Larotrectinib Before Initial Radioactive Iodine Therapy in Pediatric TRK Fusion–Positive Papillary Thyroid Carcinoma: Time to Reconsider the Treatment Paradigm for Distantly Metastatic Disease?

Steven G. Waguespack, MD1,2; Sanjit O. Tewari, MD3; Naifa L. Busaidy, MD1; and Mark E. Zafeero, MD4

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Introduction

Papillary thyroid carcinoma (PTC) diagnosed at a pediatric age (≤ 18 years), compared with its adult presentation, is associated with larger primary tumors, more extrathyroidal extension, and an increased prevalence of both locally and distantly metastatic (stage II) disease.1 Depending on the series, up to 25% of patients with pediatric PTC will develop pulmonary metastases.2,6 Stage II PTC diagnosed during childhood is enriched for oncogenic fusion genes primarily involving RET, NTRK1, and NTRK3.2,7,8 Recently, several effective and well-tolerated systemic therapies that selectively target the activated kinases resulting from these fusion genes have received regulatory approval in both children and adults.9

Management of pediatric stage II PTC includes thyroidectomy and compartment-focused neck dissection by a high-volume thyroid cancer surgeon followed by treatment with radioactive iodine (RAI).10 Rarely are kinase inhibitors needed for advanced disease that has progressed despite prior radioiodine. Traditionally, multiple courses of RAI are given until the patient either achieves cure or reaches a maximum lifetime 131I exposure, arbitrarily set at a cumulative dose of 600 mCi (22.2 GBq). However, despite repeated courses of 131I, a complete response is found in only 0%-22% of children with pulmonary metastatic disease.2,6 Furthermore, RAI can be associated with side effects such as salivary gland damage, pulmonary fibrosis, and an increased risk of second primary malignancies.11-14 Fortunately, stage II PTC is indolent in most pediatric patients and long-term survival is the norm.1,2

Because of its low cure rate and the potential for late effects arising from repeated courses of high-dose RAI, stage II PTC in children is a challenging disease to treat. Better therapeutic approaches are needed that might enhance the cure rates while minimizing the potential consequences of repeated radioiodine doses. Herein, we present an adolescent with a TRK fusion–positive PTC metastatic to the lungs who was treated using a neoadjuvant systemic approach with the selective TRK inhibitor larotrectinib before the initial dose of RAI.

Case Report

The patient is a Hispanic female who presented to our institution at age 15 years for a newly diagnosed PTC. Preoperative staging with neck ultrasonography and contrast-enhanced computed tomography (CT) of the neck and chest identified bulky central and right-sided cervical disease and evidence for bilateral micro- and macronodular pulmonary metastatic diseases. She was treated with total thyroidectomy and comprehensive central and right lateral neck dissections. Final American Joint Committee on Cancer, eighth edition stage group was II (T4aN1bM1). DNA and RNA next-generation sequencing identified a TPM3-NTRK1 fusion gene, a known oncogenic driver identified in about 8% of TRK fusion–positive thyroid cancers.15

