REVIEW

Treatment of refractory thyroid cancer

Amandine Berdelou[1], Livia Lamartina[2], Michele Klain[3], Sophie Leboulleux[1] and Martin Schlumberger[1] on behalf of the TUTHTYREF Network

[1]Department of Nuclear Medicine and Endocrine Oncology, TUTHYREF (Tumeurs de la Thyroïde Réfractaires) Network, Gustave Roussy and University Paris-Saclay, Villejuif, France
[2]Department of Internal Medicine and Medical Specialties, Sapienza University of Rome, Rome, Italy
[3]Department of Advanced Biomedical Sciences, University of Naples 'Federico II', Naples, Italy

Correspondence should be addressed to M Schlumberger: martin.schlumberger@gustaveroussy.fr

Abstract

Distant metastases from thyroid cancer of follicular origin are uncommon. Treatment includes levothyroxine administration, focal treatment modalities with surgery, external radiation therapy and thermal ablation, and radioiodine in patients with uptake of ^{131}I in their metastases. Two-thirds of distant metastases become refractory to radioiodine at some point, and when there is a significant tumor burden and documented progression on imaging, a treatment with a kinase inhibitor may provide benefits.

Key Words

- radioactive iodine
- refractory thyroid cancer
- tyrosine kinase inhibitor
- precision medicine
- risk stratification
- papillary thyroid cancer
- follicular thyroid cancer

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Introduction

Distant metastases from differentiated follicular-derived thyroid carcinoma occur in 6–7 patients/million population and are mostly located in lungs and bones. In contrast with the observed increasing incidence of small thyroid cancers, there is no evidence that their incidence changes with time. They are the main cause of thyroid cancer-related deaths, with mortality rates of 65% and 75% at 5 and 10 years after the diagnosis of the metastases (Casara *et al.* 1993, Ruegemer *et al.* 1988, Kitamura *et al.* 1999, Durante *et al.* 2006).

In recent years, major therapeutic advances have been achieved for metastatic thyroid cancers: aims of levothyroxine treatment have been better defined, thermal ablation and stereotactic external beam radiation are currently used, indications and limits of radioactive (RAI) iodine treatment have been clarified and new treatment modalities are available for radioiodine-refractory disease. This review is intended to describe these advances.

Treatment of distant metastases

Treatment of distant metastases includes levothyroxine treatment, focal treatment and RAI as first systemic treatment line in patients with RAI uptake in their metastases. There is no randomized clinical trial demonstrating the superiority of either RAI administration or TSH-suppressive thyroid hormone treatment for patients with distant metastases. Use of these treatments is supported only by retrospective cohort studies, and there are broad variations in acceptable 'standard of care' with respect to the aggressiveness of TSH suppressive therapy and to the frequency and amount of RAI to use.

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The objective of levothyroxine treatment in these patients is to maintain serum TSH below 0.5 IU/L, because increased TSH level may stimulate thyroid cancer growth (Biondi & Wartofsky 2014, Haugen *et al.* 2016). Whether serum TSH level should be undetectable is still a matter of discussion, because the benefits of subclinical thyrotoxicosis that are still not demonstrated have to be balanced in each patient with the risk of cardiovascular consequences. Focal treatment modalities for brain metastases may include surgery and stereotactic radiation therapy (rather than whole brain irradiation). In the past, focal treatment of bone metastases was based on surgery after embolization and external beam radiation therapy at palliative doses (Bernier *et al.* 2001, Durante *et al.* 2006). Percutaneous thermal ablation (radiofrequency- or cryo-ablation), cement injection and implementation of screws are currently used, because they are effective and are less aggressive than surgery (Deandreis *et al.* 2011*b*, Quan *et al.* 2012), and they may be combined with external beam radiation therapy at high doses delivered with a curative intent. Focal treatment for bone metastases is indicated when there are symptoms, neurologic or orthopedic complications or a high risk of such complications; it is also indicated when bone metastases are visible on CT scan or MRI, even in the presence of ^{131}I uptake, because in such cases, RAI treatment alone will not control the disease. In the presence of a single or few bone metastases, focal treatments are performed with a curative intent (Bernier *et al.* 2001).

Two-thirds of DTC patients with bone metastases developed skeletal-related events within a year following the diagnosis of bone metastases (Farooki *et al.* 2012). Unfortunately, bone progression commonly occurs during systemic treatment with RAI or a kinase inhibitor, and bone-directed therapy should be considered in patients with multiple progressive and/or symptomatic bone metastases. In other solid tumors, bisphosphonates (especially IV infusion of zoledronic acid every 1–3 months) and the RANK-ligand-directed agent (monthly sub-cutaneous injection of denosumab) have been shown to delay time to occurrence of skeletal-related events and to improve symptoms with similar efficacy (Wardley *et al.* 2005, Coleman *et al.* 2012). Risks of these agents include hypocalcemia, prompting the concomitant use of supplemental calcium and vitamin D therapy, and non-healing oral lesions and jaw osteonecrosis that can be partially prevented with dental/oral evaluation and treatment before initiation of the treatment.

