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Case Report

Challenges in Follicular Radioiodine-Refractory Differentiated Thyroid Cancer (RAIR-DTC), a Focus in the TKI Agents

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Abstract

Papillary carcinoma of the thyroid is a follicular type cancer, constituting the dominant histological type of all malignant neoplasms affecting the thyroid gland. His prognosis is generally favorable. The situations where this cancer becomes refractory to the action of radio-metabolic therapy are a real challenge for any clinician. The surgical resumption whenever possible, the use of chemotherapy with tyrosine kinase inhibiting agents, and external radiation therapy are the pillars of management in this type of cancer. We expose through three observations this issue and we discuss the approach toward this clinical situation.

Keywords: Papillary Carcinoma – Radioiodine-Refractory Differentiated Thyroid Cancer RAIR-DTC – Tyrosine Kinase Inhibitors TKI.

INTRODUCTION

GT malignancies represent only less than 1% of all solid cancers, of which papillary carcinoma is largely the most common tumor, immediately followed by vesicular carcinoma [1]. The prognosis of follicular (papillary and vesicular) neoplasia is excellent; with a 10-year survival ranging from 80 to 94% and a recurrence rate only around 5% [2]. This excellent survival rate is related to their -in-rule- excellent response to RAI and the suppressive treatment with levothyroxine [3]. In comparison to other histological types, this phenomenon of resistance to RAI seems to be much more interesting for oncocytic carcinomas, whose prognosis remains less good compared to vesicular strain neoplasms [4]. Other factors, especially genetic ones, which may also expose resistance to RAI; these genetic aberrations can interest both follicular-type tumours and other cell lines. The iodo-refractory character is a very bad sign of progression and it is most often indicative of lethality (the specific mortality related to the disease itself and its direct complications) [5]. Today, targeted therapy with tyrosine kinase inhibitors ITK is the first line of defense in cases of iodo-refractory disease especially in distant metastases [6]. The effectiveness of these tyrosine kinase inhibitors in terms of iodo-refractory carcinomas has been finely studied by numerous real-life cohorts, thus offering a glimmer of hope within the limit of disease progression, and in improving the quality of life of patients at advanced stages [7]. The choice of molecule depends essentially on the stage of the disease, the potential toxicity to treatment, and the availability (accessibility) of treatment in the country. The prescription of tyrosine kinase inhibitors most often requires a multidisciplinary consultation meeting, and the follow-up is also done in a collegial way including the endocrinologist, oncologist, and radiologist.

OUR CLINICAL CASES

We describe three (03) cases of 3 distinct patients who, during their follow-up for papillary cancer, were diagnosed with an iodo-refractory disease.

The first patient aged 64 years, followed since 2017 for CPT, operated with lymph node dissection, pT1bN1Mx and irradiated with iodine 131 on three

occasions (cumulative dose: 450mCi). Whose evaluation reveals a biological residual disease (Tg=100ng/mL), and morphological; CT-Scan and MRI showed a magma of retro-pharyngeal lymphadenopathy. This contrasting biological and morphological progression and an absence of fixation at the last 2 post-RAI scans, thus suggesting a cancer refractory to AKI. Functional imaging by 18-FDG-Pet-Scan confirming the presence of the residues mentioned above. An external radiotherapy was indicated, for which our patient had received six sessions, coupled with the suppressive treatment as to be under a target of TSH less than 0.1 m IU/L. The evolution is in favor of residual disease (Tg = 74 ng/mL) and stationary morphological.

The second patient is 54 years old female, followed since 2012 for PTC staged pT4N1Mx, having had already 05 surgeries and irradiated 04 times with a cumulative dose of 450 mCi. The latest biological assessments show a residual disease with thyroglobulin levels at 2.32ng/ml, Anti-thyroglobulin Antibodies at their upper limit value of 18 IU/ml. Concomitant and a morphological progression including a very hypo echogenic right thyroid tumor residue, non-vascularized measuring 15x8.5x22 mm, with suspicious-looking cervical adenopathosa. The isotopic mapping has returned white too. While functional imaging by Pet-scan confirms the presence of 5 hypermetabolic foci in the neck, and one pulmonary foci thus confirming its refractory character to radioactive iodine.