The patient proceeded to a hypothyroid 123I thyroid scan while following a low iodine diet and with a documented low random urine iodine level (Table 1). This showed no clear cervical uptake and faint uptake in the pulmonary metastases (Fig 1A). The largest lesions measured 11 mm in the right lower lobe and 10 mm in the left lower lobe (Fig 2), both of which demonstrated no evidence of iodine avidity (Fig 3A). Given the minimal pulmonary uptake and because of the significant burden of disease in the lungs, it was recommended that she start systemic therapy with larotrectinib. The goal of therapy was to debulk the tumor medically before initial RAI, anticipating that this would enhance the subsequent response to RAI because of smaller volume disease.
After informed consent, the patient commenced larotrectinib 100 mg by mouth twice a day. After the first dose, she developed headache, lightheadedness, temperature dysregulation in her hands, and tingling in the fingertips. The drug was briefly held and then resumed at the same dose. She developed transient grade 1 leukopenia and grade 1 fatigue but had no other subsequent adverse events. CT imaging showed evidence for a partial response after three months of therapy (Fig 2). After 6 months of therapy, a decision was made to proceed to high-dose ¹³¹I therapy. Unexpectedly, the recombinant human TSH-stimulated ¹³¹I thyroid scan showed significantly increased uptake in all the pulmonary metastatic disease, including the previous noniodine-avid disease (Figs 1B and 3B). Indeed, the percent uptake of the ingested dose in the lungs (26.6%) was so high that the administered dose was adjusted downward so as not to place her at undue risk for pulmonary fibrosis. An empiric activity of 98.7 mCi (3.7 GBq) ¹³¹I was administered approximately 31 hours after the last dose of larotrectinib and the same day as the diagnostic study. She tolerated RAI well with no immediate or delayed side effects. Six months after ¹³¹I therapy, there was a significant decline in the thyroglobulin level (Table 1). Twelve months after RAI, her (unintended) stimulated thyroglobulin was only 0.93 ng/mL. Chest CT revealed a significant response in all the metastatic nodules (Fig 2), including the disappearance of some of the smaller metastatic deposits.

### Discussion

The treatment of pediatric stage II PTC remains a challenge given its low complete response rates and the inherently higher risks of both surgical and RAI therapies in children. RAI has been the mainstay of treating distantly metastatic disease since the 1940s, and before 2018, there were no

###TABLE 1. Laboratory Data Before, During, and After Therapy With Larotrectinib in an Adolescent With Stage II Papillary Thyroid Carcinoma

|                          | At Diagnosis | At Initial ¹²³I Scan/Start of Larotrectinib | After 6 Months on Larotrectinib | At Second ¹³¹I Scan/¹³¹I Therapy | 6 Months After ¹³¹I Therapy | 12 Months After ¹³¹I Therapy |
|--------------------------|--------------|---------------------------------------------|---------------------------------|----------------------------------|-----------------------------|-------------------------------|
| Thyroglobulin, ng/mL     | 147.92       | 334.03                                      | 102.79                          | 176.66                           | 0.61                        | 0.93                          |
| TSH, mIU/L              | 2.41         | 116.2                                       | < 0.15                          | 120.8                            | 2.58                        | 21.3                          |
| Iodine/creatinine ratio, µg/g; random urine | 20 | 42 |                       |                                 |                             |                               |

**NOTE.** Thyroglobulin normal range: 1.59-50.03 (intact thyroid) and < 0.1 (athyrotic patients); Thyroglobulin antibodies were negative at each time point. TSH normal range: 0.27-4.20 mIU/L. Random urine iodine/creatinine normal range: not established for < 18 years and < 584 µg/g for 18+ years. Abbreviation: TSH, thyroid-stimulating hormone.

**FIG 1.** Anterior and posterior whole-body planar images from diagnostic radioactive iodine scans before and after larotrectinib therapy. (A) Hypothyroid diagnostic ¹²³I thyroid scan, before larotrectinib, showing no clear uptake in the neck and faint uptake throughout the pulmonary metastatic disease. The calculated uptake in the lungs was 10.2%. (B) Diagnostic ¹³¹I thyroid scan after recombinant human TSH showed significantly increased uptake in all the pulmonary metastatic disease (26.6% of the ingested dose) and uptake in the right superior thyroid bed, possibly correlating with residual disease left on the right recurrent laryngeal nerve at the cricothyroid joint.
systemic therapies approved for use in children with advanced PTC. Recently, it has become better appreciated that most children with stage II disease will have persistent, albeit indolent, disease and that novel therapeutic approaches are needed to improve cure rates. In particular, the long-term sequelae of high doses of RAI may add to the lifelong symptom burden of the patient and increase the risk of secondary malignancies.\textsuperscript{11-14}

