Redifferentiation Therapy—Returning to Our Roots in a Post–Kinase Inhibitor World

Maria E. Cabanillas, Naifa L. Busaidy, and Steven I. Sherman

SUMMARY

Radioactive iodine (RAI) treatment is an effective treatment for differentiated thyroid cancer (DTC); however, many patients are refractory. Using targeted drugs to reinduce RAI sensitivity ("redifferentiation therapy") has long been sought after as the holy grail in endocrine oncology.

See related article by Weber et al., p. 4194

In this issue of *Clinical Cancer Research*, Weber and colleagues add to the growing body of literature of modern approaches to redifferentiation therapy and add to our understanding of how best to target tumors based on their molecular profile (1).

The treatment of patients with metastatic disease due to DTC usually begins with total thyroidectomy followed by RAI. However, only 20% of patients >40 years old will respond to this treatment and the vast majority become RAI-refractory, which portends a worse prognosis (2). Since the original description in the 1940s, RAI was the only systemic and targeted treatment available for patients with metastatic thyroid cancer (3). However, even in the 1950s, it was recognized that RAI uptake could be heterogeneous within tumors and cures uncommon (4). On the basis of observations that expression of the sodium/iodide-symporter (NIS) is reduced in some thyroid cancers, rendering the cornerstone of treatment of metastatic DTC—RAI—ineffective, redifferentiation therapy to restore RAI uptake was proposed decades ago using retinoic acid (5, 6). While these trials from the 1990s showed that the drug could lead to tumors concentrating RAI, tumor responses were modest at best (7), and this strategy has not evolved as an effective approach to therapy.

Fast-forward to 2014 with the approval of the first kinase inhibitor (KI) for thyroid cancer, a total of 7 KIs (sorafenib, lenvatinib, larotrectinib, entrectinib, selpercatinib, pralsetinib, cabozantinib) have been FDA approved for DTC. The selective BRAF +/− MEK inhibitors have been explored in several trials for *BRAF* mutated, RAI-refractory papillary thyroid cancer and are used off-label in many centers. In 2011, Dr. Jim Fagin's lab made the observation that NIS could be upregulated in animals using a selective MEK or BRAF inhibitor (8) opening the field of redifferentiation again and leading to the first in human trial with a KI for redifferentiation (9). The KI era—particularly with more targeted options—also ushered in routine molecular testing of patients with advanced tumors to identify actionable driver mutations and fusions. This has led to a better understanding of the behavior of tumors with particular genomic alterations. *BRAF*-mutated tumors are generally recognized to concentrate RAI poorly, in contrast with those with *RAS* mutations (10). However, as tumors gain additional mutations and as patients are more heavily treated, these tumors become RAI-refractory. Some less common DTC histologies such as Hurthle cell and poorly differentiated cancers are also generally RAI-refractory.

Since the seminal publication by Ho and colleagues (9), another 7 redifferentiation trials (1, 11–15) have been published, and some centers have adopted this practice in their routine management of DTC patients. Redifferentiation treatment is complicated, as time-sensitive and critical steps leading up to RAI imaging and therapy must be factored into planning of redifferentiation (**Fig. 1**). These include (i) selection of appropriate patients, (ii) Selection of KI(s), (iii) Timing of the initiation of the KI(s) in relation to the RAI (given that patients must be on the drug(s) at the time of RAI administration), (iv) RAI planning, (low iodine diet, two recombinant TSH injections, low dose diagnostic scan and optional dosimetry) and the decision to administer therapeutic I-131, and (v) how long to continue the KI after I-131 administration.

The current report by Weber and colleagues (1), describing a prospective, single-center phase IIstudy, is the 8th redifferentiation study in human subjects to be published. RAI-refractory patients with a *BRAF*V600E mutated tumor were treated with dabrafenib/trametinib while the *BRAF* wild-type tumors were treated with trametinib for 21 ± 3 days. Diagnostic whole-body scan (WBS) with I-123 was performed and if uptake seen, I-131 was administered. The primary endpoint was the rate of redifferentiation measured by restoration of RAI uptake; secondary endpoints included treatment response measured by change in thyroglobulin (Tg) and tumor size by RECIST 1.1. The trial included 20 patients, of whom 70% were *BRAF* wild-type. Redifferentiation was achieved in 35% of patients (2/6 *BRAF* mutated and 5/14 *BRAF* wild-type). Objective responses per RECIST (all partial) were seen in 1/7 (14%) of patients treated who received RAI after successful redifferentiation. Peak standardized uptake values (SUV_{peak}) < 10 on baseline FDG-PET scan was associated with redifferentiation, not surprising given the inverse correlation between FDG avidity and RAI uptake. Redifferentiation was not successful in patients whose unstimulated Tg was less than the cohort median following KI therapy, but this did not reach statistical significance. The drugs were deemed safe, but there was no assessment of long-term safety of RAI under redifferentiation.