The 3rd case is that of a 51-year-old lady, who underwent surgery in 2022 for multifocal papillary carcinoma of the thyroid, staged p-T4aN1Mx, with several poor prognosis factors, namely an initially incomplete surgery, vascular emboli and a first scan objectifying fixations outside the thyroid bed. Having received a cumulative dose of 400 mCi of I131 RAI before being interrupted due to biological and morphological progression, that progressive disease was contrasting and a white maps over 2 consecutive scans. She kept an active carcnima with multiple foci on Pet-scann, fixing in his 2 pulmonary areas, the vertex, and the right hip in addition to a persistent cervical fixation. She has been put on Lenvatinib (Lenvima®), at a dose of 24mg per day. During the first 03 months of treatment, she maintained a stationary disease both biologically and morphologically. The kinetics of thyroglobulin quickly stagnated at around 120 ng/mL +/- 17 versus an earlier value of 238 ng/mL. The tolerance profile was marked by mainly digestive intolerance with nausea, vomiting and anorexia with slight cytolysis less than 2 times above the upper limit of normal.

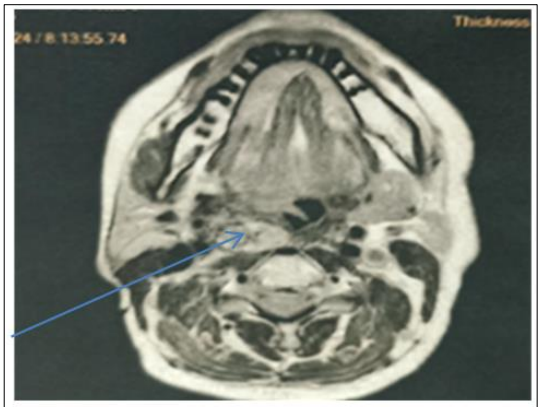
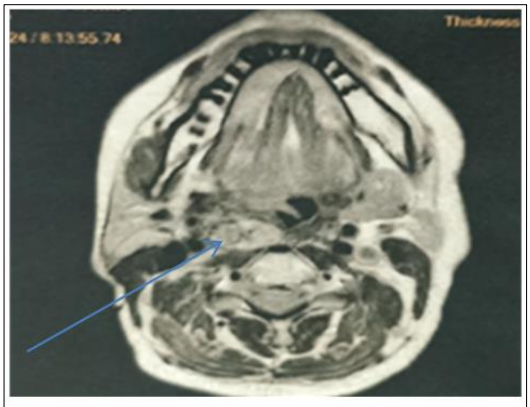


Figure 1 : scan image of retro pharyngeal ADP magma.



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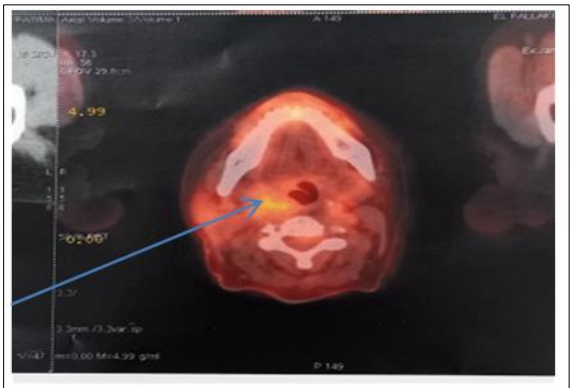

Figure 3 : PET scan Pet-Scan 18-FDG: image of retro pharyngeal ADP magma.

DISCUSSION

It is estimated today that 10% of patients followed for CPT would develop metastases, 2/3 of which would be refractory to RAI I-131 [8]. Thyroid carcinomas of vesicular strain metastatic and refractory to iodine are considered to have a poor prognosis, responsible for a reduction in 10-year survival to 10%. This entity of cancers is increasingly common, and could interest 5 to 10% of all cases operated for thyroid carcinomas [9]. Indeed, the concept of iodine-refractory cancer is not always unanimous and it can involve several stages reflecting a progressive disease or a heterogeneous expression. According to the ATA, refractoriness can be stratified into 6 stages [10]:

- The malignant/metastatic tissue cannot concentrate RAI during a radioiodine diagnostic scan.
- The malignant tissue cannot concentrate IPR during a post-I131 scan.
- The tumor loses the ability to concentrate radioiodine after previous evidence of avid disease for RAI.
- The RAI is concentrated in only some lesions.
- Progression of metastases continues even with significant absorption of RAI.
- Have totaled more than 600 mCi of cumulative iodine therapy.

According to this approach, our patients can all be classified in category 3, that of a disease that loses the ability to concentrate the radio-metabolic treatment marked with Iodine 131 essentially after the 2nd course. Yet during the first two RAIs our patients normally stared. The management of iodo-refractory carcinomas ranges from active surveillance with inhibitor therapy to targeted therapies using tyrosine kinase inhibitors as the last alternative after ineffective external radiotherapy [11].