FIG 2. CT images of the two largest pulmonary metastases. (A) A right lower lobe nodule (yellow arrowhead) measured 11 mm at baseline before larotrectinib. The best response to larotrectinib was a 36% decrease after 3 months on therapy, and 1 year after RAI, there was a 67% decrease compared with the scan at the time of RAI and a 73% decrease compared with baseline. (B) A left lower lobe nodule (red arrowhead) measured 10 mm at baseline before larotrectinib. The best response to larotrectinib was a 50% decrease after 3 months on therapy, and 1 year after RAI, there was a 63% decrease compared with the scan at the time of RAI and a 70% decrease compared with baseline. Per RECIST v1.1, the patient’s best response to larotrectinib was a partial response (−43%) at 3 months. After RAI, the response in the two target lesions was −65% compared with the scan at the time of RAI therapy and −71% compared with baseline before larotrectinib. For each grouping of CT images, top left = baseline before larotrectinib and at the time of the initial diagnostic SPECT-CT, top right = CT after 3 months of larotrectinib, bottom left = at the time of second diagnostic SPECT-CT after therapy with larotrectinib, and bottom right = CT 1 year after neoadjuvant larotrectinib and 98.7 mCi (3.7 GBq) \textsuperscript{131}I. CT, computed tomography; RAI, radioactive iodine; SPECT, single-photon emission computed tomography.

FIG 3. Single-photon emission computed tomography/computed tomography images of the two largest pulmonary metastases at the time of the diagnostic radioactive iodine scan (A) before and (B) after larotrectinib therapy. Right lower lobe (yellow arrowhead) and left lower lobe (red arrowhead) metastases were initially not iodine-avid but demonstrated significantly increased radioiodine uptake after larotrectinib therapy.
TABLE 2. Redifferentiation of PTC After Larotrectinib Therapy: Clinical Experience to Date

| Publication                  | Age at Diagnosis (years)/Sex | Histology                      | Fusion Gene          | Cumulative 131I Dose in mCi (GBq) Before Larotrectinib | Age at Larotrectinib Start (years) | Duration of Larotrectinib Before RAI Diagnostic Scan (weeks) | Treated With RAI After Larotrectinib Therapy |
|-----------------------------|------------------------------|--------------------------------|----------------------|--------------------------------------------------------|-----------------------------------|-------------------------------------------------------------|---------------------------------------------|
| Groussin et al              | 30/F                         | PTC NOS                         | EML4-NTRK3           | 1,405.4 (52.3)                                         | 64                                | 3                                                          | No                                          |
| Lee et al                   | 4/F                          | PTC classic                     | TPR-NTRK1            | 60.0 (2.2)                                             | 6                                 | 12                                                         | No                                          |
| Waguespack et al (current report) | 15/F                      | PTC, classic and follicular; focal solid component | TPM3-NTRK1           | 0 (0)                                                   | 16                                | 29                                                         | Yes                                         |

NOTE. All patients received larotrectinib 100 mg orally twice a day. The Groussin patient had also received lenvatinib with no demonstration of increased RAI uptake in the lungs.

Abbreviations: NOS, not otherwise specified; PTC, papillary thyroid carcinoma; RAI, radioactive iodine.

Larotrectinib is a selective TRK inhibitor that has been approved for the treatment of both pediatric and adult patients with advanced solid tumors that harbor an NTRK fusion gene. It is one of two available TRK inhibitors, with the other being entrectinib, which also targets ALK and ROS1. Treatment with larotrectinib has been proven to be widely effective in both adults and children across various solid malignancies, including PTC, and it is associated with a favorable toxicity profile.17,18

Metastatic PTC can lose its ability to concentrate radioiodine, and our increasing understanding of the molecular basis of PTC has given further insight into the mechanisms of RAI-refractory (RAI-R) disease. The Cancer Genome Atlas was the first study to correlate the molecular basis of PTC with a differentiation score on the basis of gene expression. BRAFV600E-like tumors have a lower differentiation score, with reduced expression of genes responsible for iodine uptake and metabolism, whereas RAS-like tumors have a higher differentiation score. NTRK1/3 fusion–positive PTC falls somewhere in between. The concept of redifferentiation therapy is a relatively new one and currently refers to the inhibition of mitogen-activated protein kinase pathway signaling by a MEK or BRAF kinase inhibitor to improve iodine uptake in metastatic tumors. Recently, two cases have been published in which larotrectinib was able to redifferentiate RAI-R PTC (Table 2). Although our patient is different in that she was not yet considered RAI-R, her diagnostic thyroid scan before larotrectinib demonstrated minimal RAI uptake in the pulmonary metastases, including the largest lesions that exhibited no appreciable iodine uptake. Larotrectinib therapy was well tolerated and resulted in tumor shrinkage and enhanced iodine uptake in both iodine-avid and nonavid diseases, which allowed the successful administration of a lower dose of 131I that, at one year, has resulted in a significant partial response radiographically and a near-complete biochemical response.

