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Case Report
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Lenvatinib for Radioactive Iodine-Refractory Papillary Thyroid Carcinoma: A Case Report

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Abstract

Thyroid cancer is the main example of neoplasia that affects endocrine glands, by frequency of presentation (9th place in world incidence 2018). Around 90% of thyroid carcinomas will correspond to the Differentiated group, obtaining adequate survival >80% at 40 years. 15% to 20% of the patients will not respond or will lose the ability to respond to radioactive Iodine, reducing the survival in 3 years to 5 years. We present the case of a female patient with criteria of Radioactive Iodine-Refractory and at the beginning had voluminous metastatic disease. The patient was assessed in a multidisciplinary manner, and started with tyrosine kinase inhibitor, obtaining a close to complete response after one year of treatment. Because hypertension, diarrhea, fatigue, and hepatic dysfunction are very common, close attention should be paid, we decided to prepare this report where lenvatinib was proved to be remarkably effective after several other ineffective multidisciplinary management.

Keywords: Papillary thyroid cancer; Radioactive iodine-refractory; Lenvatinib

Introduction

The thyroid cancer is the most common sort of endocrine cancer, because this disease has high incidence, ranking as the ninth most frequent cancer in 2018, with an estimated 5,67,000 new cases worldwide. Over the last two decades or so, there has been an increase in the incidence of thyroid cancer, may be attributed to the emergence of new diagnostic techniques [1,2].

Incidence rates are 3 times higher in women than in men, in relative terms, the disease represents 1 in 20 estimated female cancer diagnoses; but the lowest mortality rates are seen in both men and women, with rates below 0.5 per-100,000 persons per year. Lower mortality rates are associated with the higher frequency (~90%) of Differentiated Thyroid Cancer (DTC), and only a few poorly differentiated carcinoma/undifferentiated carcinoma. DTC can appear at any age, the group with the highest incidence is 45 years to 54 years old, average age of 50 years at diagnosis [2-4].

Due to early diagnosis and timely treatment, 5-year survival is >95% and at 40 years >80%. The remaining percentage (15% to 20%) will correspond to patients who despite adequate treatment (surgery, radioactive iodine and external radiotherapy) will continue without a satisfactory response, in which the main mechanism of attrition is refractoriness to radioactive iodine, which in most of the cases will be due to metastatic disease, bulky or that lose the ability to capture. At the time of diagnosis, <10% of patients will be found with unresectable or metastatic disease, and another 10% of patients will be detected metastatic disease during treatment, which is important because only 2/3rd of patients with metastases presented radioactive iodine uptake, of which only 42% will reach cure. It is in these patients where the survival is reduced obtaining as average life 3 years to 5 years [4-6].

Because it is a rare presentation of a common condition and the evolution of therapeutic tools, we decided to prepare this report in order to understand conditions not understood until now.

Case Report

We describe the case of a female patient, 54 years old, referred to a previous history of loco regionally advanced papillary thyroid cancer, treated with multiple radical neck resections, external radiotherapy and two therapeutic applications with radioiodine with cumulative dose of 250 mCi, with adequate suppression of TSH, in a time interval of 3 years, in follow-up with thyroglobulin, total body scans with Iodine-131 and Positron Emission Tomography Computed Tomography (PET-CT) with 18-flourdeoxyglucose; without achieving control of the disease.

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In reviewing recent studies we found a positive thyroid scan for disease in the right neck and left thorax, corresponding to the PET-CT that shows metabolic activity in levels IIB and III of the neck, in relation to 2 tumors (1 in each level) less than 2 cm of smaller diameter each, with SUVmax of 36 and 46 respectively, and a nodule smaller than 1 cm with SUVmax of 7 in upper left pulmonary fissure. In addition, she had a lymph node dissection report assessed by department of pathology concluding in papillary thyroid carcinoma classic pattern.

So, it concludes in regional and distance progression of the disease, suggesting new therapeutic application with radioiodine dose of 150 mCi, after suspension of levothyroxine for 5 weeks.

The cumulative dose of radioiodine until that application was 400 mCi, 4 months later, in the follow-up of the patient with tomography, total body scan with iodine-131 and thyroglobulin without suppression of TSH, we found the following results: TSH >100 mU/L, Thyroglobulin 0.20 mU/L, negative thyroid scan, but in the contrast tomography of the neck, thorax and abdomen, a lymph node of approximately 1cm larger diameter with loss of morphology in level IV of the right neck is observed, as well as persistence of activity in level IIB of right neck, suggesting to the patient the realization of an 18F-FDG PET-CT.

The new PET-CT performed at the end of the same month, reported -progression of the disease, evidencing new hyper metabolic activity points, this time in levels IIA, IIB, IV, mediastinal and left parahiliar, with measures between 2 cm to 3cm in diameter and SUVmax of 47.2 for the target lesion that in this case was the left parahiliar.

For these results, we classified the disease as Iodine-refractory, the patient was in good functional condition (as it has been up to date), so cabinet studies are requested including lipid profile, serum electrolytes, liver function tests, blood count, time of coagulation and electrocardiogram, to be assessed by cardiology, continue follow-up with endocrinology and if there is no contraindication, the initiation of targeted therapy with a Multi-Tyrosine Kinase Inhibitor was planned.

