The evolving field of thyroid cancer: refinement of old and creation of new paradigms

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Since the landmark paper by Mazzaferri and Jhiang (1) indicating the benefit of adequate surgery and postoperative radioactive iodine treatment in patients with well-differentiated thyroid cancer (DTC), a lot has been learned about prognostic factors associated with disease recurrence and mortality and the risks and benefits of treatment. In addition, over the past 3 decades we have experienced a dramatic improvement in imaging and laboratorial techniques resulting in highly sensitive and specific studies for disease detection, and have observed a significant advance in the understanding of the molecular pathogenesis of thyroid cancer.

This accumulated knowledge has confirmed a few paradigms and has provided important insights that have refined the treatment of thyroid cancer. First, surgery is the mainstay treatment of thyroid cancer and therefore an experienced surgeon and an adequate surgical treatment have the highest impact in cure. Second, the major roles and best responses of radioactive iodine treatment are in reducing recurrence rate in high-risk patients and in treating young patients with micronodular lung metastases and; third, the development of kinase inhibitors has been a major breakthrough in treating metastatic thyroid cancer, not only DTC but also medullary thyroid cancer (MTC).

In this issue of Archives of Endocrinology and Metabolism three papers describe different facets of thyroid cancer treatment. On one side of the spectrum, Furtado and cols. demonstrate the low incidence of persistent (3.5%) and recurrent disease (2.5%) in patients with papillary thyroid cancer with less than 5 lymph nodes detected only at the operative procedure and without other poor prognostic factors (2). As expected, these patients have low risk of recurrence raising the question whether radioactive iodine treatment provides any benefit, a situation in which the disease could be less harmful than the treatment. Interestingly, in the 2009 American Thyroid Association guidelines, all patients with lymph node (LN) metastases (N1 disease), regardless of number and size of LN, were considered intermediate risk and adjuvant radioactive iodine treatment was recommended (3). However, data have accumulated demonstrating that the risk of recurrence is significantly lower in patients with small LNs detected pathologically when compared to pre-operatively detected lymph nodes (4-6), findings confirmed in the study by Furtado and cols.

On the other side of the spectrum, two papers describe the “good and bad” of tyrosine kinase inhibitors. In one paper, Pitoia and cols. report a patient with advanced MTC and ectopic Cushing’s syndrome in whom treatment with vandetanib resulted in rapid resolution of hypercortisolism (7). Ectopic ACTH syndrome is rarely observed in MTC but is usually associated with extensive disease and significant symptoms. The control of cortisol hypersecretion results in symptomatic relief and better quality of life. This is an important observation that has been also demonstrated with sorafenib and sunitinib and expands the known effects of kinase inhibitors. In a second
paper, Pitoia and cols. report a patient with progressive iodine-refractory DTC in whom treatment with sorafenib provided partial tumor response but was associated with significant thrombocytopenia, requiring dose adjustment (8). Adverse events associated with kinase inhibitors are frequent and this report underlines the importance of being aware that unexpected side effects, such as thrombocytopenia, can also be observed.

In recent years a lot of progress has been made in the treatment of metastatic thyroid cancer. The discovery of the RET proto-oncogene and RAS mutations in MTC, mutations of RAS, BRAF, RET/PTC in DTC, as well as other molecular abnormalities that result in hyperactivation of kinase receptors and signaling pathways important for tumor cell proliferation, provided the basis for the investigation and approval of several multi-kinase inhibitors for the treatment of metastatic thyroid cancer including vandetanib and cabozantinib for MTC and sorafenib and lenvatinib for DTC (9-13). For both MTC and DTC, these therapies are associated with improvement of progression-free survival, tumor reduction and symptomatic control compared to patients treated with placebo. Despite the benefits observed in disease control, all of these drugs are associated with slightly different side-effect profiles, which makes clinical monitoring and careful management of adverse events a priority in the care of these patients. Despite the significant advances, the quest for the identification of newer therapies is still in progress, as the ideal treatment would be one associated with improvement of overall survival, less adverse effects and ultimately cure of disease.

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REFERENCES


2. Furtado MS, Rosario PW, Calsolar MR. Persistent and recurrent disease in patients with papillary thyroid carcinoma with clinically apparent (cN1), but not extensive, lymph node involvement and without other factors for poor prognosis. Arch Endocrinol Metab. 2015;59(4):285-91.


