Case Reports in Oncology

Case Rep Oncol 2019;12:791–795

DOI: 10.1159/000503419
Published online: October 16, 2019

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Case Report

Prolonged Response to Regorafenib in a Patient with Iodine Refractory Thyroid Cancer

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Keywords
Iodine-refractory · Regorafenib · Thyroid cancer

Abstract
Thyroid cancer is the most common type of endocrine malignancy. Cornerstones of thyroid cancer treatment include surgery, radioactive iodine ablation, and thyroid stimulating hormone suppression. The National Comprehensive Cancer Network guidelines recommend two tyrosine kinase inhibitors for thyroid cancer patients who are non-responsive to iodine: sorafenib and lenvatinib. Another oral kinase inhibitor, regorafenib, is not considered standard of care treatment for differentiated thyroid cancer. The chemical structures of regorafenib and sorafenib differ by a single fluorine atom. Given the significant improvement in progression-free survival (PFS) of sorafenib compared to placebo demonstrated in the phase 3 DECISION trial, we report on a patient with iodine-refractory follicular thyroid cancer treated with regorafenib as part of a phase 1 clinical trial. A 75 year old woman was diagnosed with follicular thyroid carcinoma in 2006 and initiated on treatment with regorafenib in 2011. She has completed 76 cycles with stable disease and pulmonary metastases 34% smaller than baseline.

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Introduction

Thyroid cancer is the most common type of endocrine malignancy. Differentiated thyroid cancer (DTC) accounts for approximately 90% of all thyroid cancers, with papillary (70–80%) and follicular (10–15%) being the most common subtypes [1–3]. The global incidence of thyroid cancer has been rising over the past three decades [4]. United States population data reveal that rates of new thyroid cancer cases have risen on average 3.8% per year for the last 10 years. The 5-year overall survival rates for localized thyroid cancer is 99.9% compared to 56.4% for those with metastatic disease [5].

Cornerstones of thyroid cancer treatment include surgery, radioactive iodine (RAI) ablation, and thyroid stimulating hormone suppression. In the case of metastatic or unresectable iodine refractory thyroid cancers, therapeutic options are significantly more limited. Unlike many other cancer types, standard systemic chemotherapies for advanced thyroid malignancies have demonstrated limited efficacy [6, 7]. With the introduction of targeted therapies, several oral tyrosine kinase inhibitors (TKIs) have shown progression-free survival (PFS) benefits and are reasonable options in iodine-refractory patients.

The National Comprehensive Cancer Network guidelines recommend two TKIs for patients with thyroid cancer who are non-responsive to iodine therapy: sorafenib and lenvatinib [8]. Another oral kinase inhibitor, regorafenib, is not considered standard of care treatment for DTC. The chemical structures of regorafenib and sorafenib differ by a single fluorine atom and given the significant improvement in PFS of sorafenib compared to placebo demonstrated in the phase 3 DECISION trial [9], we report the clinical outcome of a patient with iodine-refractory follicular thyroid cancer who has been treated with regorafenib as part of a phase 1 clinical trial (ClinicalTrials.gov identifier: NCT01287598).

Case

A 75 year old woman was diagnosed with follicular carcinoma of the thyroid in 2006. Her past medical history was significant for dyslipidemia and peptic ulcer disease, and her surgical history included a total abdominal hysterectomy and bilateral hip replacements.

She underwent a left thyroidectomy for thyroid nodules measuring up to 4 cm, followed by a total thyroidectomy after the initial pathology diagnosed follicular thyroid carcinoma. She subsequently underwent RAI ablation. There was early suspicion that her disease might be non-iodine sensitive, as her thyroglobulin continued to increase. Despite RAI treatment, multiple pulmonary parenchymal metastases and enlarging mediastinal lymph nodes were discovered. As treatment options are limited in the iodine-refractory/resistant setting, and sorafenib was not yet approved, she consented and was enrolled in a phase I trial of regorafenib in 2011, according to ICH-GCP guidelines.

Regorafenib was initiated at the standard dose of 160 mg PO daily for 21 of every 28 days. During cycle 1, she developed an acute, severe episode of chest pain that resulted in hospitalization. Diagnostic investigations did not show a clear etiology for this pain, and it resolved with conservative management. As cardiac toxicity is a known potential risk with regorafenib, she was dose reduced to 120 mg daily with cycle length remaining the same. The 120 mg dose was tolerated well until cycle 4 when she developed grade 3 hand-foot syndrome (HFS). Regorafenib was then further dose reduced to 80 mg daily. As of August 2017, she had completed 76 cycles of regorafenib. Her thyroglobulin level decreased from 7565 ug/L at the time of enrollment to 907ug/L in February 2017. Compared to her baseline CT scan in October

2011, her disease demonstrated partial response to regorafenib per RECIST criteria with reduction of her pulmonary metastases by 34% in December 2012. Her CT scan in August 2017 continued to show stability, with the pulmonary metastases 33% smaller than baseline.