Active monitoring is an important step in the management of iodo-refractory thyroid cancers [12]. Indeed, a large number of iodorefractory patients are asymptomatic, with low tumor volume, or presenting a slowly progressive disease. In this context, clinical, biological and morphological monitoring every 3-4 months can be proposed, including a TSH target of less than 0.1. The morphological monitoring in this context is based on data from functional imaging Petscann [13]. This imaging by Gallium 68-labelled PET scanner has shown its superiority over the fluorinated 18FDG PET scanner in the evaluation and monitoring of iodorefractory thyroid cancers [14].

For more than a decade, targeted therapies using tyrosine kinase inhibitors have been advocated in the first line after the failure or impossibility of other therapeutic methods. Their mechanisms of action differ from one molecule to another; some targeting VEGF-R: it is the pathway for angiogenesis, while others molecules directly target genetic mutations (such as B-RAF) as well as immunotherapy through immuno-modulatory treatments. [15]. The indications of tyrosine kinase inhibitors are well codified and subject to a thorough study on a case-by-case basis, most often during multidisciplinary consultation meetings.

Consensually, the therapeutic escalation includes a total thyroidectomy for carcinological purposes associated or not with a lymph node dissection according to well-codified rules indicating the dissection, followed by an adjuvant ARI in most cases, especially in cases of high-risk and intermediate-risk cancer recurrence [6]. Cases with poor response to these first 2 pillars of treatments must be the subject of a molecular test identifying somatic mutations exposing to refractory disease [6]. This group of patients can secondarily follow 3 treatment alternatives depending on the degree of progression of the disease (sometimes 2 alternatives combined at once); a surgical resumption in oligo-metastases with a small accessible residue, external radiotherapy according to several possible methods EBRT / SABR or SRS-SRT HA-WRT, and finally the systemic treatment route including tyrosine kinase inhibitors [6]. As a general rule, these systemic therapies should be indicated in patients with metastases, rapid tumor progression, symptomatic patients and/or suffering from a threatening progression, difficult to control by other approaches (i.e. surgical resumption and external radiation therapy) [16].

The multiple clinical trials found proven effectiveness of all tyrosine kinase inhibitors versus the 'placebo' arm. Lenvatinib (HR 0.19, 95% CrI, 0.14–0.25) would offer a better progression-free survival "PFS" compared to Sorafenib (HR 0.59, 95% CrI, 0.45–0.76), Versus Vandetanib (HR 0.70, 95% CrI, 0.55–0.89), Apatinib (HR 0.26, 95% CrI, 0.14–0.47), and finally Anlotinib (HR 0.21, 95% CrI, 0.12–0.37). As for the assessment of overall survival "OS" it was also significantly higher compared to placebo, showing a rate in the Apatinib arm (HR 0.42, 95% CrI, 0.18–0.97) and Anlotinib arm (HR 0.36, 95% CrI, 0.18–0.73). On this point, Anlotinib appeared as the most statistically beneficial agent according to the analysis of the area under the cumulative SUCRA curve. Finally, Lenvatinb, an agent used in the case of our third patient, demonstrated a better rate of "progression-free survival" PFS in patients with iodo-refractory carcinomas RAIR DTC. Thus making it the best tyrosine kinase inhibitor agent suitable for this subclass of patients [7].

CONCLUSION

Papillary thyroid cancer is the most striking histological type of all thyroid neoplasms in statistical terms. His treatment relies on total thyroidectomy, RAI, and blocking treatment. Cases of iodo-refractory cancer constitute a great challenge for the endocrinologist, and require the search for therapeutic alternatives, sometimes systemic. In this context, tyrosine kinase inhibitors

appear as a promising treatment that improves the quality of life of patients at metastatic stages.

Abreviations:
18FDG PET: 18F-fluorodeoxyglucose Positron Emission Tomography
ATA: American thyroid association
DTC: Differentiated thyroid carcinoma
EBRT: external Beam Radiation Therapy
HR: hazard ratio
OS: overall survival
PFS: progression-free survival
RAIR-DTC: adioiodine-refractory differentiated thyroid cancer
RAI : radioactive iodine
SABR: stereotaxic ablative body radiotherapy
SRS-SRT: stereotaxic radiosurgery-sterotaxic radiotherapy
SUCRA: Surface Under the Cumulative Ranking curve
VEGFR: Vascular Endothelial Growth Factor Receptor

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