

## Perspectives on the use of tyrosine kinase inhibitors in thyroid cancer

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### Abstract

**Introduction:** Thyroid cancer has generally a good prognosis after surgical and/or radioactive iodine (RAI) treatment; however, these tumors that persist or that are not candidate to these treatments have a worse prognosis, which makes the use of tyrosine kinase inhibitors (TKIs) a good management alternative, since it has demonstrated progression-free survival (PFS) and response rate benefits, and it is, therefore, important to describe new markers and future therapies for this type of tumors. **Materials and methods:** The purpose of this review is to describe the current state of the treatment of advanced or relapsing thyroid cancer that is not susceptible to management with surgery or RAI, the benefits, and limitations of the use of TKIs, as well as an analysis of this tumor's molecular biology and its clinical repercussion. **Results:** The use of sorafenib and lenvatinib in differentiated thyroid carcinoma that is refractory to RAI, and cabozantinib and vandetanib for advanced medullary carcinomas, has demonstrated benefit in this type of patients, with an impact on PFS, response rates, and disease control. There are ongoing studies with immunotherapy, and we will be alert for their results. **Conclusion:** The treatment with TKI in metastatic thyroid cancer, has shown benefit, the determination of mutations and markers will determine which is the best TKI for the different subtypes of thyroid cancer.

**Key words:** Thyroid cancer. Tyrosine kinase inhibitors. Treatment.

### Perspectivas sobre el uso de inhibidores de la tirosina quinasa en cáncer de tiroides

#### Resumen

**Introducción:** El cáncer de tiroides generalmente tiene un buen pronóstico después del tratamiento quirúrgico y/o de yodo radioactivo (RAI); sin embargo, los tumores que persisten o que no son candidatos para estos tratamientos tienen un peor pronóstico, lo que hace del uso de inhibidores de la tirosina quinasa (TKI) una buena alternativa de manejo, ya que ha demostrado supervivencia libre de progresión (SLP) y beneficios en la tasa de respuesta. Por lo tanto es importante describir nuevos marcadores y futuras terapias para este tipo de tumores. **Materiales y métodos:** El propósito de esta revisión es describir el estado actual del tratamiento del cáncer de tiroides avanzado o recidivante que no es susceptible para el tratamiento con cirugía o RAI, los beneficios y limitaciones del uso de TKI, así como un análisis de la biología molecular de este tumor y su repercusión clínica. **Resultados:** El uso de sorafenib y lenvatinib en el carcinoma diferenciado de tiroides

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que es refractario al RAI, y cabozantinib y vandetanib para carcinomas medulares avanzados, ha demostrado beneficio en este tipo de pacientes, con un impacto en la SLP, las tasas de respuesta y el control de la enfermedad. Hay estudios en curso con inmunoterapia, y estaremos atentos a sus resultados. **Conclusión:** El tratamiento con TKI en el cáncer de tiroides metastásico ha demostrado beneficios, la determinación de mutaciones y marcadores determinará cuál es el mejor TKI para los diferentes subtipos de cáncer de tiroides.

**Palabras clave:** Cáncer de tiroides. Inhibidores de la tirosina cinasa. Tratamiento.

## Epidemiology

For the year 2019, estimates of the American Cancer Society indicate that around 52,070 new thyroid cancer cases will be diagnosed and that around 2170 people will die because of thyroid cancer<sup>1</sup>.

The main histologic types of thyroid carcinoma are: (1) differentiated (including papillary, follicular, and Hurthle); (2) medullary; and (3) anaplastic, which is an aggressive undifferentiated tumor.

Of 63,324 patients diagnosed with thyroid carcinoma from 2011 to 2015, 89.8% had papillary carcinoma, 4.5% had follicular carcinoma, 1.8% had Hurthle cell carcinoma, and 1.6% had medullary carcinoma and anaplastic carcinoma<sup>2</sup>.

In about 10% of cases, patients have locally advanced or metastatic disease at diagnosis, with local invasion and/or distant metastases in the bone (25%), lungs (50%), lungs and bone (20%), and other sites (5%). In one-third of advanced Differentiated thyroid cancer, the metastatic lesions have a low avidity for iodine and RAI has no effects<sup>2,3</sup>.

