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New targets in advanced thyroid cancer refractory iodine

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ABSTRACT

The majority of deaths due to thyroid cancer occur in patients with advanced differentiated thyroid carcinoma (DTC) refractory to radioactive iodine. The spectacular advances in molecular medicine of recent years have opened new therapeutic possibilities. At present, there is general agreement that treatment with multikinase inhibitors should only be considered in patients with DTC refractory to radioactive iodine, with progressive and/or symptomatic metastatic disease that can not otherwise be treated locally. Most of these "new molecules" are multichannel inhibitors with varied action, which interact on different proteins such as: RET receptor, a protein located in the cytoplasmic membrane and with tyrosine kinase activity; BRAF, a member of the RAF kinase family that promotes signaling through the RAS-RAF-MAPK signal-transduction cascade; cKIT, a proto-oncogene and a type 3 transmembrane receptor for MGF (mast cell growth factor, also known as stem cell factor); MET, a heterodimer composed of a 50-kDa highly glycosylated alpha-chain subunit and 145-kDa beta-chain; epidermal growth factor receptor (EGFR), mitogen-activated protein kinase (MAPK) and PDGFR (derived growth factor receptor of platelets). In addition, they have the additional advantage that they markedly prevent angiogenesis by acting on vascular endothelial growth factor receptors 1, 2, and 3. The prolongation of progression-free survival has been demonstrated with sorafenib and lenvatinib compared with placebo in two phase III trials. These two drugs have been approved by the FDA and the European Medicines Agency for use in patients' refractory to radioactive iodine with metastatic disease.

Key words: Target. Cancer. Thyroid.

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RESUMEN

La mayoría de las muertes por cáncer de tiroides ocurren en pacientes con carcinoma diferenciado de tiroides avanzado refractario al yodo radiactivo (DTC). Los espectaculares avances en medicina molecular de los últimos años han abierto nuevas posibilidades terapéuticas. En la actualidad, hay un acuerdo general en que el tratamiento con inhibidores multicinasa solo deben considerarse en pacientes con DTC refractarios al yodo radiactivo, con enfermedad metastásica progresiva y/o sintomática que no puede tratarse localmente. Estas «nuevas moléculas» son inhibidores multicanales con acción variada, que interactúan en diferentes proteínas como la RET (protooncogén que codifica un receptor transmembrana), la BRAF (miembro de la familia cinasa RAF), la cKIT (protooncogén y un receptor transmembrana tipo 3 para el MGF [factor de crecimiento de mastocitos]), la MET (proteína transmembrana), el receptor del factor de crecimiento epidérmico (EGFR), la MAPK (proteincinasa activada por mitógenos) y el PDGFR (factor de crecimiento derivado de plaquetas). Además tienen la ventaja adicional de que previenen notablemente la angiogénesis, al actuar sobre el receptor del factor de crecimiento del endotelio vascular (VEGFR) 1, 2 y 3. La prolongación de la supervivencia libre de progresión se ha demostrado con sorafenib y lenvatinib en comparación con placebo en dos ensayos de fase III. Estos dos medicamentos han sido aprobados por la *Food and Drug Administration* (FDA) y la Agencia Europea de Medicamentos para su uso en pacientes con cáncer de tiroides refractario al yodo radiactivo con enfermedad metastásica. (J CANCEROL. 2018;5:118-26)

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Palabras clave: Objetivo. Cáncer. Tiroides.

INTRODUCTION

About one-third of patients with differentiated thyroid carcinoma (DTC) who develop metastatic disease are refractory to radioactive iodine[1].

Between 1975 and 1999, 15 clinical trials with cytotoxic chemotherapy were initiated. Treatment with doxorubicin and cisplatin only achieved complete remissions in 12% of patients with thyroid carcinoma of follicular origin. The combination of bleomycin, doxorubicin, and cisplatin achieved an average survival of 11 months and the response to etoposide was zero. Something similar happened in patients with medullary thyroid carcinoma, in which only 25% responded to treatment partially or completely[2].