Although the current case is an exciting one that suggests a potential shift in the traditional management of distantly metastatic PTC, caution must be undertaken as we learn more about the possible long-term side effects of systemic TRK inhibition, particularly in the context of the concomitant use of RAI. It is also important to better understand the optimal duration of therapy and if it is safe to administer RAI while actively receiving larotrectinib; in the current case, we stopped the medication the day before RAI was administered. It also remains unknown if such an approach would apply to the other commercially available TRK inhibitor entrectinib or to the selective RET inhibitors, selpercatinib and pralsetinib, although recent publications would suggest a similar therapeutic effect with selpercatinib. Ideally, despite the challenges of recruitment and the issues surrounding the assessment of response in nonmeasurable disease, which is typical in young patients with stage II PTC, well-designed clinical trials should be considered to answer these important questions.

In conclusion, to our knowledge, we report the first case of a patient who achieved clinical benefit from initiation of the selective TRK inhibitor larotrectinib in a neoadjuvant fashion before the first dose of RAI. Although the initial goal of therapy was to medically debulk her tumor to allow more effective delivery of 131I, the patient’s tumor also demonstrated an unexpected and significant increase in RAI avidity (redifferentiation), which we believe improved the therapeutic outcome and permitted the use of a lower administered dose of 131I. The time may be upon us to reconsider our treatment paradigm and incorporate selective fusion gene inhibitors such as larotrectinib earlier in the treatment course to maximize the tumor response to RAI in advanced PTC.

AFFILIATIONS
1Department of Endocrine Neoplasia and Hormonal Disorders, University of Texas MD Anderson Cancer Center, Houston, TX
2Department of Pediatrics-Patient Care, University of Texas MD Anderson Cancer Center, Houston, TX
3Department of Nuclear Medicine, University of Texas MD Anderson Cancer Center, Houston, TX

CORRESPONDING AUTHOR
Steven G. Waguespack, MD, Department of Endocrine Neoplasia & Hormonal Disorders, The University of Texas MD Anderson Cancer Center, 1400 Pressler St, Unit 1461, Houston, TX 77030; e-mail: swagues@mdanderson.org.

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**AUTHOR CONTRIBUTIONS**

Conception and design: Steven G. Waguespack  
Provision of study materials or patients: Steven G. Waguespack  
Collection and assembly of data: Steven G. Waguespack, Sanjit O. Tewari  
Data analysis and interpretation: All authors  
Manuscript writing: All authors  
Final approval of manuscript: All authors  
Accountable for all aspects of the work: All authors