Discussion

It is notable how long regorafenib has been able to control this patient's iodine-refractory thyroid cancer. Sorafenib, lenvatinib, and regorafenib are all TKIs with similar targets and mechanisms of action. Sorafenib was the first TKI approved for the treatment of iodine-refractory DTC in 2014, with targets including Raf family kinases and receptor tyrosine kinases, such as VEGFR, PDGFR, RET [10, 11]. It is approved for the treatment of metastatic renal cell carcinoma [12], hepatocellular carcinoma [13], as well as radioactive iodine-refractory DTC. In the phase 3 DECISION trial by Brose et al. [9] which included 417 patients, treatment with sorafenib significantly improved median PFS compared to placebo in patients with RAI-refractory DTC (10.8 vs. 5.8 months; hazard ratio [HR] 0.59, 95% confidence interval [CI], 0.45–0.76, $p < 0.0001$). Difference in overall survival was not statistically significant (HR 0.80, 95% CI, 0.54–1.19, $p = 0.14$). The most common adverse events were HFS, diarrhea, alopecia, and rash/desquamation.

Lenvatinib, another multikinase inhibitor of VEGFR , FGFR, PDGFR, RET and KIT, was subsequently shown to improve PFS in the phase 3 SELECT trial by Schlumberger et al. [14]. Three hundred and ninety-two patients were included, with 261 randomized to receive lenvatinib compared to 131 given placebo. Significant median PFS was seen in the lenvatinib group (18.3 vs. 3.6 months; HR 0.21, 99% CI 0.14–0.31, $p < 0.001$). The most common adverse events were hypertension, diarrhea, fatigue, decreased appetite, and decreased weight.

Regorafenib and sorafenib are very similar in their atomic structure. Regorafenib has inhibitory effects on VEGFR, PDGFR, FGFR, KIT, RET, and BRAF. It is approved for treating metastatic colorectal cancer [15], gastrointestinal stromal tumors [16], and second-line in hepatocellular carcinoma after sorafenib [17]. The difference between regorafenib and sorafenib is the addition of one fluorine to the center phenyl ring allowing for its increased anti-angiogenic activity over that of sorafenib [18, 19]. Angiogenesis is not only crucial for tumor cell proliferation, but also in development of recurrence and distant metastases [20, 21]. Furthermore, the superior effects of regorafenib demonstrated with this case may be due to regorafenib being a more potent inhibitor of RET than sorafenib (IC50, or inhibitory concentration of 50%, of 1.5 ± 0.7 nM versus approximately 47 nM, respectively [19, 22]), as it is known that the RET (rearranged during transfection) gene plays a crucial role in thyroid carcinogenesis [23, 24].

Given multi-targeted kinase inhibitors are not without potential adverse effects, it is important that patients are made aware of potential toxicities. This is particularly evident with patients who were previously treated with RAI ablation followed with levothyroxine, both of which are generally well tolerated with minimal side effects. Specifically for sorafenib, HFS is the most common side effect (up to 80% of patients) which leads to dose reduction, interruption, or treatment withdrawal [25, 26]. Similarly, HFS is also the most common (overall rate of 61%) and most clinically significant adverse effect with regorafenib [27]. In this case, HFS developed at 120 mg daily and was subsequently dose reduced to 80 mg with complete resolution of symptoms.

The cause for this patient's isolated episode of chest pain requiring hospital admission remains unknown. The chest pain may be related to tumor response rather than a side effect

of regorafenib. During her admission, work-up for cardiac and other life-threatening causes were negative. A CT scan of her chest was negative for pulmonary embolism; it did, however, demonstrate a left sided pleural effusion adjacent to known left lower lobe parenchymal tumor deposits located adjacent to the pleural space. These nodules were reported to have decreased in size and density, along with a target right upper lobe nodule that had decreased by 3 mm compared with a baseline CT scan done 7 days prior to starting regorafenib. We hypothesize that her chest pain was related to tumor flare phenomenon: pain that occurs secondary to acute inflammation, or potentially hemorrhage, from release of intracellular contents during rapid destruction of malignant cells.

Conclusion

This patient had been on regorafenib for 76 cycles with continued response. These results far exceed the median PFS of 10.8 months in the pivotal study of sorafenib for treatment of iodine-refractory, recurrent or metastatic DTC. Taking into consideration both the recent phase III trial (RESORCE) of regorafenib in HCC patients who have failed or are intolerant to sorafenib [17] as well as the exceptional clinical benefit demonstrated in this case, clinical trials of regorafenib in treatment naïve or sorafenib pretreated iodine-refractory, recurrent, or metastatic differentiated thyroid cancer are warranted.