Two-thirds of patients with distant metastases have significant RAI uptake. They are treated with ^{131}I either with an empiric activity of 3700–7400 MBq (100–200 mCi) every 4–6 months during the first two years and then at longer intervals or with an activity based on a dosimetric approach. Two dosimetric approaches have been described: quantitative tumor dosimetry estimates the activity needed to deliver an effective radiation dose to the metastases, based on the initial RAI tumor concentration (the ratio between initial RAI uptake and tumor volume) and the effective half-life of RAI in the tumor tissue: studies have suggested that radiation doses to the tumor >80 Gy will provide best effects, whereas doses <35 Gy will induce minimal or no effect (Maxon *et al.* 1983, Sgouros *et al.* 2004); the other approach is blood dosimetry that determines the largest activity that can be administered while keeping bone marrow exposure ≤2 Gy (Deandreis *et al.* 2017). Activities based on weight (37–74 MBq/kg body weight) are given to children (Rivkees *et al.* 2011). Between ^{131}I treatments, levothyroxine is used to maintain a low serum TSH level. In the few available retrospective studies in patients with distant metastases, there is no evidence that dosimetry may increase the efficacy of RAI treatment over empiric activities: in one study, the outcome of patients with distant metastases (tumor response and overall survival) was similar after treatment with empiric activities or with activities based on dosimetry (Klubo-Gwiezdzinska *et al.* 2011); in another study, the outcome (overall survival) was similar after treatment with empiric activities of 3700 MBq and with higher activities determined with blood dosimetry (Deandreis *et al.* 2017).

There are several reasons why RAI may not be effective, even in the presence of RAI uptake (Schlumberger *et al.* 2007*a*). Radiation dose is usually lower in tumor thyroid tissue than in normal thyroid tissue because the uptake is lower and the effective half-life is shorter. Tumor dosimetry may be used to deliver radiation doses to the tumor that are high enough to be effective, but this may be not achievable for low tumor uptake or short effective half-life. Furthermore, the distribution of the radiation dose is heterogeneous among patients, and in a given patient, among functioning metastases as shown by positron emission tomography (PET) scanning with ^{124}I and also within a given metastasis (Sgouros *et al.* 2004). Heterogeneity in the RAI uptake is also observed at the cellular level and because of the short path of the beta emitted by ^{131}I, this will result in a heterogeneous dose distribution despite significant mean uptake on whole body scan (WBS) (Schlumberger *et al.* 2007*a*). These observations may explain why higher activities may not improve the outcome.

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For RAI treatment to be effective, appropriate levels of TSH stimulation and absence of iodine contamination are essential. Excess iodine is eliminated one month after administration of an iodinated contrast CT scan (Padovani *et al*. 2012). Prolonged withdrawal of thyroid hormone treatment with a serum TSH above an arbitrary level of 30 IU/L usually induces higher uptake in neoplastic foci than injections of recombinant human TSH (rhTSH) and is the preferred method of TSH stimulation in patients with known metastatic disease (Potzi *et al*. 2006, Plyku *et al*. 2017). Similar short-term survival rates were observed in patients with distant metastases after ^{131}I treatment prepared with either withdrawal or rhTSH (Tala *et al*. 2011), but no comparative data are available on long-term outcome. RhTSH-mediated therapy may be indicated in selected metastatic patients with underlying comorbidities making iatrogenic hypothyroidism potentially risky and in patients with pituitary disease who are unable to raise their serum TSH (Schlumberger *et al*. 2007*b*).

Fluoro-deoxyglucose (FDG) PET is performed in patients with distant metastases for several reasons: it may reveal metastases without RAI uptake that are not visible on RAI-WBS, including in bones; RAI treatment is less effective in patients with metastatic uptake of FDG and FDG uptake indicates more aggressive disease (Robbins *et al*. 2006, Rivera *et al*. 2008, Deandreis *et al*. 2011*a*, Nascimento *et al*. 2015). However, some tumor responses have been observed in patients with both RAI and FDG uptake in their metastases and the decision not to treat with RAI should not be based only on the presence or intensity of FDG uptake; furthermore, in a given patient, metastases with the highest FDG uptake do not have a more aggressive behavior than the other metastases (Terroir *et al*. 2017).

Favorable responses to RAI treatment are characterized by parallel decreases in tumor volume on anatomical imaging and in functional parameters (^{131}I uptake in metastases on post-therapy WBS and serum thyroglobulin (Tg) level). Disappearance of imaging abnormalities have been obtained overall in about 45% of the patients with distant metastases showing initial avidity for ^{131}I with a median cumulative activity of 7400 MBq and almost all complete responses being achieved with a cumulative activity of 22,000 MBq (Durante *et al*. 2006). Complete responses are more frequently achieved in younger patients, in those with small pulmonary metastases, who had a well-differentiated cancer and who have no or low FDG uptake (Durante *et al*. 2006, Robbins *et al*. 2006, Rivera *et al*. 2008, Deandreis *et al*. 2011*a*). Relapse after complete response occurred in less than 10% of patients, even though serum Tg levels were persistently detectable in some patients (Durante *et al*. 2006). In these patients, overall survival after the discovery of distant metastases is favorable. When the tumor mass is considered, the location of the distant metastases, be it in the lungs or bone, has no independent prognostic influence. Small radio-avid bone metastases with no structural abnormalities respond to therapy (Robenshtok *et al*. 2014) and the poor prognosis of most patients with bone metastases is linked to the large size of their lesions (Ruegemer *et al*. 1988, Casara *et al*. 1993, Bernier *et al*. 2001, Durante *et al*. 2006).

