AMERICAN THYROID ASSOCIATION
Optimal Thyroid Health for All

Volume 13 | Issue 8 | August 2020

Clinical Thyroidology® for the Public

THYROID AND CANCER

Development of thyroid problems with immunotherapy drugs for certain cancers is associated with favorable survival

BACKGROUND

New chemotherapy drugs for the treatment of cancer have been activating the immune system to target and kill cancer cells. One major new category of immunotherapy drugs is known as immune checkpoint inhibitors that activate the immune system. These immunotherapy drugs have significantly improved survival for various types of cancers. However, these treatments may be associated with many immune-related side effects. In particular, many patients treated with the immune checkpoint inhibitor anti-PD-1 develop thyroid problems. Most often, this results in an inflammation of the thyroid (thyroiditis) that causes a short period of hyperthyroidism followed by hypothyroidism. Compared to common forms of thyroiditis (subacute thyroiditis, post-partum thyroiditis), there is usually no associated thyroid pain and the time from hyperthyroidism to hypothyroidism is shorter (3 months vs 6-9 months). This is often associated with an increase in levels of anti-thyroid antibodies (TPO and thyroglobulin antibodies).

Prior studies have suggested that the cancer patients who develop thyroid problems while taking immunotherapy drugs have improved survival. The goal of this study is to evaluate the association between thyroid function test results, anti-thyroid antibody concentrations and survival rates in a large group of cancer patients treated with anti-PD-1 drugs.

THE FULL ARTICLE TITLE

Basak EA et al. 2020 Overt thyroid dysfunction and anti-thyroid antibodies predict response to anti-PD-1 immunotherapy in cancer patients. Thyroid. Epub 2020 Mar 10. PMID: 32151195.

SUMMARY OF THE STUDY

This is a study of 168 patients with non-small-cell lung cancer, renal-cell cancer and melanoma followed at Erasmus Medical Center in the Netherlands. The patients started anti-PD-1 treatment with nivolumab (every 2 weeks) or pembrolizumab (every 3 weeks). Thyroid function tests, including thyroid-stimulating hormone (TSH) and free thyroxine (FT_4) levels were measured every 2 or 3 weeks before each anti-PD-1 infusion. Antibody levels to thyroid peroxidase (anti-TPO) and thyroglobulin (anti-Tg) were measured at baseline and after 2 months of treatment. The patients were followed for an average time of 15 months. Overall survival (OS) was defined as the period between the start of therapy until death, while progression-free survival (PFS) was calculated until tumor progression, based on standard Response Evaluation Criteria In Solid Tumors (RECIST) criteria or death.

A total of 27 patients (16%) had pre-existing thyroid problems, 9 patients being hyperthyroid and 18 patients being hypothyroid before starting treatment. Among these patients, 22 patients had mild thyroid disease. During the study period, 34 patients (20%) developed subclinical thyroid dysfunction and 20 patients (12%) developed overt thyroid dysfunction on treatment. The average time to develop thyroid dysfunction was 2.8 months.

Patients who developed overt thyroid dysfunction during anti-PD-1 treatment had significantly higher survival rates than patients without thyroid dysfunction at 1 year (OS, 94% vs. 64%; PFS, 64% vs. 33% patients). During treatment, patients with higher anti-thyroid antibody levels had higher survival rates than patients with lower anti-thyroid antibody level, with 1-year OS rates of 83% and 49% and PFS rates of 54% and 20%, respectively. For the majority of patients (84%), the antibody status did not change from baseline until the end of treatment. Most patients with higher levels of antibodies during the treatment were also observed to have a higher antibody count before treatment.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Development of overt thyroid problems and higher antithyroid antibody levels during anti-PD-1 treatment were associated with a significant improvement in both overall and progression-free survival rates. These data suggest that this could be used as a predictive marker

THYROID AND CANCER, continued

for response to treatment. Additionally, higher baseline antithyroid antibody levels usually remain at the same level during the treatment and predict better survival rates among cancer patients treated with anti-PD-1 immunotherapy.

— Alina Gavrila, MD, MMSC

ATA THYROID BROCHURE LINKS

Hypothyroidism (Underactive): https://www.thyroid.org/hypothyroidism/
Hyperthyroidism (Overactive): https://www.thyroid.org/hyperthyroidism/
Thyroiditis: https://www.thyroid.org/thyroiditis/

ABBREVIATIONS & DEFINITIONS

Immunotherapy: a type of treatment that helps a person's immune system fight diseases, such as cancer. A class of immunotherapy drugs is known as immune checkpoint inhibitors.

Anti–programmed cell death 1 (anti-PD-1) immunotherapy: treatment that targets the programmed cell death protein 1 (PD-1) to activate the immune system to attack cancer. PD-1 is an immune checkpoint protein found on the surface of human cells that decreases the response of the immune system to its own cells. PD-1 prevents the development of autoimmune diseases, however, it also prevents the immune system from killing cancer cells.

Autoimmune thyroid disease: a group of disorders that are caused by antibodies that get confused and attack the thyroid. These antibodies can either turn on the thyroid (Graves' disease, hyperthyroidism) or turn it off (Hashimoto's thyroiditis, hypothyroidism).

Thyroiditis: inflammation of the thyroid, most commonly cause by antibodies that attack the thyroid as seen in Hashimoto's thyroiditis. It can also occur in response to a viral infection.

Hypothyroidism: a condition where the thyroid gland is underactive and doesn't produce enough thyroid hormone. Subclinical hypothyroidism is a mild form where the only abnormal hormone level is an increased TSH. Overt hypothyroidism is clear hypothyroidism with an increased TSH and a decreased T_4 level. All patients with overt hypothyroidism are usually treated with thyroid hormone pills.

Hyperthyroidism: a condition where the thyroid gland is either overactive or inflamed and produces too much thyroid hormone. Subclinical hyperthyroidism is a mild form where the only abnormal hormone level is a decreased TSH. Overt hyperthyroidism is clear hyperthyroidism with a decreased TSH and an increased T_4 level.

TSH: thyroid stimulating hormone — produced by the pituitary gland that regulates thyroid function; the best screening test to determine if the thyroid is functioning normally.

Thyroxine (T_4): the major hormone produced by the thyroid gland. T_4 gets converted to the active hormone T_3 in various tissues in the body.

TPO antibodies and Thyroglobulin antibodies: these are antibodies that attack the thyroid instead of bacteria and viruses, they are a marker for autoimmune thyroid disease, which is the main underlying cause for hypothyroidism and hyperthyroidism in the United States.

RECIST: Response Evaluation Criteria in Solid Tumors — this is a set of published rules that define when cancer patients improve ("respond"), stay the same ("stable") or worsen ("progression") during treatments.