The trend of thyroid cancer new cases in some reference hospitals with high patient concentration in Mexico as, for example, in a cohort of the Mexican Institute of Social Security Centro Médico Nacional Siglo XXI Oncology Hospital for the 2005-2012 period that showed an increase, with 212 new cases in 2005 and 434 in 2012, for a total of 2737 in this 8-year cohort with an average age of 52 years (38-64), which reflects a similar trend to that internationally reported<sup>4</sup>.

## Treatment overview

Thyroid cancer typically has a good outcome following standard treatments, which include surgery, radioactive iodine (RAI) ablation for differentiated tumors and treatment with thyrotropin hormone-suppressive levothyroxine. Thyroid cancers that persist or recur following these therapies have a poorer prognosis. Cytotoxic chemotherapy or external beam radiotherapy (EBRT) has low efficacy in these patients. During cytotoxic chemotherapy, when doxorubicin was used as a single

drug or in combination with cisplatin, the response rate was 0-20%. Furthermore, all responses were partial and short-lived only for a few months. The combination of 5-fluorouracil with dacarbazine seemed to be more effective with a response rate of about 20%. The use of chemotherapy is limited to the few patients with rapidly progressive metastatic disease<sup>3,5</sup>.

“Targeted therapy” with tyrosine kinase inhibitors (TKIs) represents an important therapeutic option for the treatment of advanced cases of radioiodine refractory (RAI-R) differentiated thyroid carcinoma (DTC), medullary thyroid carcinoma (MTC), and possibly for cases of poorly DTC (PDTC) and anaplastic thyroid carcinoma (ATC)<sup>3,6</sup>.

Surgical thyroidectomy is the standard initial management for patients with thyroid cancer, and most patients with DTC can be fully treated with either surgery and thyrotropin (thyroid-stimulating hormone [TSH]) suppression or with addition of adjuvant radioiodine (RAI) ablation for select patients<sup>7-10</sup>. Efficaciousness of TSH suppression and RAI depends on the presence of sufficiently differentiated follicular cells, and these modalities are ineffective and not recommended for use in MTC or ATC<sup>5,7,8,10</sup>. In addition to its utility in the adjuvant setting, RAI can also be used as effective systemic therapy for patients with unresectable or metastatic DTC, so long as tumor cells maintain the ability to take up and concentrate RAI<sup>7,9-11</sup>. In 5-15% of patients with DTC; however, this ability is lost and the tumor is classified as RAI-R<sup>12-15</sup>.

Although outcomes in DTC are generally excellent, with 5-year overall survival (OS) reported at 97.8%<sup>6</sup>, the 5-year disease-specific survival for patients with RAI-R DTC is 66%, and 10-year survival is only 10%<sup>12</sup>. Patients with RAI-R DTC and distant metastasis survive approximately 2.5-3.5 years<sup>12,16,17</sup>.

PDTC is an aggressive rare form of thyroid cancer that carries a high risk of recurrence and metastatic spread to lung and bones. Patients are often treated with a combination of surgery, RAI and/or radiation therapy (RT), and molecular targeted therapies as these tumors are frequently insensitive to RAI<sup>18</sup>.