Patients with advanced disease that does not respond to ^{131}I treatment (refractory disease) have a median life expectancy of 3–6 years (Durante *et al*. 2006). This occurs more frequently in older patients, in those with large metastases or with poorly differentiated thyroid cancer and in those with FDG uptake (Durante *et al*. 2006, Robbins *et al*. 2006, Rivera *et al*. 2008, Deandreis *et al*. 2011*a*). Fortunately, major advances have been achieved in recent years for the treatment of these rare patients.

Definition of radioiodine-refractory thyroid cancer

Radioiodine-refractory thyroid cancer occurs in the two-thirds of distant metastases in whom a complete response is not achieved with radioiodine (Durante *et al*. 2006). It is an uncommon condition, with an estimated incidence of 4–5 cases per million population (around 250 patients per year in France) (Schlumberger *et al*. 2014).

It is important to recognize at which point RAI treatment is no longer beneficial for DTC patients, in order to avoid unnecessary treatments that may lead to adverse events (AEs) and also that may delay the initiation of systemic treatment to a point when this treatment may be less effective. Most patients with RAI refractory differentiated thyroid carcinoma fall into four categories (Table 1): (a) Patients with metastatic disease that does not take-up RAI at the time of the initial treatment. This group includes patients with structurally evident disease with no RAI uptake on a diagnostic WBS, because in such patients, the administration of a therapeutic activity of ^{131}I, even in the presence of uptake on post-therapy scans, will not induce benefits (Sabra *et al*. 2012). (b) Patients whose tumors lose the ability to take-up ^{131}I after previous evidence of uptake. This may be due to the heterogeneous dose distribution in the thyroid tumor tissue that leads to the eradication of differentiated cells able to take-up ^{131}I, but not of less differentiated cells that do not take-up ^{131}I. (c) Patients with ^{131}I uptake retained in some lesions but not

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Table 1 Definition of radioactive iodine (RAI) refractory disease and criteria for initiating TKI treatment.

Definition of RAI refractory disease	1. Absence of initial RAI uptake in metastases 2. Absence of RAI uptake in metastases after treatment with RAI 3. Presence of RAI uptake in some metastases, but absence in others 4. Progression despite RAI uptake in all metastases 5. Controversial: high FDG uptake, aggressive histology, persistence of disease after several RAI treatment courses
Main criteria for initiating a TKI treatment in a patient with a RAI refractory disease	1. Large tumor burden: tumors greater than 1–2 cm in size 2. RECIST progressive disease in <12 months 3. Symptomatic disease and risk of local complications
Other criteria for initiating a TKI treatment in a patient with a RAI refractory disease	1. Good performance status and acceptable life expectancy 2. Absence of comorbidities or contraindications 3. Good compliance to treatment and to follow-up procedures

in others. This is frequently seen in patients with multiple large metastases (Sgouros *et al.* 2004), and progression is likely to occur in metastases without ^{131}I uptake (Robbins *et al.* 2006, Rivera *et al.* 2008, Deandreis *et al.* 2011*a*). (d) Patients with metastatic disease that progresses despite significant RAI uptake in their metastases and following courses of adequate radioiodine treatment (Vaisman *et al.* 2011). In any of these patients with refractory disease, further ^{131}I treatment will not provide benefits and should be abandoned.

Less clear is the situation for patients with poorly differentiated thyroid cancer, with high uptake of FDG on PET or with persistent visible RAI uptake in all or most lesions which are not cured despite several treatment courses but whose disease does not progress. For these patients, long-term stabilization may be achieved, but the probability of obtaining a cure with further ^{131}I treatment is low (Durante *et al.* 2006) and side effects may increase, including the occurrence of secondary cancers and leukemias (Rubino *et al.* 2003). Also, the outcome of patients who achieved a complete response with a cumulative activity higher than 22,000 MBq was not better than that of patients who never achieved a complete response (Thies *et al.* 2014). The decision to continue ^{131}I treatment in such patients (particularly after receiving more than 22,000 MBq of ^{131}I) is generally based on their response to previous treatment courses, persistence of a significant level of ^{131}I uptake on the previous post-therapy WBS, low FDG uptake in tumor foci and absence of side effects (Durante *et al.* 2006).

Some patients may experience dissociated response to ^{131}I treatment, with a tumor response in some lesions and progression in other lesions; in such patients, focal treatment modalities may be applied on progressive lesions and other ^{131}I treatment courses may be given according to the above-mentioned criteria. When the thyroid gland has not been removed, RAI treatment is usually not administered and RAI uptake status cannot be assessed. These patients are usually managed as iodine-refractory patients.

