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Case Report

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NTRK Fusion as an Acquired Mechanism of Resistance to Selpercatinib in RET Positive Thyroid Cancer

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Abstract

Background: *Rearrangement during Transfection (RET) proto-oncogene is involved in the pathogenesis of various thyroid cancer subtypes and drugs that block the RET tyrosine kinase pathways are used in the management of locally advanced and metastatic Medullary Thyroid Cancer (MTC). Acquired resistance to RET inhibitors likely occurs via two different mechanisms: (1) On-target mutations that prevent drug binding and (2) Activated alternative mechanisms which bypass the targeted kinase. We present a unique mechanism of selpercatinib resistance via secondary NTRK fusion mutation in a case of RET altered medullary thyroid cancer.*

Case Presentation: *The patient is a 72-year-old female with stage III metastatic MTC who developed recurrence with newly found RET mutation 7 years after complete surgical resection. Despite initial stable response with selpercatinib for 2 years she rapidly progressed with widespread disease. Cell-free DNA (cfDNA) testing done at the time of progression revealed an NTRK1 fusion. Unfortunately, the patient succumbed to the disease despite starting targeted therapy with larotrectinib.*

Conclusion: *This case highlights the importance of further investigation into mechanisms of resistance to RET inhibitors and drug studies directed towards overcoming them.*

Keywords: Selpercatinib, NTRK Fusion, RET, Medullary Thyroid Cancer

Abbreviations

RET: Rearrangement during Transfection
MTC: Medullary Thyroid Cancer
NTRK: Neurotrophic Tyrosine Receptor Kinase
KRAS: Kirsten Rat Sarcoma Virus
CEA: Carcinoembryonic Antigen
CfDNA: Cell-free DNA
NGS: Next Generation Sequencing
MIKs: Multi-Kinase Inhibitors
TKIs: Tyrosine Kinase Inhibitors
FDA: Food and Drug Administration
TRK: Tropomyosin Receptor Kinase
MAPK: Mitogen-Activated Protein Kinase
PI3K: Phosphatidylinositol 3-Kinase
CK7: Cytokeratin 7
PAX 8: Paired-Box-Gene 8
TTF-1: Thyroid Transcription Factor 1
Ba/F3 cells: Pro-B murine cell line dependent on interleukin-3

1. Introduction

The RET proto-oncogene is involved in the pathogenesis of various thyroid cancer subtypes. Mutations in RET give rise to both hereditary and sporadic medullary thyroid cancer. Germline activating point mutations of RET are present in about 25%-40% of MTC and account for hereditary MTC in the form of multiple endocrine neoplasia 2A and 2B, whereas 45% of sporadic MTC have a somatic RET mutation [1]. Wider accessibility and use of Next Generation Sequencing (NGS) have influenced the therapeutic landscape by real-time identification of such treatable oncoproteins. Drugs that block the RET tyrosine kinase pathways

have been investigated for the management of locally advanced and metastatic MTC.

Multi-Kinase Inhibitors (MKIs), vandetanib and cabozantinib, are approved by the FDA for treatment of progressive, unresectable, locally advanced, or metastatic MTC [2,3]. MKIs display non-selective RET inhibition which also targets a spectrum of non-RET kinases; at the expense of possible drug related adverse events, which can lead to dose reduction, interruption, and discontinuation [4]. All of which ultimately limit the efficacy of these drugs. Highly selective first-generation RET inhibitors selpercatinib and pralsetinib showed marked and durable antitumor activity in patients with RET-mutant medullary thyroid cancer with and without previous vandetanib or cabozantinib treatment in phase 1-2 trial LIBRETTO-001 (NCT03157128) and ARROW (NCT03037385) respectively [5,6].

Despite significant progress made in precision oncological treatment focused on targeting these specific tumorigenic pathways there are several proposed mechanisms of resistance that could cause treatment failure. Acquired resistance to RET inhibitors likely occurs via two different mechanisms:
(1) On-target mutations (target modification) that prevent drug binding and
(2) Activated alternative mechanisms which bypass the targeted kinase (bypass signaling) [7].

Target modification includes RET gate keeper mutations V804M/L which prevents binding of MKIs [8,9]. The selective RET inhibitors, like selpercatinib, were designed to overcome gatekeeper mutations. RET solvent front mutations have been found to be a common cause of selective RET inhibitor resistance [10]. RET-altered tumors can develop escape mechanisms to drug receptor inhibition by activating oncogenic alternative or downstream pathways independent of RET activation [11]. Hu et al. reported the emergence of kirsten rat sarcoma virus (KRAS) pan G12/G13 bypass mutation alone or combined with RET gatekeeper mutation V804M in sporadic MTC patients with progressive disease after a minimum of 6-month treatment with cabozantinib and vandetanib [12].

We present a unique mechanism of selpercatinib resistance via secondary Neurotrophic Tyrosine Kinase Receptor (NTRK) fusion mutation in a case of RET altered medullary thyroid cancer.