**Table 1.** Drugs used for thyroid cancer

Drug	Article	n	Histology	RR (%)	PFS	OS	Ref
Pazopanib 800 mg	Phase II 2008-2009	39	Papillary, follicular, Hürthle c.	49	11.7 m	NR	50,55
Pazopanib 800 mg	Phase II	-	Medullary	14	9.4 m	18.4 m	50,55
Sunitinib 37.5 mg	Phase II 2007-2009	35	Papillary, follicular, Hürthle cell, insular medullary	31	8 m	NR	55
Sunitinib	Retrospective	11	Papillary, follicular	27	NR	NR	55
Axitinib 5 mg	Phase II	60	Papillary, follicular, medullary, anaplastic	30	18.1 m	NR	53
Axitinib 5 mg	Phase II	60	Papillary, follicular, medullary, anaplastic	38	15 m	35 m	53
Axitinib 5 mg	Phase II 2006-2008	52	Papillary, follicular, medullary	32	16.1 m	27.2 m	55
Cabozantinib 140 mg	PHIII 2008-2011	330	Medullary	C: 2.8 P: 0	C: 11.2 m P: 4.2 m	NR	47,49,50
Vandetanib 300 mg	Phase II 2004-2006	30	Medullary	20	27.9 m	NR	50
Vandetanib 300 mg	Phase II 2010-2012	60	Medullary	22	16 m	2 years 60%	49,50
Vandetanib 300 mg	Phase II 2007-2008	145	Papillary, follicular poorly diff.	22	V: 11.1 m P: 5.9 m	NS	49,50
Vandetanib 300 mg	Phase III 2006-2007	331	Medullary	45	V: 30 m P: 19	NR	49,50

The notably poor survival in late stage MTC and RAI-R DTC compared with earlier stages reflects the lack of effective durable systemic treatment options for advanced disease<sup>15</sup>. Until 2011, the standard of care for systemic therapy for such patients was doxorubicin, which was approved in 1974 for advanced thyroid cancer<sup>19-22</sup>.

Based on this lack of efficacy and the promising results of newer TKIs, traditional cytotoxic chemotherapy is no longer recommended as first-line therapy in either MTC or RAI-R DTC<sup>7,9,10</sup>.

Thyroid molecular markers are genetic alterations originating in malignant thyroid cells, which are recognizable by molecular biology techniques<sup>18,19,23</sup>. Most evidence with single gene tests is with *BRAF* mutations. In thyroid cancer, the most common *BRAF*-activation mechanism (98-99%) is a point mutation that involves the substitution of thymine by adenine in position 1799, which results in the replacement of one valine by a glutamate in residue 600 (*BRAF*<sup>V600E</sup>). Other alterations include Lis601Glu point mutation, which is typically found in papillary carcinoma follicular variant. *BRAF*<sup>V600E</sup> mutation is the most common in thyroid

cancer and is found in 40-45% of these tumors, as well as in 20-40% of poorly differentiated tumors and in 30-40% of anaplastic carcinomas<sup>24-26</sup>.

Although *BRAF*<sup>V600E</sup> mutation alone has a specificity of approximately 99%, its sensitivity is too low to rule out the presence of malignancy. The second most common mutations are those in *RAS* since they are found in 10-20% of papillary carcinomas, 40-50% of follicular carcinomas, and in 20-40% of poorly differentiated and anaplastic carcinomas at its three isoforms: *HRAS*, *KRAS*, and *NRAS*, with mutations of *NRAS* and *HRAS* codon 61 being the most common. *RAS* is an activator of cell division, growth, proliferation, apoptosis, and metabolism through the mitogen-activated protein kinase and phosphoinositide-3-kinase-AKT signaling pathways. *RAS* mutation predictive value for malignancy in thyroid nodules has been reported to range between 74% and 88%<sup>25,27,28</sup>.

Apparently, there is an association between tumor microenvironment and the *BRAF*<sup>V600E</sup> mutation<sup>29</sup>, and the expression of immunosuppression molecular markers, CTLA-4, PD-L1, and *HLA-G* can be a therapeutic target. Recent investigations indicate evidence

of apparent tumor-related immune dysfunction in patients with follicular cell thyroid cancer<sup>30</sup>. There is an increase in the number of immune cells in patients with the *BRAFV600E mutation*<sup>29</sup>, and immunotherapy might, therefore, be indicated in this type of patient. At present, there are 564 studies underway for this type of tumors, where immunotherapy appears to play an important role, pioneering studies have evaluated immunotherapy in thyroid cancer more recently a case has been described involving anaplastic thyroid cancer treated with vemurafenib and nivolumab, with substantial regression and complete radiographic and clinical remission further studies are urgently needed<sup>31</sup>.