Fortunately, today things have changed and we are witnessing a new leap in the treatment of thyroid carcinoma. The spectacular advances in molecular medicine of recent years have opened new therapeutic possibilities[2].

New treatment strategies are needed; therefore, new strategies under investigation include targeted therapy (e.g., axitinib and sorafenib), vascular disrupting agents (such as combretastatin A4 phosphate, human vascular endothelial growth factor (VEGF) monoclonal antibodies, bevacizumab, and cetuximab), and tumor suppressor gene therapy. Until now, none of these agents has shown good results in the treatment of anaplastic thyroid carcinoma, so further research is needed to contrast the aggressiveness of this tumor[3].

At present, there is general agreement that treatment with multikinase inhibitors (MKI) should only be considered in patients with DTC refractory to radioactive iodine, with progressive and/or symptomatic metastatic disease that cannot otherwise be treated locally. The reasons for such limitations arise from clinical trials. Given that, the first multicenter therapeutic trial of a tyrosine kinase inhibitor (TKI) was performed in progressed DTC; the evidence favored the clinical use of Tirosin Kinase Inhibitors but they also revealed limitations due to the drug toxicity and patient eligibility[1].

Most of these "new molecules" are multichannel inhibitors with varied action, which interact (selectively or together) on various proteins such as RET, BRAF, cKIT, MET, epidermal growth factor receptor (EGFR), MAPK, and PDGFR. In addition, they have the additional advantage that they markedly prevent angiogenesis by acting on VEGFR receptors (VEGFR 1, 2, and 3)[2].

The prolongation of progression-free survival (PFS) has been demonstrated with sorafenib and lenvatinib compared with placebo in two Phase III trials. These two drugs have been approved by the FDA and the European Medicines Agency for use in patients' refractory to radioactive iodine with metastatic disease[1].

It should be noted, and more in the context of thyroid carcinoma, that the use of TKIs has been associated with the appearance of thyroid dysfunction. This effect has been seen, especially after the administration of sunitinib and sorafenib. The most common dysfunction is the development of hypothyroidism, which has sometimes been described after a brief episode of thyrotoxicosis (mimicking the clinical stages of thyroiditis)[2]. For this reason, it is recommended to carefully and frequently evaluate the thyroid function in any patient treated with these molecules[2].

MAIN BODY

Unfortunately, most deaths due to thyroid cancer occur in patients with advanced DTC refractory to radioactive iodine[1].

In studies based on treatment with doxorubicin and cisplatin only achieved complete remissions in 12% of patients with thyroid carcinoma of follicular origin. The combination of bleomycin, doxorubicin, and cisplatin achieved an average survival of 11 months and the response to etoposide was zero. Something similar happened in patients with medullary thyroid carcinoma, in which only 25% responded to treatment partially or completely[2].

External beam radiation therapy has a limited role in patients with advanced DTC or medullary thyroid carcinoma and is not commonly used. Retrospective studies have found controversial about the use of external beam radiotherapy. The NCCN guidelines and the guidelines of the American Thyroid Association suggest that external beam radiation therapy should be considered for patients with locally unresectable thyroid carcinoma or medullary thyroid carcinoma to optimize locoregional control. External beam radiation therapy can also be considered for patients with distant metastases such as in the brain and spinal column[4].

In DTC, distant metastases have greater benefit if they are iodine-refractory, small and localized in the lungs; otherwise, only palliation and prolongation of survival are feasible. Chemotherapy is not indicated and participation in clinical trials should be encouraged[3].

In medullary thyroid carcinoma in advanced disease, mono- or poly-chemotherapy has not shown a significant clinical benefit (< 20% response rate), whereas radiotherapy is frequently used palliatively[3].

In anaplastic carcinoma of the thyroid, the most common single cytotoxic agent used is doxorubicin alone or in combination with cisplatin. The results have been disappointing. The addition of bleomycin or other agents does not improve the efficacy of this combination. Recently, paclitaxel has been used in clinical trials and has shown some improvement in response rates, but not in survival[3].

At present, there is general agreement that treatment with MKI should only be considered in patients with DTC refractory to radioactive iodine, with progressive and/or symptomatic metastatic disease that cannot otherwise be treated locally[1].