2. Case Presentation

The patient is a 72-year-old female with stage III sporadic recurrent medullary carcinoma of the thyroid with lymph node involvement and metastases to the bone. Initially, she was treated with a total thyroidectomy and central compartment cervical lymph node dissection. The margins were not involved and no lympho-vascular or extrathyroidal extension was identified, but, 2 out of 3 left paratracheal lymph nodes were positive for metastasis. Germline genetic testing performed at the time was negative for a RET mutation. She was monitored with interval CT scans, regular laboratory studies, and tumor markers including serum carcinoembryonic antigen (CEA), calcitonin, and chromogranin A. Seven years after the initial diagnosis a new rise in serum CEA prompted evaluation with a Gallium 68 (Ga-68) DOTATATE PET/CT revealing innumerable marked hypermetabolic uptake throughout the axial and appendicular skeleton, previously not observed on CT scans. Given that the overall impression was widespread osseous metastatic disease molecular testing at Caris Laboratory was repeated and a biopsy of the right iliac crest was performed. Molecular testing at this point was positive for a RET mutation and the biopsy proved that the morphology was compatible with patient's history of medullary carcinoma of thyroid. Tumor cells were positive for cytokeratin 7 (CK7), chromogranin, synaptophysin, paired-box-gene 8 (PAX 8), thyroid transcription factor 1 (TTF-1), and focal positivity for CD56. She was subsequently started on selpercatinib (LIBERTTO-001 trial, NCT03157128) which initially resulted in consistently stable disease on interval CT scans as well as progressive reduction in calcitonin and CEA from pre-treatment values of 26pg/mL and 222ng/mL respectively down to <2.0pg/mL and 21.9ng/mL.

Unfortunately, 2 years into treatment with selpercatinib she progressed with a sudden rise in serum CEA level and Ga-68 DOTATATE PET/CT imaging revealed a more diffuse pattern of distribution throughout the axial and appendicular skeleton as compared to previous scans. Given clinical progression, selpercatinib was held and cfDNA (Guardant) analysis was performed revealing previously known RET mutation and a new ARHGEF11-NTRK1 fusion mutation. Based on the new NTRK fusion the patient was started on larotrectinib. Due to poor tolerance to larotrectinib with worsening fatigue, anorexia, transaminitis, and simultaneous increase in calcitonin and CEA the drug was stopped, and she was started on cabozantinib (EXAM trial, NCT00704730). Unfortunately given ongoing fatigue, weight loss, and elevated transaminases the patient was unable to tolerate cabozantinib as well. Ultimately, the patient's clinical performance worsened rapidly and she succumbed to the disease and died.

3. Discussion

We report a case of NTRK1 fusion secondary mutation emerging as a mechanism of resistance to selpercatinib in a patient with RET altered medullary thyroid cancer. The presence of de novo NTRK fusions in thyroid cancer is rare and the frequency ranges from 2.3 to 3.4% in predominantly adult papillary thyroid cancer cohorts [13,14]. The NTRK1, NTRK2, and NTRK3 genes encode the transmembrane proteins tropomyosin receptor kinase (Trk) receptors - TrkA, TrkB, and TrkC respectively. They are important for the normal development and functioning of the nervous system. When these genes fuse abnormally, chimeric Trk receptors are produced, which are constitutively active and can activate downstream signaling pathways such as MAPK and phosphatidylinositol 3-kinase PI3K [15]. This abnormal fusion of NTRK genes has been found to be a cause of cancer in various solid tumors, including thyroid cancer [16].

To our knowledge this is the first case of RET altered medullary thyroid cancer showcasing NTRK1 fusion as a mechanism for treatment failure on selpercatinib. Subbiah et al. reported NTRK3 fusion as an acquired mechanism of resistance in RET-fusion positive lung cancer. This was confirmed with next generation sequencing carried out on both fusion negative pre-treatment biopsy and fusion positive progressed-on-treatment biopsy. Cell cultures using mutation transformed Ba/F3 cells (pro-B murine cell line dependent on interleukin-3 for growth) were used and confirmed resistance when treated with selpercatinib alone and exhibited apoptosis when co-treated with selpercatinib and larotrectinib [17]. In 2022 Park et al. reported the frequency of NTRK gene alterations in thyroid cancer from available public databases (The Cancer Genome Atlas, Tempus, and American Association for Cancer Research - Genie). Of 2,362 thyroid specimens identified from afore mentioned databases 51 patients (2.2%) were found to have NTRK1 or NTRK3 gene fusions [18]. However, there were no cases of combined RET and NTRK fusion thyroid cancers reported.

Two NTRK inhibitors have received FDA approval for the treatment of NTRK gene fusion-positive tumors entrectinib and larotrectinib [19,20]. Repotrectinib (TPX-0005), another TRK inhibitor, has been granted a breakthrough therapy designation by the FDA for the treatment of patients with solid tumors harboring an NTRK gene fusion who experienced progression after being treated with 1 to 2 previous TRK Tyrosine Kinase Inhibitors (TKIs) plus or minus chemotherapy and who have no other treatment options [21]. A novel agent, ICP-723 is also under active investigation for the treatment of TRK fusion-positive cancers and undergoing multi-center, open-label phase I/II clinical trial (NCT04685226) [22].

In summary, this case emphasizes the importance of real time incorporation of molecular sequencing into clinical oncological care both at the time of diagnosis and especially during times of progression for detection of emergent mutations that may be targetable. Ongoing studies for novel agents to overcome these emerging mechanisms of resistance are warranted.

4. Conclusion

This case highlights the importance of further investigation into mechanisms of resistance to RET inhibitors and drug studies directed towards overcoming them.

Declarations

Ethics Approval

MedStar Health Institutional Review Board has determined that a case report of less than three (3) patients does not meet the DHHS definition of research (45 CFR 46.102(d)(pre-2018)/45 CFR 46.102(l)(1/19/2017)) or the FDA definition of clinical investigation (21 CFR 46.102(c)) and therefore are not subject to IRB review requirements and do not require IRB approval.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Authors' Contributions

All authors were involved in the preparation of this manuscript.

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