Across all of the published prospective and retrospective trials to date (1, 9, 11–15) about 136 patients have been studied. The rate of redifferentiation is not clear, given that some patients were treated empirically with RAI, while others were treated based on demonstration of RAI uptake or based on dosimetry. Nonetheless, given these

Department of Endocrine Neoplasia and Hormonal Disorders, The University of Texas MD Anderson Cancer, Houston, Texas.

Corresponding Author: Maria E. Cabanillas, University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1461, Houston, TX 77030. Phone: 713-563-0764; E-mail: mcabani@mdanderson.org

Clin Cancer Res 2022;28:4164–6

doi: 10.1158/1078-0432.CCR-22-1710

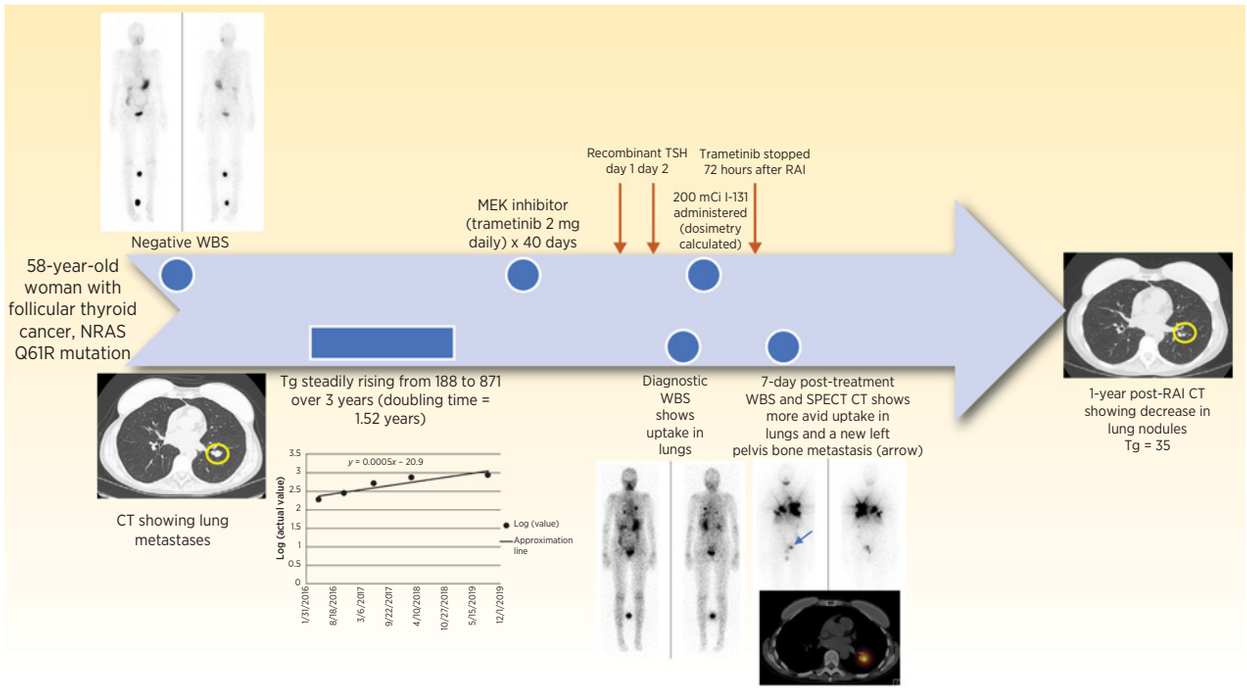

Figure 1.