When considering the use of TKI, these factors should be taken into account:

– TKIs are associated with PFS but not curative.

– TKI causes adverse effects that can affect the quality of life.

The natural history of differentiated thyroid and medullary thyroid cancer with rates of disease progression ranging from a few months to a few years[5].

Patients who are asymptomatic are not those indicated to receive TKI, particularly if the adverse effects of the treatment affect the quality of life. On the other hand, if the disease progresses rapidly, they may have a greater benefit from TKI; even when adverse effects occur.

Optimal management of the adverse effects of TKI is also essential. Especially because of the adverse dermatological, hypertensive, and gastrointestinal effects, since dose modification must be done, including dose reduction[5].

In a multicenter, randomized, double-blind, placebo-controlled trial, Phase 3 study (DECISION), sorafenib (400 mg orally twice daily) was investigated in patients with cancer refractory to radioactive iodine or metastatic differentiated thyroid cancer that had progressed within the past 14 months. Adult patients (≥ 18 years of age) with this type of cancer were enrolled from 77 centers in 18 countries. As inclusion criteria, participants had to have at least one lesion measurable by computed tomography or magnetic resonance imaging according to the criteria for the evaluation of response in solid tumors (RECIST), with PS 0-2, adequate functioning of bone marrow, liver, and renal function, and serum thyroid-stimulating hormone (TSH) concentration < 0.5 mIU/L. The primary endpoint was PFS assessed every 8 weeks[6].

About 5% of patients develop DTC refractory to radioactive iodine, which generally does not respond to conventional chemotherapy, resulting in a long-term overall survival of approximately 10%. On November 22, 2013, the FDA approved sorafenib for the treatment of refractory, progressed thyroid cancer; based on the results of a randomized, placebo-controlled trial (n: 471) that demonstrated a statistically significant improvement in PFS (PFS; HR, 0.59; 95% confidence interval [CI], 0.45-0.76; $p < 0.001$), with a median PFS time of 10.8 months in the sorafenib arm and 5.8 months in the placebo arm[7].

Sorafenib has clinically relevant antitumor activity in patients with metastatic refractory thyroid carcinoma, resistant to iodine, with a general clinical benefit rate of 77%, a median PFS of 79 weeks, and a generally acceptable safety profile. These results represent a significant advance over chemotherapy in both the response rate and the PFS[8].

Sorafenib significantly improved PFS compared to placebo in patients with differentiated iodine-refractory thyroid cancer. These results suggest that sorafenib is a new treatment option for patients with thyroid cancer refractory iodine as shown in figure 1[6].

Lenvatinib is approved for thyroid cancer differentiated by the FDA but has also been studied in