A potential way of treating RAI refractory patients is to restore the ability of radioiodine uptake in tumor cells, and then to treat with radioiodine. In fact, in papillary thyroid cancer, dedifferentiation is associated with the activation of the MAP kinase pathway that is more pronounced in case of *BRAF* V600E mutation. This dedifferentiated phenotype is characterized by an impaired iodide metabolism, a higher FDG uptake and RAI refractory and more aggressive disease (Durante *et al.* 2007, Cancer Genome Atlas Research Network 2014, Nagarajah *et al.* 2015, Fagin & Wells 2016). This may act through the expression of TGF-beta that in turn stimulates, through the smad3 pathway, the production of reactive oxygen species by NOX4. This results in a decreased expression of thyroid functional proteins, including NIS and TPO that is likely to be due to epigenetic changes and is reversible (Azouzi *et al.* 2017). In a pilot study on 20 patients with metastatic differentiated thyroid carcinoma who had no significant RAI uptake in their metastases, lesional dosimetry with ^{124}I PET imaging was performed following rhTSH stimulation after 4 weeks of treatment with the MEK inhibitor, selumetinib. Twelve patients demonstrated increased tumoral ^{124}I uptake, and 8 of these 12 patients achieved sufficient iodine reuptake to warrant treatment with ^{131}I: 5 achieved Response Evaluation Criteria in Solid Tumor (RECIST) partial responses (PR) and 3 had a stable disease. Of the 20 patients, 9 patients had tumors with the V600E *BRAF* mutation and 5 patients had tumors with *NRAS* mutations at codon 61. Interestingly, of the 8 patients with a major increased ^{124}I uptake, 5 were found to have *NRAS* mutations and one a *BRAF* mutation (Ho *et al.* 2013). In another trial on 10 patients with a *BRAF* mutation, the BRAF inhibitor dabrafenib induced the reappearance of RAI uptake in 6 who were treated with radioiodine and 2 patients achieved a PR (Rothenberg *et al.* 2015). This approach may be relevant in patients

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with small distant metastases with a slow progression rate and with a baseline radioiodine uptake that is undetectable or too low to allow significant radiation doses to be delivered. In patients with baseline RAI uptake in their metastases, this therapeutic intervention may also lead to the delivery of higher radiation doses with a more homogeneous radiation dose distribution in tumor foci.

Treatment of refractory thyroid cancer

In patients with refractory thyroid cancer, ^{131}I treatment is abandoned, levothyroxine treatment is administered to maintain a low serum TSH level (unless contraindications are present) and focal treatment on metastases is performed whenever needed, as well as bone-directed therapies in patients with bone metastases. Surveillance includes an FDG-PET or a CT scan with contrast of the head, neck, chest, abdomen, and pelvis, at an interval of 3–12 months that is dictated by tumor burden, tumor location and by the pace of prior disease progression and of serum Tg doubling time (Miyauchi *et al.* 2011). Most patients with refractory advanced disease have an aggressive course, but the disease can be asymptomatically stable for long periods of time, in particular in young patients with small lung metastases from a well-differentiated carcinoma who are maintained on levothyroxine treatment, because in such patients, the benefits of novel therapies may be largely outweighed by drug toxicities.

The decision to initiate systemic treatment in patients with radioiodine-refractory disease should be taken by a multidisciplinary board and is based on several parameters, including tumor burden, disease progression, location of tumor foci with a high risk of local complications, presence of symptoms and comorbidities (Table 1). Progression rate can be estimated by the doubling time of serum Tg (Miyauchi *et al.* 2011), but should always be confirmed by imaging using RECIST (Eisenhauer *et al.* 2009, Schlumberger *et al.* 2014, Haugen *et al.* 2016, Brose *et al.* 2017*a*, Tuttle *et al.* 2017). RECIST progression is defined by a 20% increase of the sum of the diameters of target lesions that corresponds to a doubling in tumor volume.

Indeed, patients with multiple lesions >1–2 cm and with documented progression within less than 12 months are considered for systemic treatment, that should be initiated at an earlier stage in case of rapid progression. On the contrary, asymptomatic patients with few and/or small metastatic lesions <1 cm and those with no evidence of progression are considered for no treatment but for follow-up every 3–12 months. In patients with few metastases or with a predominant metastasis, or with symptoms, focal treatment modalities may control these tumor foci and may allow postponing initiation of systemic treatment. Some patients with large tumor burden for whom there are no data on progression may be considered for systemic treatment when there is a high risk of local complications (Eisenhauer *et al.* 2009, Schlumberger *et al.* 2014, Haugen *et al.* 2016, Brose *et al.* 2017*a*, Tuttle *et al.* 2017).

Cytotoxic chemotherapy

Cytotoxic chemotherapies provided low response rates (from 0% to 22% with the most frequently used agent, doxorubicin at a dose of 60 mg/m^2 every 3–4 weeks) and toxicity was high (Sherman 2010). However, cytotoxic chemotherapy with recent drugs such as gemcitabine, oxaliplatin or taxane may be used since they were effective in anecdotal patients (Crouzeix *et al.* 2012, Spano *et al.* 2012).

Molecular-targeted therapy

In most DTC patients, an initiating carcinogenic event can be found and molecular-targeted therapy could be given with a scientific rationale (Phay & Ringel 2013, Cancer Genome Atlas Research Network 2014, Fagin & Wells 2016). The MAP kinase pathway is activated in the majority of papillary thyroid cancers, mainly by either gene rearrangements (*RET-PTC* and *NTRK*) or point mutations of the *RAS* and *BRAF* genes. Point mutations of the *RAS* genes are frequently found in follicular and poorly differentiated carcinomas. Additional genetic abnormalities may be found in poorly differentiated thyroid carcinomas. Angiogenesis is activated in thyroid cancers (Bunone *et al.* 1999, Durante *et al.* 2011), by activation of the VEGFR pathway and other pathways may also be activated, including the FGFR and PDGFR pathways (Voce *et al.* 2011).