## Treatment

### Differentiated thyroid cancer

Treatment consists of surgery as the first treatment, followed by TSH suppression therapy; however, specific risk factors tumor cell eradication can be achieved by means of RAI<sup>3,32</sup>.

Patients with recurrent or metastatic thyroid cancer refractory to RAI who are not candidates to surgery, the used of local therapy, radiotherapy, or systemic treatment could be considered in patients younger than 40 years with slowly progressing disease have been associated improvement and survival<sup>3,33,34</sup>.

The use of chemotherapy has been tried with different regimens, including bleomycin, methotrexate, melphalan, mitoxantrone, etoposide, Adriamycin, and taxanes, out of which adriamycin, platinum salts and docetaxel have produced responses, but for very short periods (anaplastic thyroid cancer)<sup>30,32</sup>.

Several trials have demonstrated tyrosine kinase inhibitors (TKI) efficacy in the treatment of radioactive iodine<sup>28,30</sup> refractory metastatic or locally advanced thyroid carcinomas<sup>34,46</sup> (Table 1). The treatment initiation is based on tumor-associated deleterious events: small tumors that progress rapidly (< 6-12 months) or bulky tumors with slow growth (< 12 months), and although there is little evidence with Eastern Cooperative Oncology Group > 2 for these therapies, each case should be individualized, taking into account that there is a directly proportional relationship of the target lesion with the percentage and doubling time when the lesion is larger than 1 cm, with this relationship being higher in those larger than 2 cm<sup>34,32</sup>.

Sorafenib is an antiangiogenic multikinase inhibitor with multiple kinase targets, including vascular endothelial growth factor receptor (VEGFR1-3), platelet-derived

growth factor receptor (PDGFR), rearranged during transfection (*RET*), c-KIT, and RAF (including *BRAF*)<sup>35,37</sup>. Its efficacy in patients with metastatic RAI-refractory DTC was first described by several Phase II trials with an objective response rate (ORR) between 30% and 12%<sup>38,39</sup>.

Sorafenib was the first TKI drug approved by the Food and Drug Administration (FDA) in 2013 as first-line therapy for patients with locally recurrent or metastatic, progressive, RAI refractory DTC based on the findings of a Phase III randomized, double-blind, multicenter trial named the Study of Sorafenib in Locally Advanced or metastatic patients with RAI-refractory thyroid cancer (DECISION) trial<sup>40</sup>. A total of 417 patients were randomly assigned in a 1:1 ratio to either sorafenib 400 mg twice daily or placebo. In the sorafenib arm, no complete responses were observed and response rate was 12.2%. A significant difference in progression-free survival (PFS) was reported between the two groups (10.8 vs. 5.8 months; hazard ratio [HR]: 0.59; 95% confidence interval [CI]: 0.45-0.76;  $p < 0.0001$ ) meeting its primary endpoint, irrespective of mutation status. Neither a primary analysis nor delayed ones, has demonstrated any significant differences in OS between the two arms in part due to 71% of placebo patients who crossed over to treatment<sup>32,42</sup>. Remarkably, those patients in the placebo arm who started receiving sorafenib after tumor progression showed a comparable PFS to those who started receiving the drug from the beginning of the trial (9.6 vs. 10.8 months)<sup>3</sup>. Moreover, an interesting PFS of 6.7 months was observed in patients treated with sorafenib beyond progression suggesting that in the absence of an alternative drug, it may be better to continue to treat patients with sorafenib<sup>3</sup>.

Regarding safety; dose interruptions, reductions, or withdrawals due to adverse events (AEs) occurred in 66.2%, 64.3%, and 18.8% of patients receiving sorafenib, respectively, and hand-foot syndrome was the most common reason<sup>32</sup>. There have been reports of acute myocardial infarction (3.8%), heart failure (2.2%), and deaths without relation to the progression of the disease (3.7%)<sup>4</sup>. Recently, it has been reported that a dose reduction after two cycles of 800 mg/day does not affect therapeutic benefit but may mitigate adverse events<sup>32</sup>.