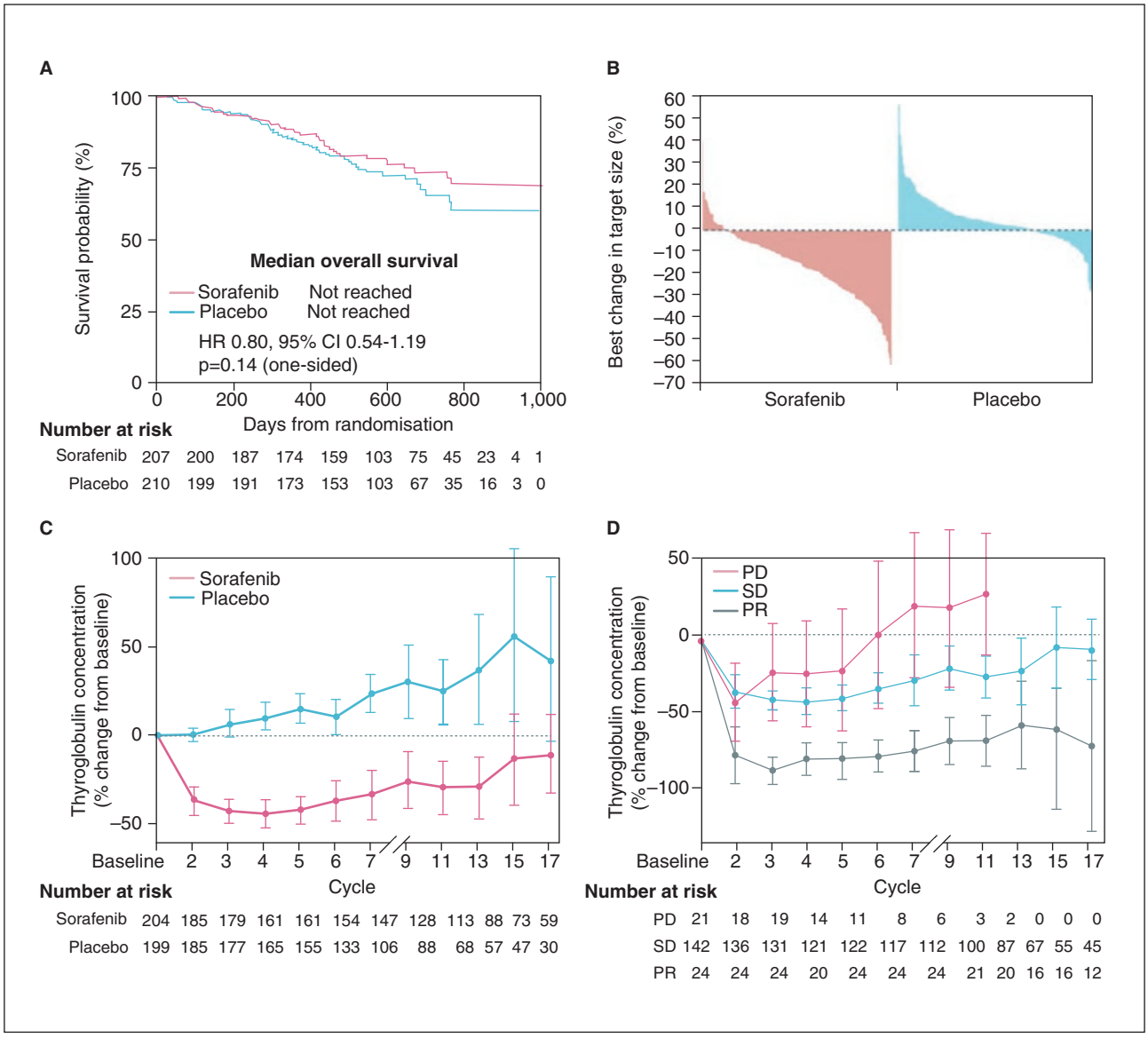

Figure 1. Decision study. Sorafenib versus placebo in advanced thyroid cancer refractory iodine. Overall survival, changes in target lesions and serum thyroglobulin concentrations **A:** Kaplan-Meier global survival curve. **B:** Cascade diagram showing the best change in the size of the target lesion for individual patients. **C:** Changes in thyroglobulin concentrations according to the treatment group. **D:** Changes in thyroglobulin concentrations in patients treated with sorafenib according to the tumor response. The error bars in **(C)** and **(D)** are 95% CI. HR: hazard ratio; PD: progressive disease; SD: stable disease; PR: partial response[6].

medullary thyroid cancer[9]. Lenvatinib is an oral TKI, which inhibits the kinase activities of the vascular endothelial growth factor receptor (VEGFR) (FLT1), VEGFR2 (KDR), VEGFR3 (FLT4), FGFR1, 2, 3, and 4, and the derived growth factor receptor of alpha platelets (PDGFRa), KIT, and RET. A single randomized controlled trial (E7080-G000303 or SELECT [here in after referred to as study 303]) together with a safety database of 1108 patients who were exposed to lenvatinib in several clinical trials was submitted to support approval in the United States[7].

