatinib at dose level -2 and was last evaluated after initiation of her twenty-eighth cycle. Imaging, thyroglobulin response, and resolution of anti-Tg antibodies (Figs. 1-2), as well as elimination of supplemental oxygen need, has continued despite dose adjustments. We plan to continue therapy indefinitely barring disease progression or intolerable toxicities.

Discussion

While disease-specific mortality for pediatric patients with DTC is very low, and surgery with adjuvant RAI is curative for most patients, approaches are not without associated toxicity. The American Thyroid Association has recommended selective use of RAI in children with DTC, including those with distant metastases which occurs in upwards of 30% of patients.[10-12] Early toxicities of RAI administration in children can include radiation thyroiditis, xerostomia and transient bone marrow suppression, with late complications of permanent salivary gland dysfunction, bone marrow suppression, pulmonary fibrosis, and secondary cancers.[13]

Furthermore, no standard limit for cumulative RAI therapy in pediatrics exists.[14] Consideration of usage and appropriate timing of alternative therapeutic approaches may not be needed to decrease mortality, but may reduce morbidity and improve quality of life in patients with DTC.

RET fusions retaining the kinase domain are drivers of PTC with *CCDC6-RET* and *NCOA4-RET* reported as the most common rearrangements.[15] Inhibition of RET was previously achieved by multi-tyrosine kinase inhibitors such as lenvatinib and cabozantinib, but the emergence of selective RET-inhibitors has provided a targeted approach with a potentially reduced side effect profile.[16,17] In our patient with metastatic PTC who was not achieving desired response to repeated doses of RAI, discovery of a *NCOA4-RET* fusion allowed for initiation of systemic therapy with selpercatinib, which quickly provided clinical, radiographic, and biochemical response. She has not experienced the more common selpercatinib-related adverse events, such as hypertension, transaminitis, diarrhea or constipation,[5-9] but was noted to have weight gain which while likely multifactorial, has been reported with selpercatinib[18] and was deemed to be possibly related to medication use.

Our patient's treatment response has continued despite two dose reductions of selpercatinib, allowing us to minimize possible associated toxicity without compromising efficacy. Given the chronic need for targeted therapy without knowledge of long-term side effects, understanding the minimal dose required for desired effect is of utmost importance. More precise administration of tyrosine kinase inhibitors is being studied, and it is proposed that the wider therapeutic index of targeted agents may allow for pediatric dosing to be less than the maximum tolerated dose documented in adults.[19] In summation, a better understanding of the molecular landscape of pediatric PTC offered an effective systemic treatment modality, and we will continue to closely observe the dose response in our patient.

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Figure 2. Patient's thyroglobulin and antithyroglobulin antibody levels prior to and throughout selpercatinib therapy. The timing of the two dose reductions are depicted by arrows above the trendline; sustained drop in thyroglobulin levels are seen despite reduced dosing. The horizontal line demarcates when antithyroglobulin antibodies are undetectable (<1.8 IUnits/mL) thus not interfering with the measurement of thyroglobulin levels.

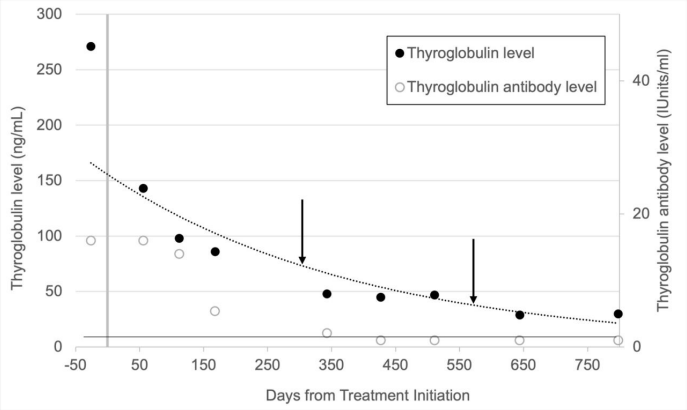

Figure 1. Representative computed tomography images at baseline (A) and after 2 cycles of selpercatinib (B) showing decrease in pulmonary disease burden, which was maintained after 9 cycles at dose level -1 (18 total cycles) (C) and approximately 10 cycles at dose level -2 (28 total cycles) (D)