The results and assessments showed a safe profile for the start of the drug, the treatment plan is explained to the patient (objectives and unwanted effects), accepting the therapy. So, we decided to prescribe Lenvatinib, considering the encouraging results of SELECT study, Schlumberger et al., with a dose of 24 mg orally once a day and appointment in 28 days to evaluate the next injection with control studies. After one month, the patient presented severe hypocalcemia and arterial hypertension with figures of up to 170 mmHg/90 mmHg, she was stabilized by cardiology with which continuous monitoring and treatment with calcium antagonist, we decided adjustment of lenvatinib at a dose of 20 mg. After the 3rd month of the drug and without presenting adverse effects during that time, 18F-FDG PET-CT is requested, reporting a partial response by PERCIST, in head and neck with resolution of previous hypermetabolic regions, left parahiliar adenopathy remains the target lesion, but it shows a size reduction in more than 50% of the diameters and SUVmax of 17 (previous 47.2). We continue with the medication, but during the sixth month appeared G2 diarrhea (CTCAE v.4), we started toxicity management, however, due to the fact that the improvement of the symptoms is minimal, we decided to change the dose to 14 mg of lenvatinib and re-quote the 18F-FDG PET-CT study for follow-up.

One year and 2 months after initiation of the drug, the most metastatic tumors in the lung disappeared, without adverse effects, deciding to continue with lenvatinib, the result of last PET-CT reports a new partial response by decreasing the single hypermetabolic lesion in 50% of the diameters and current SUVmax in 9.2.

Currently, the patient is in excellent condition, performing her life in a normal way, without toxicities and clinically without data of her illness.

Discussion

Radioactive Iodine-Refractory DTC is a condition in which there is no curative treatment so far, the use of chemotherapy is very toxic, has little response (around 10% to 20%) and without impact on survival, External radiotherapy because it is a local treatment is limited to palliation. This panorama has begun to change in these last two decades thanks to the study of molecular alterations in thyroid cancer and the development of white therapy with the purpose of inhibiting the mechanisms of activation and immortalization of neoplastic cells, generating control of the disease and impacting on survival. It is necessary to be scrupulous in which patients will benefit from these treatments.

- Several oncology committees have worked on the definition of refractoriness to radioactive iodine in patients with differentiated thyroid cancer, sharing the following parameters [7,8]:Patients with metastatic DTC at diagnosis without radioactive iodine uptake in the thyroid scan prior to initial treatment.

- Patients, who, in radioactive iodine scan, present partial (not total) uptake of the number of lesions.

- Patients who initially had uptake to radioactive iodine and that later lose the capacity of uptake and continue with evidence of disease.

- Patients with metastatic disease and uptake of all lesions in the thyroid scan, which after the therapeutic application of radioactive iodine, show progression of the disease.

- Patients with uptake by thyroid screening, but with no or minimal response (without being partial) to the therapeutic application of radio iodine, with a cumulative dose of 600 mCi.

- Patients in whom the disease is unresectable and voluminous, where radioactive iodine is not indicated as inefficient and palliative external radiotherapy.

In those patients is necessary to continue with CT and in the best case with PET-CT every 3 months to 4 months, if there is progression of the disease in less than 12 months, worsening of symptoms, bulky tumors or with serious risk of local complication, it is advisable to start systemic treatment [8].

The molecular studies in DTC have shown us that the main mutation is the substitution of glutamic acid instead of valine in the amino acid 600 of the BRAF protein, this BRAF Val600Glu mutation usually presents between 50% to 60%, predominating in the classic carcinoma variant thyroid papillary, and this mutation is associated with more aggressive clinical pictures. Of which 20% to 25% present rearrangement RET/PTC1-3, PAX8-PPARγ, mutations in RAS, among others, as well as the over-expression of receptors such as vascular endothelial growth factor (1-3), fibroblast growth factor (1-4) and α-platelet-derived growth factor [9].

All these alterations have given way to the creation of targeted therapies, such as the motesanib studied in 2008 in iodine-refractory DTC patients, achieving partial responses and improvement of symptoms. At this time the targeted therapy with better results are multi-target, which in this condition the drugs that have generated the greatest impact, getting approval by the European and American medicines safety agencies are Lenvatinib and sorafenib [9,10].

Sorafenib in the phase 3 study by Brose et al., got partial responses in 12.2%, stable disease >6 months in 42% and an average in progression free survival of 10.8 months. On the other hand, the phase 3 study by Schlumberger et al., in which lenvatinib was used; partial answers were obtained in 64.8%, stable disease >6 months in 29.8% and a progression-free period (average) of 18.3 months. Due to the need for evidence-based medicine that demonstrates which drug is better, a study comparing both therapies is necessary to generate more effective and safe decisions for patients [11,12].

Conclusion

Radioactive Iodine-Refractory Differentiated Thyroid Cancer continues to be an unfavorable condition, with no curative treatment option until now, but with the proper identification of patients and the use of targeted therapy, we can have a positive impact on survival and more importantly in the quality of life, existing improvement from the second month of beginning of the treatment. Without forgetting the unwanted effects, which in some (hypertension) was related to response to treatment, needing a closer monitoring and therapeutic modifications.

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