Redifferentiation therapy in an NRAS-mutated follicular thyroid cancer patient. A 58-year-old woman with RAI-refractory, NRAS Q61R mutated follicular thyroid cancer with slow progression disease (by imaging and thyroglobulin tumor marker) was treated with trametinib (MEK inhibitor) for 40 days prior to receiving 2 doses of recombinant TSH followed by a diagnostic whole-body scan (WBS) with I-123. Diagnostic WBS showed uptake in the lungs; therefore, she received 200 mCi of I131, which was calculated by dosimetry. Trametinib was stopped 72 hours after administration of RAI. Post-treatment scan was performed 7 days later, and this showed more avid uptake in the lungs and a new left pelvic bone metastasis. One year post-RAI showed shrinking lung metastases and declining thyroglobulin.

differences, 33%–69% of patients had restoration of RAI uptake on diagnostic WBS reported, resulting in a partial response per RECIST (within 6–12 months) in 25%–75% of those treated with RAI, and approximately 22% (range: 5%–50%) of those in whom redifferentiation was attempted.

There is agreement that BRAF inhibitors ± MEK inhibitors can be used for *BRAF*-mutated tumors while MEK inhibitors alone should be used for non-*BRAF* mutated tumors. However, in recent years selective NTRK and RET inhibitors, which modulate signaling along the MAPK pathway, have also been reported to result in redifferentiation in patients with these gene alterations (16–18).

The major advantage of redifferentiation is that the toxicity (both clinical and financial) of the long-term use of KIs could be mitigated by stopping these drug(s) if the tumors concentrated RAI—allowing the RAI to do its job controlling the tumor. However, what is not clear is whether adding a MEK inhibitor to a BRAF inhibitor is more efficacious than BRAF inhibitor alone for redifferentiation in *BRAF*-mutated tumors. Future trials could address this question.

Clinical trials for redifferentiation are quite challenging and long-term outcomes of this strategy, particularly overall survival, are still unknown. Differences in success of redifferentiation could be attributed to differing definitions of RAI-refractoriness, potency and mutation-specificity of the different drugs used in these trials, and empiric selection of RAI administered activity vs. dosimetry calculated vs. treatment based on uptake on diagnostic WBS. Clinical predictors that indicate a more well-differentiated state such as pre-redifferentiation Tg and FDG-PET activity could be useful adjunct information to select patients for redifferentiation therapy. Data thus far suggest that patients with higher baseline Tg (1, 13) and lower SUV_{peak} on baseline FDG-PET (1) could predict efficacy of this strategy. Jaber and colleagues (12) hypothesized that a sustained increase in Tg while on the KI could be a marker of redifferentiation, as 7 of 9 patients who were treated with RAI had increasing Tg without evidence of radiographic progression.

Another unknown is the amount of administered I-131 that should be given after redifferentiation. Furthermore, smaller metastatic lesions, non-bony lesions and younger age of the patient predict success of RAI in non-redifferentiation settings, and these differences may not be accounted for across trials. Some trials only allowed patients with macroscopic disease because this is what is accepted to reliably measure oncologic response rates. However, RAI is best used in micro-metastatic disease and therefore in these trials the accepted entry criterion of "measurable disease" may not be optimal to allow assessment of maximal benefit of redifferentiation. Finally, with increasing RAI administration there may be concern for leukemia, secondary solid tumors and anaplastic thyroid cancer transformation, therefore long-term data are needed.

Authors' Disclosures

M.E. Cabanillas reports grants from Genentech and Merck; grants and personal fees from Eisai; and personal fees from Bayer, Eli Lilly, and Exelixis during the conduct of the study. N.L. Busaidy reports other support from Exelixis and Eisai outside the

submitted work. S.I. Sherman reports personal fees from Eli Lilly outside the submitted work.

Acknowledgments

We would like to acknowledge Dr. Mimi Hu and Dr. Steven Waguespack for their assistance with the images for this manuscript. This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Received June 14, 2022; revised July 5, 2022; accepted July 13, 2022; published first July 27, 2022.