Off-label uses have been described too. Danilovic et al. reported the first case in which sorafenib was used as an induction therapy resulting in total thyroidectomy, and radioactive iodine treatment<sup>9</sup> and a Phase II trial with 21 MTC patients observed a median PFS of 17.9 months, with a stable disease (SD) in 19 patients, and a PR noticed only in two subjects<sup>41</sup>.

Lenvatinib is indicated for the treatment of DTC (papillary, follicular, and Hürthle) in patients with locally advanced and metastatic disease in patients refractory to treatment with RAI. It is a selective multi-kinase inhibitor of VEGFR1-3, FGFR1-4, *RET*, c-KIT, and PDGFR, which consists of drug binding not only at the site of ATP binding but also to neighboring allosteric regions, which seems to imply a slower dissociation rate of the receptor than other types of inhibitors<sup>42</sup>.

Symptomatic disease or progressive progression is preferred lenvatinib over the other treatment options considered; this based on randomized clinical trials where you have a response rate of 65% for lenvatinib when compared to 12% for sorafenib, although these agents have not been directly compared<sup>32,34,42</sup>. However, the decision to use lenvatinib or some other medication must be individualized for each patient based on the likelihood of response and comorbidities.

The SELECT trial, a multicenter, randomized, double-blind, and placebo-controlled trial, showed that the benefit of lenvatinib in patients with differentiated metastatic thyroid cancer that was refractory to RAI; the information included 392 randomized patients with a 2: 1 ratio to receive lenvatinib 24 mg daily (n = 261) or placebo (n = 131); demonstrating a statistically significant prolongation of PFS of 18.3 months in the group treated with lenvatinib compared with 3.6 months for those who received placebo (HR: 0.21; 99% CI: 0.14-0.31; p < 0.001)<sup>34</sup>.

A subgroup analysis of this first trial showed that the benefit of PFS of lenvatinib in comparison with placebo is maintained in older patients (> 65 years), younger (≤ 65 years) and that even a longer median overall duration general elderly patients with lenvatinib compared to placebo (HR: 0.27; 95% CI: 0.31-0.91; p = 0.20), although with higher rates of Grade 3 toxicity and higher adverse effects of treatment, suggesting that lenvatinib is an appropriate treatment option for patients of any age with DTC refractory to RAI<sup>32,43</sup>.

In the SELECT study, the duration of treatment was 13.8 months with lenvatinib versus 3.9 months with placebo. Lenvatinib was more toxic than placebo since 97.3% of the patients who received the treatment developed an adverse effect and 75.9% an adverse effect Grade 3 or higher; against 59.5% and 9.9% in the placebo arm<sup>34</sup>.

## Medullary thyroid carcinoma (MTC)

MTC arises from calcitonin producing C-cells and accounts for 3-5% of all thyroid cancers. About 75% of

MTC cases present in sporadic form and the remainder in a hereditary pattern. A germline mutation in *RET* reported in nearly all cases of hereditary medullary thyroid cancer and a somatic *RET* mutation in up to 50% of sporadic tumours<sup>23</sup>.

The most common treatment method of the disease is surgical intervention, including total thyroidectomy and central neck dissection, given that metastatic spread to cervical lymph nodes is a common event. Surgical cure is possible, but in progressive cases of the disease and distant metastatic spread, this treatment method is not sufficient. Distant metastases are present in 13-15% of cases, and occur most often in the lungs, liver, and bone. These patients have a poor prognosis<sup>44,45</sup>.

The primary treatment of hereditary or sporadic MTC is total thyroidectomy with dissection of ipsilateral and central lymph nodes, extended in some cases to contralateral dissection, serum calcitonin level is not detectable in > 60% of patients without lymph node involvement, as opposed to < 20% of patients with lymph node involvement. When the regional metastases recurrence systemic disease localized in the neck or mediastinum, a new surgery can be performed; however, some patients with distant metastases may survive for several years or rapidly progress and die of their disease<sup>49</sup>. External beam radiotherapy (EBRT), other non-surgical therapies should be considered to achieve local tumor control and systemic medical therapy how first-line treatments approved for medullary thyroid cancer (MTC)<sup>3,35</sup> based on treating tumor-associated deleterious events<sup>44-46</sup>.