In the study 303, the most common adverse reactions were hypertension (73 vs. 16% placebo), fatigue (67 vs. 35%), diarrhea (67 vs. 17%), arthralgia/myalgia (62 vs. 28%), decreased appetite

(54 vs. 18%), decreased weight (51 vs. 15%), nausea (47 vs. 25%), stomatitis (41 vs. 8%), headache (38 vs. 11%), vomiting (36 vs. 15%), proteinuria (34 vs. 3%), palmar-plantar erythrodysesthesia (32 vs. 1%), abdominal pain (31 vs. 11%), and dysphonia (31 vs. 5%). Hemorrhagic events occurred in 35% of patients treated with lenvatinib versus 18% who received placebo. The use of lenvatinib also resulted in an increase in the levels of TSH the etiology of this increase is not understood, in 68% of the patients who received lenvatinib and in 5% of the patients who received placebo, there were adverse reactions that led to dose reductions: 18% of the patients discontinued the treatment or with lenvatinib and 5% suspended placebo due to adverse reactions. The most frequent adverse reactions (at least 10%) that resulted in the reduction of the dose of lenvatinib were hypertension (13%), proteinuria (11%), decreased appetite (10%), and diarrhea (10%). Adverse events of Grade 3 to 4 also occurred more frequently in the lenvatinib arm[7].

Lenvatinib demonstrated antitumor activity in Phase I studies against several solid tumors including advanced medullary thyroid cancer. This Phase II study demonstrated an objective response rate (ORR) for lenvatinib of 36% in patients with progressive medullary thyroid carcinoma. The ORR was similar between patients with (35%) and without previous treatment with anti-VEGF (36%). It is associated with greater tumor reduction and prolonged PFS. These findings support the continued investigation of lenvatinib for the management of medullary thyroid carcinoma[10].

Based on the Phase II trials, there are other MKIs available such as sunitinib, axitinib, cabozantinib, or pazopanib that may produce some kind of clinical benefit, but only Phase III results with vandetanib are expected in the near future[1].

Axitinib is a potent selective inhibitor of VEGFR 1, 2, and 3 and 10 times less potent to inhibit PDGFR and C-kit. A Phase I trial of 36 patients with advanced solid tumors took axitinib 5 mg twice daily. It was shown that axitinib was rapidly absorbed, with peak plasma concentrations from 2 to 6 h after administration. Based on the recognized importance of thyroid cancer angiogenesis and preliminary evidence of antitumor activity, the activity of this drug was investigated in a Phase II trial[11].

Axitinib has significant antitumor activity in all histological subtypes of thyroid cancer, as evidenced by the high response rate, the prolonged duration of response, and overall survival. The modulation of VEGFR-2 and VEGFR-3 by axitinib demonstrates the selectivity of this oral inhibitor against VEGFRs. These results also validate the therapeutic efficacy of VEGFR inhibition in patients with advanced thyroid cancer[11].

Pazopanib is another targeted agent that has shown promising activity in patients with differentiated thyroid cancer and in preclinical studies of anaplastic thyroid cancer. These results led to a Phase II study (n = 16) of pazopanib in patients with advanced anaplastic thyroid cancer. However, the data from this trial showed minimal activity with pazopanib in this context; no confirmed RECIST responses were observed[9].

Cabozantinib and vandetanib are approved by the FDA for the treatment of advanced medullary thyroid carcinoma[4].

On April 6, 2011, the FDA approved vandetanib[12], which is an oral inhibitor of RET kinase, PDGFR, and EGFR[13]; for the treatment of advanced thyroid cancer in patients with unresectable, locally advanced disease or metastatic disease[12] based on the ZETA study[14].

Patients were randomized 2:1 with vandetanib, 300 mg/d orally (n = 231), or placebo (n = 100). The main objective was the demonstration of improvement in PFS with vandetanib compared with placebo. Another approach was to evaluate the

global survival and the ORR. The analysis of PFS randomized to vandetanib (hazard ratio: 0.35; 95% CI: 0.24-0.53; p < 0.0001). The ORR for the vandetanib arm was 44% compared to 1% for the placebo arm. The most frequent Grade 3 and 4 toxicities (> 5%) were diarrhea and/or colitis, hypertension, fatigue, hypocalcemia, skin rash, and prolongation of the QT interval. This approval was based on a statistically significant and clinically significant improvement in the PFS[12].