Acknowledgement

We would like to thank the patient for giving us consent to publish her results.

Statement of Ethics

Written informed consent was provided by the patient to publish her case.

Disclosure Statement

The authors have no conflicts of interest to disclose.

Funding Sources

The authors have no funding sources to disclose.

References

1 Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al.; American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009 Nov;19(11):1167–214.
2 Lin JS, Bowles EJ, Williams SB, Morrison CC. Screening for Thyroid Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2017 May;317(18):1888–903.

3 Sherman SI. Thyroid carcinoma. Lancet. 2003 Feb;361(9356):501–11.
4 Kilfoy BA, Zheng T, Holford TR, Han X, Ward MH, Sjodin A, et al. International patterns and trends in thyroid cancer incidence, 1973-2002. Cancer Causes Control. 2009;20(5):525–31.
5 National Cancer Institute. Thyroid Cancer Stat Facts 2016 [cited 2017 July 10]. Available from: https://seer.cancer.gov/statfacts/html/thyro.html
6 Sherman SI. Cytotoxic chemotherapy for differentiated thyroid carcinoma. Clin Oncol (R Coll Radiol). 2010 Aug;22(6):464–8.
7 Sherman SI. Targeted therapies for thyroid tumors. Mod Pathol. 2011 Apr;24(S2 Suppl 2):S44–52.
8 National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology 2017 [cited 2017 July 10]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf
9 Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet. 2014;384(9940):319–28.
10 Wilhelm S, Carter C, Lynch M, Lowinger T, Dumas J, Smith RA, et al. Discovery and development of sorafenib: a multikinase inhibitor for treating cancer. Nat Rev Drug Discov. 2006 Oct;5(10):835–44.
11 Wilhelm SM, Adnane L, Newell P, Villanueva A, Llovet JM, Lynch M. Preclinical overview of sorafenib, a multikinase inhibitor that targets both Raf and VEGF and PDGF receptor tyrosine kinase signaling. Mol Cancer Ther. 2008 Oct;7(10):3129–40.
12 Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, et al.; TARGET Study Group. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med. 2007 Jan;356(2):125–34.
13 Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al.; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008 Jul;359(4):378–90.
14 Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med. 2015 Feb;372(7):621–30.
15 Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, et al.; CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013 Jan;381(9863):303–12.
16 Demetri GD, Reichardt P, Kang YK, Blay JY, Rutkowski P, Gelderblom H, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):295–302.
17 Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, et al.; RESORCE Investigators. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017 Jan;389(10064):56–66.
18 Krishnamoorthy SK, Relias V, Sebastian S, Jayaraman V, Saif MW. Management of regorafenib-related toxicities: a review. Therap Adv Gastroenterol. 2015;8(5):285–97.
19 Wilhelm SM, Dumas J, Adnane L, Lynch M, Carter CA, Schütz G, et al. Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. Int J Cancer. 2011 Jul;129(1):245–55.
20 Ellis LM. Angiogenesis and its role in colorectal tumor and metastasis formation. Semin Oncol. 2004 Dec;31(6 Suppl 17):3–9.
21 Maeda K, Chung YS, Takatsuka S, Ogawa Y, Sawada T, Yamashita Y, et al. Tumor angiogenesis as a predictor of recurrence in gastric carcinoma. J Clin Oncol. 1995 Feb;13(2):477–81.
22 Carlomagno F, Anaganti S, Guida T, Salvatore G, Troncone G, Wilhelm SM, et al. BAY 43-9006 inhibition of oncogenic RET mutants. J Natl Cancer Inst. 2006 Mar;98(5):326–34.
23 Carlomagno F. Thyroid Cancer: Role of RET and Beyond. Eur Thyroid J. 2012;1(1):15–23.
24 Santoro M, Carlomagno F. Central role of RET in thyroid cancer. Cold Spring Harb Perspect Biol. 2013;5(12):a009233.
25 Pitoia F, Jerkovich F. Selective use of sorafenib in the treatment of thyroid cancer. Drug Des Devel Ther. 2016;10:1119–31.
26 Shen CT, Qiu ZL, Luo QY. Sorafenib in the treatment of radioiodine-refractory differentiated thyroid cancer: a meta-analysis. Endocr Relat Cancer. 2014 Feb;21(2):253–61.
27 McLellan B, Ciardiello F, Lacouture ME, Segaert S, Van Cutsem E. Regorafenib-associated hand-foot skin reaction: practical advice on diagnosis, prevention, and management. Ann Oncol. 2015;26(10):2017–26.