Up to now, most drugs used in refractory thyroid cancers are anti-angiogenic and some also target kinases in the MAP kinase pathway. With these agents, PR were observed (Cohen *et al.* 2008, Gupta-Abramson *et al.* 2008, Sherman *et al.* 2008, Hoftijzer *et al.* 2009, Kloos *et al.* 2009, Bible *et al.* 2010, Carr *et al.* 2010, Ahmed *et al.* 2011, Capdevila *et al.* 2012, Leboulleux *et al.* 2012, Brose *et al.* 2014, Cabanillas *et al.* 2014, 2015, 2017, Locati *et al.* 2014, Schlumberger *et al.* 2015, Bastholt *et al.* 2016) and even more importantly median progression-free survival (PFS) was prolonged in phase III trials when compared with

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Table 2 Efficacy of anti-angiogenic in RAI refractory thyroid cancer.

	VEGFR	Other targets	*n*	PR (%)	SD >6 month (%)	Median PFS vs placebo	
						Drug (months)	Placebo (months)
Axitinib	+	RET, PDGFR, KIT					
Cohen			45	31	38		
Locati			45	38	29		
Cabozantinib	+	RET, C-MET	15	53	40		
Cabanillas							
Lenvatinib	+	RET, FGFR, PDGFR,C-KIT	392	65		18.3	3.8
Select (phase III vs placebo)							
Schlumberger							
Motesanib	+	PDGFR, KIT, RET	93	14	33		
Sherman							
Pazopanib	+	PDGFR, KIT	37	49			
Bible							
Sorafenib	+	RET, BRAF, PDGFR, KIT				10.8	5.8
Decision (phase III vs placebo) Brose			417	12			
Sunitinib	+	RET, PDGFR, KIT					
Cohen			31	13	68		
Carr			29	28	46		
Vandetanib	+	RET, EGFR					
Zacthyf (phase II vs placebo)			145	0		11.1	5.9
Leboulleux			238			10	5.7
Verify. Bastholt							

PFS, progression-free survival; PR, partial response; SD, stable disease.

placebo (Table 2). The lack of demonstrated improvement in overall survival might have been related to the crossover design of the studies with treatment in an open phase in case of progression in the placebo arm and the long survival of some patients after their participation to the trial during which other treatment modalities were used. Three medications have been evaluated in randomized phase III trials vs placebo.

ZACTHYF phase II randomized trial with vandetanib (300 mg/day) vs placebo on 145 patients with RAI refractory locally advanced or metastatic DTC that had progressed within the past 14 months produced a significant prolongation of the median PFS (hazard ratio (HR): 0.63, $P=0.008$; median: 11.1 vs 5.9 months, respectively) and an objective partial response rate of 8% (Leboulleux *et al.* 2012). The subsequent VERIFY phase III trial with vandetanib vs placebo on 238 patients produced a non-significant improvement of median PFS (HR: 0.75; $P=0.08$; median PFS: 10.0 vs 5.7 months, respectively) (Bastholt *et al.* 2016).

DECISION phase III trial was performed on 417 naïve patients with RAI refractory locally advanced or metastatic DTC that had progressed within the past 14 months (Brose *et al.* 2014). Patients were randomized 1:1 either to sorafenib (400 mg administered orally twice-daily) or placebo. Sorafenib treatment significantly improved median PFS compared with placebo (HR: 0.587; 95% CI: 0.454–0.758; $P<0.0001$; median PFS: 10.8 vs 5.8 months, respectively). The improvement in PFS was seen in all clinical subgroups. The partial response rate was 12% and stable disease for 6 months or longer was achieved in 41.8% of patients. The safety profile of sorafenib was as expected, but with a higher incidence of AEs than in patients with other cancer types. Most AEs were grade 1 and 2, the most common being hand-foot skin reaction (76%), diarrhea (69%), alopecia (67%) and rash/desquamation (50%). Toxicities led to dose reduction in 64% of patients and to drug withdrawal in 19%.

SELECT phase III trial was performed on 392 patients with RAI refractory locally advanced or metastatic DTC that had progressed within the past 13 months; progression was confirmed by an independent radiological review (Schlumberger *et al.* 2015). Patients were randomized 2:1 either to lenvatinib (24 mg/day) or placebo. Lenvatinib treatment significantly improved median PFS compared with placebo (HR: 0.21; 99% CI: 0.14–0.31, $P<0.001$; median PFS: 18.3 vs 3.6 months, respectively) and the objective response rate was 65% with complete responses in 2%. The improvement in PFS was seen in all clinical subgroups, including in the 20% of patients who had received prior VEGF-targeted therapy. Treatment-related adverse events were reported in all patients in the lenvatinib group, including hypertension (68%), fatigue (64%), diarrhea (59%) and decreased appetite

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(50%). Proteinuria occurred in 32% and thromboembolic events in 11%. Toxicities led to dose reduction in 68% of the patients, to dose interruption in 82% and to drug withdrawal in 14% of patients. Investigators attributed 6 fatalities (2%) to the use of lenvatinib (pulmonary embolism in one, hemorrhagic stroke in one and general health deterioration in the other 4). In a subsequent analysis, a rapid decline in tumor size by 25% was reported at the 8-week evaluation; the duration of PFS was related to the magnitude of the initial tumor size decrease, and a multivariate analysis identified two predictive indicators for the decrease in size, performance Eastern Cooperative Oncology Group (ECOG) status of 0 or 1 and small size of metastases (Robinson *et al.* 2016). In the real-life experience in France on 75 patients, the ORR was 31%, but when excluding patients with poor performance status, those who had been heavily pretreated and those with very large metastases, results were similar to those of SELECT (Berdelou *et al.* 2017). There was no benefit of lenvatinib treatment in the overall survival rate in SELECT patients, but in a subgroup analysis, a significant benefit was observed in patients aged above 65 years, related to the beneficial effects of lenvatinib in patients with more aggressive disease (Brose *et al.* 2017*b*).