Cabozantinib was approved by the FDA based on the results of the randomized Phase III trial in medullary thyroid cancer (MTC). Cabozantinib is a TKI that selectively inhibits *RET* and VEGFR 2, which demonstrated a median PFS of 11.2 months in comparison with placebo 4.0 months, (HR: 0.28; 95% CI: 0.19-0.40; p < 0.001), a response rate of 28% and 1-year PFS of 47.3% in comparison with 7.2% in the placebo group<sup>45</sup>, cabozantinib significantly prolonged PFS versus a placebo in patients with progressive, metastatic MTC (MTC; p < 0.001). An exploratory analysis of Phase III trial data evaluated the influence of *RET* and *RAS* (*HRAS*, *KRAS*, and *NRAS*) mutations on cabozantinib clinical activity. The *RET* M918T subgroup achieved the greatest observed PFS benefit from cabozantinib versus the placebo; cabozantinib provides the greatest clinical benefit to patients with MTC who have *RET* M918T or *RAS* mutations. Grade 3 toxicities were reported in the group that received cabozantinib: diarrhea, 21%, hand-foot syndrome, 12.6%, hypertension,



8.9%, and fatigue, and 9.8% decreased appetite 7%, in 2011 and 2013, vandetanib was approved for the treatment of symptomatic and progressive MTC by the FDA and the European Medicines Agency, based on the results of Phase III clinical trial ZETA in the treatment of metastatic MTC. The results showed an improvement in median PFS of 30.5 months in the treatment group versus 19.3 months (HR: 0.46; 95% CI: 0.31-0.69;  $p < 0.001$ ), response rate was 46% a subgroup analysis of PFS positive had a higher response; however, 31 patients discontinued treatment due to an AE: twenty-eight patients (12%) receiving vandetanib discontinued. Common AEs are diarrhea, rash, nausea, and hypertension in 30%, QTc prolongation in 8%, but there were no reports of torsades de pointes<sup>46</sup>.

Despite these good results in PFS, both cabozantinib and vandetanib seem unable to prolong OS in MTC patients even if in the subgroup of *M918T RET*-mutated patients those treated with cabozantinib were demonstrated to have a higher OS than those treated with placebo (44.3 vs. 18.9 months). Despite that they are cytostatic and not cytotoxic; however, a significant objective response of the target lesions has been observed after few weeks/months of treatment. Both drugs have several AEs that represent the major limitations of these therapies; one of the reasons for which TKI systemic therapy is delayed until disease progression according to Response Evaluation Criteria In Solid Tumors is that AEs can severely affect the quality of life of these patients. The different designs of the two Phase III trials (EXAM and ZETA) do not allow a direct comparison of the two drugs. For this reason, when a systemic therapy is needed, the choice between these drugs should be made by carefully considering patient comorbidities, potential toxicities, need of a more or less rapid response, and history of previous treatments. In this regard, it is relevant to say that several reports demonstrated that vandetanib can reverse or control ectopic Cushing syndrome that can be present in advanced MTC and associated with a poor prognosis. All this evidence and these considerations indicate that the management of these patients should be done by an experienced team, including at least endocrinologists, oncologists, cardiologists, dermatologists, and radiologists<sup>44,46,47</sup>.

TKIs also act systemically and can give rise to a multitude of different AEs, although they are generally better tolerated than other cytotoxic chemotherapeutics. Not surprisingly, among the most common AEs are those related to the cardiovascular system, such as hypertension or chronic heart failure in combination

with dermatologic (skin rash, skin and hair hypopigmentation, and alopecia), abnormal laboratory value (anemia and leukopenia) or more unspecific AEs such as diarrhea, nausea, fatigue, or anorexia<sup>47</sup>.

## New treatment options of TKI

Over the past 12 years, TKIs have shown their ability to block cell proliferation, although > 500 kinases have been currently identified as possible therapeutic targets<sup>3,48</sup>.