References

1. Weber M, Kersting D, Riemann B, Brandenburg T, Fuhrer-Sakel D, Grunwald F, et al. Enhancing radioiodine incorporation into radio iodine refractory thyroid cancer with MAPK inhibition (ERRITI): a single-center prospective two-arm study. Clin Cancer Res 2022;28:4194–202.
2. Durante C, Haddy N, Baudin E, Leboulleux S, Hartl D, Travagli JP, et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. J Clin Endocrinol Metab 2006;91:2892–9.
3. Siegel E. The beginnings of radioiodine therapy of metastatic thyroid carcinoma: a memoir of Samuel M. Seidlin, M. D. (1895–1955) and his celebrated patient. Cancer Biother Radiopharm 1999;14:71–9.
4. Trunnell JB, Brayer FT. Factors governing the development of the chick embryo thyroid. I. Determination of the time at which I 131 collection begins. J Clin Endocrinol Metab 1953;13:89–94.
5. Grunwald F, Menzel C, Bender H, Palmedo H, Otte R, Fimmers R, et al. Redifferentiation therapy-induced radioiodine uptake in thyroid cancer. J Nucl Med 1998;39:1903–6.
6. Simon D, Koehrle J, Reiners C, Boerner AR, Schmutzler C, Mainz K, et al. Redifferentiation therapy with retinoids: therapeutic option for advanced follicular and papillary thyroid carcinoma. World J Surg 1998;22:569–74.
7. Handkiewicz-Junak D, Roskosz J, Hasse-Lazar K, Szpak-Ulczok S, Puch Z, Kukulska A, et al. 13-cis-retinoic acid re-differentiation therapy and recombinant human thyrotropin-aided radioiodine treatment of non-Functional metastatic thyroid cancer: a single-center, 53-patient phase 2 study. Thyroid Res 2009;2:8.
8. Chakravarty D, Santos E, Ryder M, Knauf JA, Liao XH, West BL, et al. Small-molecule MAPK inhibitors restore radioiodine incorporation in mouse thyroid cancers with conditional BRAF activation. J Clin Invest 2011;121:4700–11.
9. Ho AL, Grewal RK, Leboeuf R, Sherman EJ, Pfister DG, Deandreis D, et al. Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. N Engl J Med 2013;368:623–32.
10. Sabra MM, Dominguez JM, Grewal RK, Larson SM, Ghossein RA, Tuttle RM, et al. Clinical outcomes and molecular profile of differentiated thyroid cancers with radioiodine-avid distant metastases. J Clin Endocrinol Metab 2013;98:E829–36.
11. Rothenberg SM, McFadden DG, Palmer EL, Daniels GH, Wirth LJ. Redifferentiation of iodine-refractory BRAF V600E-mutant metastatic papillary thyroid cancer with dabrafenib. Clin Cancer Res 2015;21:1028–35.
12. Jaber T, Waguespack SG, Cabanillas ME, Elbanan M, Vu T, Dadu R, et al. Targeted therapy in advanced thyroid cancer to resensitize tumors to radioactive iodine. J Clin Endocrinol Metab 2018;103:3698–705.
13. Dunn LA, Sherman EJ, Baxi SS, Tchekmedyian V, Grewal RK, Larson SM, et al. Vemurafenib Redifferentiation of BRAF Mutant, RAI-Refractory Thyroid Cancers. J Clin Endocrinol Metab 2019;104:1417–28.
14. Iravani A, Solomon B, Pattison DA, Jackson P, Ravi Kumar A, Kong G, et al. Mitogen-activated protein kinase pathway inhibition for redifferentiation of radioiodine refractory differentiated thyroid cancer: an evolving protocol. Thyroid 2019;29:1634–45.
15. Leboulleux S, Cao CD, Zerdoud S, Attard M, Bournaud C, Benisvy D, et al. MERAIODE: a redifferentiation phase II trial with trametinib and dabrafenib folowed by radioactive iodine refractory differentiated thyroid cancer patients with a BRAFV600E mutation (NCT 03244956). J Endocr Soc 2021;5(Suppl 1):A876.
16. Groussin L, Clerc J, Huillard O. Larotrectinib-enhanced radioactive iodine uptake in advanced thyroid cancer. N Engl J Med 2020;383:1686–7.
17. Groussin L, Bessiene L, Arrondeau J, Garinet S, Cochand-Priollet B, Lupo A, et al. Letter to the editor: selpercatinib-enhanced radioiodine uptake in RET-rearranged thyroid cancer. Thyroid 2021;31:1603–4.
18. Waguespack SG, Tewari SO, Busaidy NL, Zafereo ME. Larotrectinib before initial radioactive iodine therapy in pediatric TRK fusion-positive papillary thyroid carcinoma: time to reconsider the treatment paradigm for distantly metastatic disease? JCO Precis Oncol 2022;6:e2100467.