In conclusion, results of DECISION and SELECT were positive and led to the approval of sorafenib and lenvatinib for advanced, refractory and progressive DTC by FDA and by EMA. Both vandetanib and sorafenib improved median PFS by 5 months over placebo, but with few PR and are mainly considered as cytostatic. Despite the absence of direct comparison, lenvatinib seems more effective: it improves median PFS by almost 15 months over placebo and induces a response rate as high as 65%, with few complete responses. Both in SELECT trial and in real life, maximal benefits were achieved in patients with an ECOG performance status of 0–1, who were not heavily pretreated and who had a limited tumor burden. There was no unexpected toxicity, but toxicity was frequent and should be managed by experienced teams. Because the initial dosage of lenvatinib (24 mg/day) had to be reduced in two-thirds of patients after a median time of 3 months (Schlumberger *et al.* 2015), an ongoing randomized trial is comparing efficacy and safety of initial daily doses of 18 mg vs 24 mg (NCT02702388). Also, it may be safe to initiate lenvatinib treatment at a lower dose in elderly patients and in those at risk of toxicities.

Predictive biomarkers are aimed to allow a better selection of patients for any treatment modality and also an early assessment of the tumor response to the drug. Oncogenic events that have been described in thyroid cancers have been studied in several trials. In DECISION and in SELECT trials, PFS was improved in all biomarker subgroups, irrespective of *BRAF* and *RAS* mutation status (Brose *et al.* 2014, Schlumberger *et al.* 2015). In patients treated with motesanib, decrease from baseline in serum placental growth factor after 1 week of treatment correlated with best tumor response, and a decrease in soluble VEGF receptor 2 after 3 weeks of treatment separated between responders and non-responders. Lower baseline VEGF levels were associated with longer PFS (Bass *et al.* 2010). In SELECT trial, low baseline levels of angiopoietin-2 were associated to maximum tumor shrinkage, overall response rate and longer PFS; fibroblast growth factor 23 (FGF23) upregulation after 15 days of treatment was associated with longer PFS (Tahara *et al.* 2017). These studies have shown the promise of using biomarkers in predicting drug efficacy, which needs to be refined before they can be used in clinical practice in individual patients.

There are few available data on the use of FDG-PET for an early prediction of response to TKI treatment: comparison of FDG uptake at 1–2 weeks with baseline FDG uptake has produced inconsistent results and the interest of repeated FDG-PET/CT in the management of DTC patients during treatment is still unclear. During the treatment with sunitinib, a decrease in FDG uptake was associated with subsequent tumor response and an increase with subsequent tumor progression (Carr *et al.* 2010). However, in ZACTHYF, no such relationship was observed (Leboulleux *et al.* 2012).

Drugs directed against other targets

Mutation screening should be performed on a routine basis in RAI refractory patients, because the presence of a driver mutation may lead to the use of a specific inhibitor. Many data have been obtained on thyroid tumor tissues that were resected long before treatment and analysis of the metastatic tumor tissue at the time of treatment would probably be more informative (Ricarte-Filho *et al.* 2009).

The presence of *BRAF* mutation was an inclusion criterion in phase 2 trials with a BRAF inhibitor, either vemurafenib or dabrafenib (Dadu *et al.* 2015, Falchook *et al.* 2015, Brose *et al.* 2016) and positive results were observed, and these results may be improved by a combination with a MEK inhibitor. Mutation in *ALK* (anaplastic lymphoma kinase) gene has been reported in few patients with refractory DTC and can be the target of an ALK inhibitor (Kelly *et al.* 2014). Other pathways, such as the PI3K-AKT pathway (Ringel *et al.* 2001, Xing 2010)

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that is activated in follicular and poorly differentiated carcinoma may also be a target for treatment.

Immunological intervention may use two directions. One is guided by the increased number of tumor-associated macrophages (TAMs) in aggressive tumors that culminates in anaplastic thyroid cancer (Ryder *et al*. 2008, Caillou *et al*. 2011). In transgenic mice, depletion of TAMs through inhibition of the colony-stimulating factor 1 (CSF1) pathway that attracts TAMs into the tumor impairs tumor progression (Ryder *et al*. 2013). Another one is the fact that some tumors evade immunosurveillance, possibly through changes over time of their immunological profile (Ott *et al*. 2013). In a phase II trial, pembrolizumab, a PD-1 inhibitor induced 2 PR in 22 treated patients (Mehnert *et al*. 2016). Combination therapy with an anti-angiogenic medication may permit to obtain high rates of complete responses with longer durations of responses.