In 2012, the FDA approved cabozantinib for the same indication based on the efficacy of XL184 (cabozantinib) in the advanced medullary thyroid cancer (EXAM) trial[14] which is a double-blind Phase III trial comparing oral cabozantinib at 140 mg/day with a placebo in 330 patients with documented radiographic progression of metastatic medullary thyroid carcinoma. The main end point is PFS. Other end points are the response rate, overall survival, and safety. This study also used a 2:1 randomization scheme, but unlike the ZETA trial, the EXAM study did not allow the active drug to cross. The study reached its main endpoint of PFS prolongation: 11.2 months for the use of cabozantinib and 4 months for the placebo (hazard ratio: 0.28; 95% CI: 0.19-0.4; p < 0.001). Objective rates of tumor response and biochemical responses were also significantly improved with cabozantinib[14].

The frequent occurrence of weakness, arterial hypertension, gastrointestinal discomfort (abdominal pain, diarrhea, constipation, vomiting, and anorexia), skin lesions (erythema palmoplantar, or hand-foot syndrome), or fatigue has been described. Patients may also report paresthesias in the hands and feet, hypopigmentation, instability, blurred vision, alteration in the sense of taste, or flu-like symptoms. The appearance of anemia, leukopenia, or decreased platelet count has been seen, with an increased risk of bleeding. Rarely (< 10% of cases), there may be alterations in liver or kidney function tests, changes in the ionogram, or appearance of severe hemorrhage. Usually, the adverse effects are dose dependent, so they tend to be reduced by temporarily stopping the drug or decreasing the dose[2].

At present, the non-randomized Phase I/II trial of the combination of vandetanib plus bortezomib is recruiting patients with solid tumors (including medullary thyroid carcinoma)[15].

Table 1 shows the therapeutic effects of the different TKI in clinical trials that recruited patients with differentiated and medullary thyroid cancer[3].

Figure 2 shows how the different treatments in advanced thyroid cancer refractory iodine have evolved[16].

Table 2 shows the most frequent adverse effects of the TKI[17].

CONCLUSIONS

The present study concludes the importance of the new molecular targets for the treatment of advanced thyroid cancer, refractory iodine since around one-third of patients with DTC develop metastatic disease. New treatment strategies have been developed which include targeted therapy (e.g., axitinib and sorafenib), vascular disrupting agents (such as combretastatin A4 phosphate and human VEGF monoclonal antibodies, bevacizumab, and cetuximab), and tumor suppressor gene therapy.

At present, there is general agreement that treatment with MKI should only be considered in patients with DTC refractory to radioactive iodine, with progressive and/or symptomatic metastatic disease that can not otherwise be treated locally.

Patients who are asymptomatic are not those indicated to receive TKI, particularly if the adverse effects of the treatment affect the quality of life. On the other hand, if the disease progresses rapidly,

Table 1. Therapeutic effects of different TKI in clinical trials recruiting patients with CDT or CMT

Drug	Histologic subtype	Number of patients	Phase	RP (%)	SD %)	SD > 6 months (%)	mPFS (weeks)
Motesanib	CMT	91	II	2	81	48	48
	CDT	93	II	14	67	35	40
Sunitinib	CMT	23	II	35	57		28
	CMT	6	II		83		
	CMT	15	II	33	27		
	CDT	31	II	14	68		
Vandetanib	CMT	30	II	20	73	53	
	CMT	19	II	16	64	53	
	CMT	331	III	45	42	83	30.5 months
Sorafenib	CMT	16	II	6	87	56	60
	CDT	41	II	15		53	79
	CDT	30	II	23			
	CDT	31	II	25	34		
XL184	CMT	37	I	29		41	
Axitinib	CMT	11	I	18	27		
	CDT	45	II	31	42		
Pazopanib	CDT	37	II	49			

MT: medullary thyroid carcinoma; CDT: differentiated thyroid carcinoma; RP: partial response; SD: stable disease; mPFS: median progression-free survival.
Adapted from ESMO 2012.