## Differentiated thyroid cancer

Axitinib one potent, selective, and second-generation inhibitor of VEGFRs was evaluated in the phase 2 study dose 5 mg twice daily in 52 patients with cancer thyroid papillary, follicular, RAI-refractory (with or without doxorubicin-refractory disease) or RAI-inappropriate, metastatic or unresectable, locally advanced thyroid cancer, with results overall OR was 35% (95% CI: 22-49%), median duration of response was 17.2 months (95% CI: 13.6-25.8 months). Axitinib-related AEs (neuropathy, dyspnea, proteinuria, lower leg ulceration, myocardial infarction, or cerebral ischemia/respiratory insufficiency (n56; 12%) post-hoc landmark analysis demonstrated that patients who developed diastolic BP > 90 mmHg during axitinib treatment had longer median PFS and OS compared with those who had diastolic BP < 90 mmHg. The small sample size and lack of a control group and the minimal change from baseline QoL may limit the applicability of results from the current trial<sup>49</sup>.

In 25 patients with advanced thyroid cancer (papillary, follicular, Hurthle cell, or poorly differentiated) RAI-refractory disease with progression on prior VEGFR targeted therapy; cabozantinib an MKI was administered orally at a starting dose of 60 mg daily in 28-day cycles with the following answers 10 (40%) had a confirmed PR, 13 (52%) had SD (SD; including two patients with unconfirmed PR) median duration of PR was 11.3 (95% CI: 10.3 to not evaluable) months, PR was achieved in 10 of 21 patients (48%) with only one prior VEGFR targeted therapy, whereas zero of four responses (0%) were seen in patients who received two prior VEGFR-targeted therapies, the changes in serum Tg levels showed significant correlation between Tg response and radiographic objective responses ( $p = 0.0178$ ). Median PFS was 12.7 (95% CI: 10.9-34.7) and median OS was 34.7 (95% CI: 18.3 to not reached) months; one estimated OS at 12 months was 80% (95% CI: 65-97%). Notable serious AEs included Grade 1 thrombotic thrombocytopenic

purpura (n = 1), Grade 2 deep venous thrombosis (n = 1), Grade 4 perianal hidradenitis suppurativa (n = 1), and Grade 3 AEs (n = 6) comprising left ventricular systolic dysfunction, asymptomatic increased lipase, osteonecrosis of the jaw, decubitus ulcer, pneumonia, and meningitis (one of each events)<sup>49-51</sup>.

## Medullary thyroid cancer

One Phase II study enrolled 91 patients with sporadic MTC and mutation in *RET M918T* in 70% of the cases, locally advanced or metastatic to received motesanib 125 mg/d orally for up to 48 weeks a inhibitor of the VEGFR 1, 2, and 3; platelet-derived growth factor receptor; and stem cell factor receptor (Kit). It also inhibits wild-type but not mutant *RET in vitro* and induces regression of MTC xenografts in mice. Results were ORR 2%; (95% CI: 0.3-7.7%); 81% of the patients had SD; and 48% had durable SD (24 weeks). The clinical benefit rate (defined as confirmed objective response or durable SD) was 51%. Sixty-nine patients (76%) experienced a decrease from baseline in target lesion measurement, PFS at week 48 was 50% (95% CI: 37-63%), the OS was 75% (95% CI: 65-84%), the ORR for *RET* mutation – negative (n = 10) and positive patients (n = 28) with sporadic MTC was 10% and 0%, respectively; the rate of durable SD was 70% and 39%, respectively; and the clinical benefit rate was 80% and 39%, respectively. About 83% (69 of 83 patients) had a decrease from baseline in the plasma concentration of calcitonin, and 75% (63 of 84 patients) had a decrease in the serum concentration of carcinoembryonic antigen (CEA). AE most commonly was diarrhea (41%), fatigue (41%), hypertension (27%), anorexia (27%), and nausea (26%), treatment with motesanib was tolerable<sup>3</sup>.