Clinical practice and future developments

Abandon of RAI therapy, modalities of follow-up, initiation of TKI treatment and its termination are best decided in the frame of a multidisciplinary team with the participation of nuclear medicine specialists, endocrinologists and medical oncologists. Indeed, the participation of other specialists in surgery, diagnostic imaging, interventional radiology, radiation oncology and in other fields may enrich the decisions. This permits to deliver a unified message regarding treatment options, empower patients with well-informed choices and increase confidence through consensus. Once the decision to treat with TKI has been taken, treatment and follow-up are best realized with a co-management by the treating physician and a medical oncologist.

Initiation of systemic treatment

One main challenge is to properly select patients for systemic therapy. As all these medications can cause a significant decrease in quality of life (QoL) and adverse effects that may be life threatening, patients with distant metastases that are over 1–2 cm in size and that progress are candidates for systemic treatment (Schlumberger *et al*. 2014, Haugen *et al*. 2016). Dyspnea, painful bone lesion, symptomatic brain metastases, as well as lesions with high risk of complication should first be submitted to focal therapy. Also, symptomatic treatment modalities are always warranted, as well as bisphosphonates or anti-RANK ligand antibody in patients with bone metastases. The presence of tumor foci in certain location may be an indication to initiate treatment, even in patients with no demonstrated progression: treatment should be initiated before the occurrence of tumor involvement of the trachea or esophagus and before encasement of great vessels that may contraindicate the use of TKI with respect of the risk of bleeding or fistula (Blevins *et al*. 2014, Lamartina *et al*. 2016). External beam radiation therapy on metastases may be performed during TKI treatment, and there is no evidence that irradiation of brain metastases before the initiation of TKI treatment may decrease the risk of bleeding (Tallet *et al*. 2017).

Before initiation, evaluation includes assessment of the patient's performance status. Tolerance and efficacy are lower in patients with a poor performance status (e.g. ECOG 2 or more). Symptomatic treatments may be needed to improve performance status before initiation of TKI treatment. The absence of comorbidities or contraindications should also be assessed, including cardiovascular history, control of blood pressure, absence of hematological, renal and hepatic abnormalities that may contraindicate any TKI treatment or may indicate treatment initiation at a lower dosage (Table 3).

Finally, due to the duration of treatment, the potential for toxicities, and the need for regular monitoring, the patients must be aware that the follow-up will be close and may be prolonged for years.

In countries where several drugs are labeled, the most effective drug should be used as first-line treatment, as in other cancer types. Furthermore, it has been shown that lenvatinib is more effective in patients with a general good ECOG performance status who have not been heavily pretreated and in whom the tumor burden is limited. Also, only a fraction of these patients will receive a second-line treatment. Lenvatinib that appeared to be the most effective drug is thus used as first-line treatment in the absence of contraindication. Treatment should be initiated when tumor burden is still limited, preferably before the appearance of symptoms and at a stage when large vessels and the tracheoesophageal tracts are not involved by the disease (Blevins *et al*. 2014, Lamartina *et al*. 2016). Trial consideration should be given to all patients, even in countries where a drug is currently approved.

In those at risk of toxicities, the initial dose of lenvatinib may be reduced to 18 or even 14 mg/day. In patients with a poor tolerance and as an alternative to dose reduction, an intermittent drug administration may be offered when a tumor response has been achieved, and this may improve the QoL and allows patients to program their social activities during drug holidays.

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Table 3 Contraindications or factors discouraging TKI treatment.

Contraindications	Comments
Intestinal or liver disease	Active or recent diverticulitis, inflammatory bowel disease, recent bowel resection Laboratory: AST-ALT >5 times the upper limit of normal range; increased bilirubin level
High risk of bleeding and/or fistula	Recent gastrointestinal hemorrhage or hemoptysis Coagulopathy or anticoagulant treatment Tumor involvement of the trachea-bronchus and of the pharyngo-esophagus tracts Encasement of great vessels
High cardiovascular risk	Unstable angina, myocardial infarction or stroke within 6 months prior TKI initiation, left ventricular dysfunction Avoid TKI in patients with recent thromboembolic events in the preceding 6–12 months. Withhold treatment upon occurrence and consider permanent discontinuation for arterial thrombosis Use long-term low-molecular-weight heparin
Hypertension	Uncontrolled hypertension may occur during the first days of treatment with lenvatinib. Initiate antihypertensive treatment if blood pressure is >14/9. Initiate TKI treatment only when blood pressure is normalized
Prolonged QTc interval	QTc >450 ms at baseline History of ventricular and bradyarrhythmias Control blood levels of calcium, potassium, magnesium and TSH Avoid the use of other drugs that may prolong QT Minor QTc prolongation during sorafenib or lenvatinib treatment
Renal	Creatinine clearance <60 mL/min Proteinuria >1 g/24 h
Cachexia, poor nutrition, sarcopenia	Symptomatic care should improve performance status Provide dietary recommendations and encourage physical exercise
Untreated brain metastases	Controversial risk of bleeding. No evidence that radiation therapy of brain metastases before initiation of TKI treatment may decrease the risk of bleeding
Concomitant medication that induce or inhibit CYP3A4	Avoid or substitute for another drug. If cannot be eliminated, consider a dose reduction in the TKI

Control of safety and of efficacy

AEs are frequently under-reported (from 13% up to 50%) by care providers (Di Maio *et al.* 2015). They occurred more frequently in patients aged older than 65 years (Brose *et al.* 2017*b*). Patients should be encouraged to declare their AEs as soon as they appear because their treatment at an early stage is more effective and may improve compliance. Pharmacokinetics may permit to avoid these AEs, by guiding the treatment dose according to blood levels. Safety may be improved by treating patients with an ECOG performance status of 0–1, by searching for contraindications and correcting major defects, including by treating high blood pressure, before treatment initiation.