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

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**REFERENCES**

1. Hay ID, Johnson TR, Kaggal S, et al: Papillary thyroid carcinoma (PTC) in children and adults: Comparison of initial presentation and long-term postoperative outcome in 4432 patients consecutively treated at the Mayo Clinic during eight decades (1936-2015). World J Surg 42:329-342, 2018  
2. Nies M, Vassiliopoulou-Sellin R, Bassett RL, et al: Distant metastases from childhood differentiated thyroid carcinoma: Clinical course and mutational landscape. J Clin Endocrinol Metab 106:e1683-e1697, 2021  
3. Sugino K, Nagahama M, Kitagawa W, et al: Distant metastasis in pediatric and adolescent differentiated thyroid cancer: Clinical outcomes and risk factor analyses. J Clin Endocrinol Metab 105:dga545, 2020  
4. Cheson AD, Vali R, Hemmati SH, et al: Lung metastasis in children with differentiated thyroid cancer: Factors associated with diagnosis and outcomes of therapy. Thyroid 31:50-60, 2021  
5. Alzahrani AS, Alsweilem M, Moria Y, et al: Lung metastasis in pediatric thyroid cancer: Radiological pattern, molecular genetics, response to therapy, and outcome. J Clin Endocrinol Metab 104:103-110, 2019  
6. Zhang XY, Song HJ, Qiu ZL, et al: Pulmonary metastases in children and adolescents with papillary thyroid cancer in China: Prognostic factors and outcomes from treatment with (131)I. Endocrine 62:149-158, 2018  
7. Lee YA, Lee H, Im SW, et al: NTRK- and RET-fusion-directed therapy in pediatric thyroid cancer yields a tumor response and radioiodine uptake. J Clin Invest 131:e144847, 2021  
8. Stosic A, Fuligni F, Anderson ND, et al: Diverse oncogenic fusions and distinct gene expression patterns define the genomic landscape of pediatric papillary thyroid carcinoma. Cancer Res 81:5625-5637, 2021  
9. Lorusso L, Cappagli V, Valerio L, et al: Thyroid cancers: From surgery to current and future systemic therapies through their molecular identities. Int J Mol Sci 22:3117, 2021  
10. Francis GL, Waguespack SG, Bauer AJ, et al: Management guidelines for children with thyroid nodules and differentiated thyroid cancer. Thyroid 25:716-759, 2015  
11. Lee SL: Complications of radioactive iodine treatment of thyroid carcinoma. J Natl Compr Canc Netw 8:1277-1286, 2010; quiz 1287  
12. Adly MH, Sobhy M, Rezk MA, et al: Risk of second malignancies among survivors of pediatric thyroid cancer. Int J Clin Oncol 23:625-633, 2018  
13. Marti JL, Jain KS, Morris LG: Increased risk of second primary malignancy in pediatric and young adult patients treated with radioactive iodine for differentiated thyroid cancer. Thyroid 25:681-687, 2015  
14. Albano D, Bertagna F, Panarotto MB, et al: Early and late adverse effects of radioiodine for pediatric differentiated thyroid cancer. Pediatr Blood Cancer 64, 2017  
15. Pekova B, Sykova V, Mastnikova K, et al: NTRK fusion genes in thyroid carcinomas: Clinicopathological characteristics and their impact on prognosis. Cancers (Basel) 13:1932, 2021  
16. Laetsch TW, Hong DS: Trp53/Trp53 receptor kinase inhibitors for the treatment of TRK fusion cancer. Clin Cancer Res 27:4974-4982, 2021  
17. Hong DS, DuBois SG, Kummor S, et al: Larotrectinib in patients with TRK fusion-positive solid tumours: A pooled analysis of three phase 1/2 clinical trials. Lancet Oncol 21:531-540, 2020  
18. Laetsch TW, DuBois SG, Mascarenhas L, et al: Larotrectinib for paediatric solid tumours harbouring NTRK gene fusions: Phase 1 results from a multicentre, open-label, phase 1/2 study. Lancet Oncol 19:705-714, 2018  
19. Fagin JA, Wells SA Jr: Biologic and clinical perspectives on thyroid cancer. N Engl J Med 375:1054-1067, 2016  
20. Cancer Genome Atlas Research Network: Integrated genomic characterization of papillary thyroid carcinoma. Cell 159:676-690, 2014  
21. Lamartina L, Anizan N, Dupuy C, et al: Redifferentiation-facilitated radioiodine therapy in thyroid cancer. Endocr Relat Cancer 28:T179-T191, 2021  
22. Groussin L, Clerc J, Huillard O: Radioiodine uptake in advanced thyroid cancer. J Clin Endocrinol Metab 104:103-110, 2019  
23. Groussin L, Bessi`ene L, Arrondeau J, et al: Selpercatinib-enhanced radioiodine uptake in RET-rearranged thyroid cancer. Thyroid 31:1603-1604, 2021