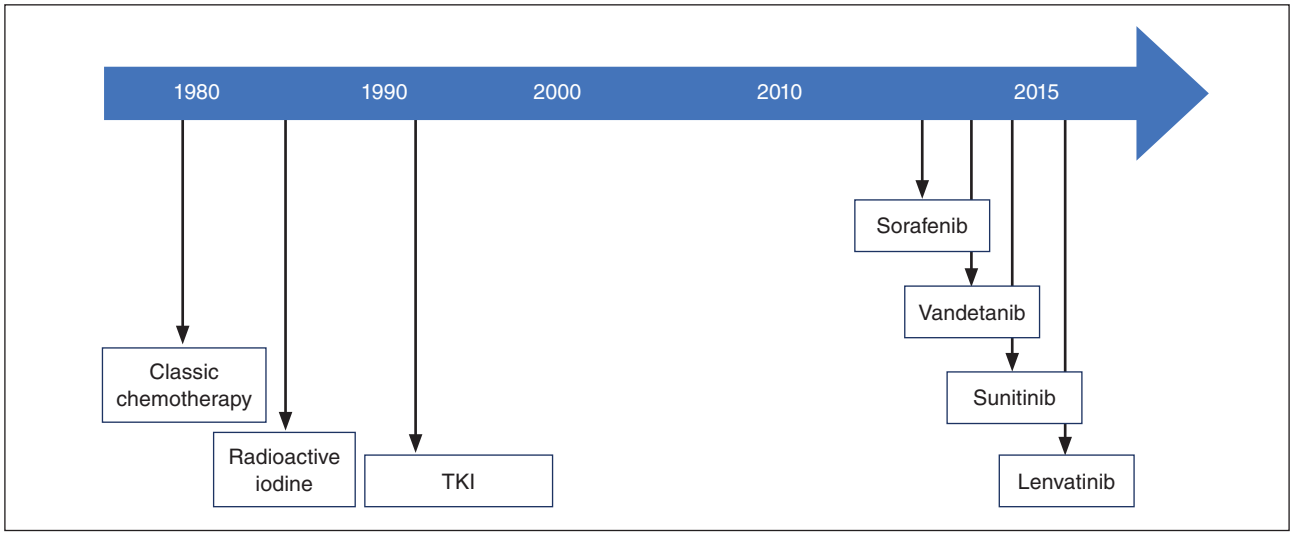

Figure 2. Evolution of treatment of advanced thyroid cancer refractory iodine[16].

they may have a greater benefit from TKI; even when adverse effects occur.

The prolongation of PFS has been demonstrated with sorafenib and lenvatinib compared with placebo in two Phase III trials. These two drugs have been approved by the FDA and the European Medicines Agency for use in patients' refractory to radioactive iodine with metastatic disease.

Sorafenib has clinically relevant antitumor activity in patients with metastatic refractory thyroid

Table 2. Most frequent adverse effects related to TKI[17]

Adverse effects	TKI frequency (%)
Fatigue and weight loss	Everybody (26-59)
Diarrhea	Everybody (30-68)
Arterial hypertension	Everybody (30-67)
Rash	Everybody (20-50)
Increase in TSH	Everybody (30-60)
Hand-foot syndrome	Sorafenib (76)
Alopecia	Sorafenib (67)
Proteinuria	Lenvatinib (31)
Mucositis	Everybody (30)
Hypocalcemia	Sorafenib (18)
QTc prolongation	Vandetanib (23 G > 3.14)

TKI: tyrosine kinase inhibitors.

carcinoma, resistant to iodine, with a general clinical benefit rate of 77%, a median PFS of 79 weeks, and a generally acceptable safety profile. These results represent a significant advance over chemotherapy in both the response rate and the PFS.

Lenvatinib is approved for thyroid cancer differentiated by the FDA but has also been studied in medullary thyroid cancer.

Cabozantinib and vandetanib are approved by the FDA for the treatment of advanced medullary thyroid carcinoma.

Based on the Phase II trials, there are other MKIs available such as sunitinib, axitinib, or pazopanib that can produce some kind of clinical benefit and therefore need further investigation.

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