Pazopanib is an orally bioavailable competitive (with respect to ACT) multitargeted kinase inhibitor, which most potently inhibits VEGFR1-3, platelet-derived growth factor- $\alpha/\beta$ , c-KIT, and FGFR1/3/4 and other much less potently; in particular, VEGFR1/2 > 2 orders of magnitude more potently than *RET in vitro*, one study Phase II enrolled patients with advanced or metastasized MTC pazopanib was administered orally once daily at 800 mg until disease progression or intolerability cycle length was  $28 \pm 3$  days, the results followed the median PFS and OS times were estimated to be 9.4 months and 19.9 months, respectively, exploratory studies assessed the median percent change at CEA nadir from baseline levels was -23% (n = 31; range 55-90%) for CEA and -50% (n = 33; range 33-89%) for

calcitonin. PFS was found to be significantly longer among those whose decrease in CEA was at least 25% relative to baseline (p = 0.0230) pazopanib appears to have promising clinical activity in MTC, with a confirmed RECIST tumor response rate of 14.3% and manageable toxicities, with this results the intriguing possibility that *RET* may not necessarily represent the sole kinase target of therapeutic relevance in MTC<sup>51</sup>.

## Anaplastic thyroid carcinoma (ATC)

Anaplastic thyroid cancer is one of the most lethal malignancies. The clinical presentations of ATC are associated with a rapidly enlarging neck mass, in operable patients the combination of surgery, RT, and chemotherapy is recommended to improve the locoregional and distant while in inoperable patients, RT more chemotherapy had better results, due to the rare nature of this malignancy, most of these studies were single-institutional based researches or results of clinical trials reported by high-volume institutions<sup>52</sup>.

In a Phase II, patients with *BRAF V600E- mutated* rare malignancies, including 28 patients with ATC locally advanced or metastatic, were treated with dabrafenib (150 mg twice daily) plus the *MEK* inhibitor trametinib (2 mg once daily). Results was overall response rate (complete response plus partial response as the best overall response) of 69% (complete response [n = 1], partial responses [n = 10], Independent radiologic review of response demonstrated similar results, with overall response rates of 63%. At 12 months of duration of response, PFS, and OS were 90%, 79%, and 80%, respectively, 93% of patients experienced any AE and 42% experienced any grade 3 or 4 event. However, the small size of this cohort limits conclusions and requires confirmation in additional clinical studies<sup>53</sup>.

## Conclusions

Medicine is with no doubt one of the professions with more changes through time, and oncology is one of the disciplines that have dramatically changed the management of patients with cancer due to the advance in molecular biology, in this case, of patients with advanced thyroid carcinoma without response to iodine where, historically, chemotherapeutic management has not been resorted to because it is considered to be a chemoresistant neoplasm. However, today, we have an important number of drugs that have been approved by international regulatory entities such as the Food and Drug Administration and that have

demonstrated efficacy and safety in the control of this disease. It should be borne in mind that thyroid tumors are the most common endocrine neoplasms that the behavior of differentiated tumors is different to that of non-differentiated and that there are iodine-refractory thyroid carcinomas, which represent a type of disease that is associated with poor prognosis. The use of TKI has demonstrated benefits in disease control and PFS in well-differentiated tumors. Unfortunately, no targeted therapy with a good response is yet available for anaplastic tumors. Sorafenib, lenvatinib, cabozantinib, and vandetanib have demonstrated their benefits in clinical practice; however, toxicities that can jeopardize patients' quality of life, or even their lives, should be taken into account. Sorafenib is a multikinase inhibitor that targets the Raf, VEGFR, PDGF, and *RET* pathways and that helps in the control of iodine-refractory disease. In the case of lenvatinib, it is a drug with not only higher response rates but also with higher toxicity and therefore, we should consider all these parameters to make the best decision at the moment of directing the efforts of a TKI for our patients. Expert recommendation is to use them in rapidly-progressing, symptomatic disease, but not for indolent disease. Trying to find any marker, *BRAFV600E* determination appears to provide a strategy for offering a targeted therapy. Similarly, immune therapy appears promising for this type of patients, especially in anaplastic tumors, but we will have to wait some time to get to know the impact of these innovative therapies, which can be one more tool for the oncologist and a door of hope for patients.

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