



THYROID CANCER

Thyroid cancer that no longer responds to radioactive iodine may become sensitive after starting anti-cancer drugs

BACKGROUND

The usual treatment for thyroid cancer is surgery to remove the thyroid gland. If the patient is at increased risk for thyroid cancer recurrence, surgery is followed by radioactive iodine therapy to destroy any remaining thyroid cancer cells. Most patients with thyroid cancer that require radioactive iodine therapy respond to the initial treatment. Those rare patients with either high risk thyroid cancers or those that continue to have recurrence or persistence of the thyroid cancer often receive additional radioactive iodine treatments. However, thyroid cancer cells can lose their capacity to take up iodine from the circulation and, therefore, they can become resistant to radioactive iodine therapy. Certain gene mutations in the thyroid cancer cells, especially BRAF mutations, can affect the thyroid cells ability to take up iodine. A few, small clinical studies have showed that targeted therapy with drugs that inhibit BRAF and MEK, another gene mutation in thyroid cancer cells, may restore the ability of the thyroid cancer cells to take up radioactive iodine. This study performed at the University of Texas MD Anderson Cancer Center evaluated whether the radioactive iodine sensitivity is restored in 13 patients with advanced, radioactive iodine resistant thyroid cancer treated with either a single drug or a combination of BRAF and/or MEK inhibitors.

THE FULL ARTICLE TITLE

Jaber T et al 2018 Targeted therapy in advanced thyroid cancer to resensitize tumors to radioactive iodine. *J Clin Endocrinol Metab* 103:3698–3705. PMID: 30032208.

SUMMARY OF THE STUDY

This is a study of 13 patients with advanced, radioactive iodine resistant thyroid cancer who underwent a radioactive iodine whole-body scan (WBS) while being treated with BRAF and/ or MEK inhibitor drugs. The average age was 55.6 years. A total of 10 patients (77%) had classic or follicular variant of papillary thyroid cancer, 2 patients (15%) had poorly differentiated thyroid cancer and 1 patient (8%) had follicular thyroid cancer. The 9

patients with thyroid cancer with a BRAF mutation were treated with a BRAF inhibitor (7 with dabrafenib, 1 with vemurafenib, and 1 with a combination dabrafenib and trametinib). The 3 patients with thyroid cancer with a RAS mutation were treated with a MEK inhibitor (2 with trametinib, 1 with an investigational drug). One patient who had no identified mutations was treated with a MEK inhibitor (trametinib). The average duration of drug therapy before the radioactive iodine scanning was 14 months.

A total of 8 of the 13 patients (62%) showed radioactive iodine uptake on the whole-body scan and received additional radioactive iodine treatment. One additional patient received radioactive iodine treatment despite of having a negative radioiodine scan. Of note, all 3 patients with RAS mutations showed uptake on the scan and received radioactive iodine treatment. The average I-131 dose was 204 mCi. The cancer drug was discontinued 2 days after the radioactive iodine treatment. During an average follow-up period of 14 months after the radioactive iodine treatment, all nine patients remained off the cancer drugs.

Among the 9 patients who received radioactive iodine therapy, 8 had stable disease and 1 had progressive disease on drug therapy prior to the radioactive iodine treatment. After the radioactive iodine therapy, 3 patients had a partial response, while 5 patients had stable disease. The patient with progressive disease prior to the radioactive iodine therapy had 88% shrinkage of the metastatic cancer lesions after the radioactive iodine therapy. When comparing the responses in the 9 patients on drug therapy prior to the radioactive iodine treatment, 5 patients showed greater responses after the radioactive iodine therapy than with the prior drug therapy.

With regard to adverse effects, 2 patients had an inflammation of the lungs and 1 patient had severe inflammation of the salivary glands after the radioactive iodine therapy. The symptoms of all 3 patients resolved within three months.





THYROID CANCER, continued

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Targeted therapy with BRAF or MEK inhibitor drugs in patients with advanced thyroid cancer with BRAF and/or RAS mutations can re-sensitize the cancers to radioactive iodine and subsequent radioactive iodine therapy can result in a positive clinical response. This provides hope

for the rare patients with advanced, progressive thyroid cancers. Additional studies are needed to identify the patients who are most likely to benefit from this treatment, and to evaluate the magnitude and duration of the clinical response and its impact on survival.

—Alina Gavrila, MD, MMSC

ATA THYROID BROCHURE LINKS

Thyroid Cancer (Papillary and Follicular): <https://www.thyroid.org/thyroid-cancer/>

Radioactive Iodine: <https://www.thyroid.org/radioactive-iodine/>

ABBREVIATIONS & DEFINITIONS

Differentiated thyroid cancer (DTC): includes papillary and follicular thyroid cancer.

Cancer recurrence: this occurs when the cancer comes back after an initial treatment that was successful in destroying all detectable cancer at some point.

Iodine: an element found naturally in various foods that is important for making thyroid hormones and for normal thyroid function. Common foods high in iodine include iodized salt, dairy products, seafood and some breads.

Radioactive iodine (RAI): this plays a valuable role in diagnosing and treating thyroid problems since it is taken up only by the thyroid gland. I-131 is the destructive form used to destroy thyroid tissue in the treatment of thyroid cancer and with an overactive thyroid. I-123 is the non-destructive form that does not damage the thyroid and is used in scans to take pictures of the thyroid (Thyroid Scan) or to take pictures of the whole body to look for thyroid cancer (Whole Body Scan).

Radioactive iodine uptake (RAIU): this is a measurement of thyroid tissue activity, either normal or cancerous, and is reported as the percent of a dose of radioactive iodine that is retained in the thyroid tissue 24 h after the dose is given.

Targeted therapy (TTx): drugs that specifically attack the cancer cells without damaging the normal cells, thus resulting in fewer side effects.

Mutation: A permanent change in one of the genes.

Cancer-associated genes: these are genes that are normally expressed in cells. Cancer cells frequently have mutations in these genes. It is unclear whether mutations in these genes cause the cancer or are just associated with the cancer cells. The cancer-associated genes important in thyroid cancer are BRAF, RET/PTC, TERT and RAS.

BRAF gene: this is a gene that codes for a protein that is part of a chain of molecules working together to signal the cells when to grow and divide. Mutations in the BRAF gene in adults appear to cause cancer. Dabrafenib and vemurafenib are anticancer drugs that target the mutated BRAF proteins within the cancer cells, thus slowing down the cancer growth.

MEK 1 and 2: are proteins located further down the chain of molecules in the BRAF pathway. Trametinib is an anticancer drug that targets these proteins, thus affecting the cancer growth.

Sialadenitis: inflammation of salivary gland.