Education should be provided to each patient and to care providers. It is highly recommended after initiation of treatment to follow-up patients at 2-week intervals for the first 2–3 months and then once a month in order to proactively manage AEs, in accordance with the tolerance of each individual patient.

The most common AEs and their management are presented in Table 4. Fortunately less common, serious AEs are hypertension, arterial and venous thrombotic events, bleeding, gastrointestinal fistula and perforation, acute myocardial infarction, heart failure, cytopenias, hepatotoxicity, renal failure and reversible posterior leukoencephalopathy syndrome.

With any of these anti-angiogenic medications, the dose of levothyroxine treatment had to be increased in the majority of patients, and an increased need in calcium and vitamin D analog may also occur, particularly in patients treated for post-operative hypoparathyroidism.

Efficacy is assessed every 8–12 weeks with imaging. Tumor responses were observed in a fraction of patients that was more important with some agents (lenvatinib, pazopanib, cabozantinib) but even with these agents, most responses were partial. Long-term stabilization of the disease that was demonstrated to be progressive before the initiation of treatment may indeed be beneficial.

Termination of treatment

The duration of treatment is not yet validated and for this reason, treatment is usually given as long as toxicities remain manageable and there is evidence of benefits. In patients with a dissociated response with only a few progressive metastases that may be controlled by local treatment modalities, systemic treatment may be maintained. Rapid

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Table 4 Principal side effects of tyrosine kinase inhibitors and their management.

Adverse events	Frequency (any grade)	Frequency (grade ≥3)	Management
Hypertension	Lenvatinib 69% Sorafenib 41% Sunitinib 36% Pazopanib 48% Vandetanib 32%	Lenvatinib 42% Sorafenib 10% Sunitinib 13% Pazopanib 3%	Cardiac assessment with left ventricular fraction measurement before TKI start and every 3 months during treatment Educate patients at frequent blood pressure surveillance and self-measurement Target blood pressure ≤140/90 mmHg (lower in case of overt proteinuria) 1st-line anti-hypertensive medications Angiotensin-converting enzyme inhibitors Angiotensin II receptor blockers Non-dihydropyridine calcium channel blockers If diuretics are used, monitor electrolytes and avoid dehydration
Diarrhea	Lenvatinib 58% Pazopanib 48% Selumetinib 45% Sorafenib 68.6% Vandetanib 74% Vemurafenib 46%	Lenvatinib 8% Sorafenib 5.3%	Exclude other causes of diarrhea Diet adjustment (low fiber food, avoid high fat and spicy foods, alcohol, caffeine and carbonated drinks) Search for steatorrhea (fat >6g/24 h and low fecal elastase) and if present administer pancreatic extracts and vitamin D Loperamide and codein Probiotics may be beneficial
Fatigue	Lenvatinib 59% Pazopanib 78% Selumetinib 80% Sorafenib 50% Vandetanib 49% Vemurafenib 69%	Lenvatinib 10% Vandetanib 9% Sorafenib 6%	Assessment with validated questionnaires (e.g. EORTC QLQ C30 or Brief Fatigue Inventory) Regular physical activity Take pills in the evening Monitor other causes of fatigue (anemia, depression, electrolytes and calcium disturbances)
Nausea	Lenvatinib 41% Pazopanib 73% Selumetinib 40% Sorafenib 21% Vandetanib 25% Vemurafenib 46%	Lenvatinib 2.3%	Metoclopramide Ondansetron, Granisetron (consider risk of QT prolongation)
Stomatitis	Lenvatinib 36% Selumetinib 35% Sorafenib 23%	Lenvatinib 4% Sorafenib <1%	Oral hygiene and frequent mouthwash with water and baking soda Topic analgesics alone or in combination (lidocaine 2%, diphenhydramine, bismuth subsalicylate, aluminum or magnesium hydroxide)
Weight loss	Lenvatinib 46% Sorafenib 47%	Lenvatinib 10% Sorafenib 6%	Nutritional assessment at baseline and then periodically Oral nutritional supplements Enteral nutritional supplements if needed
Proteinuria	Lenvatinib 31% Pazopanib 37% Sunitinib 22% Vemurafenib 23%	Lenvatinib 10%	Baseline and periodic assessment (urine stick and if >1+, 24 h proteinuria) Angiotensine-converting enzyme inhibitors Dose reduction Discontinuation in case of nephrotic syndrome (nephrologic advice in case of proteinuria >3 g/24 h)
Increased TSH	Lenvatinib 62% Sorafenib 33%		Periodic TSH testing and levothyroxine dose adjustment
Skin rash	Lenvatinib 16% Selumetinib 70% Sorafenib 502% Vandetanib 74% Vemurafenib 73%	Lenvatinib <1% Sorafenib 5%	Sunscreen with very high sun protection factor (≥50) in case of photosensitivation Doxycycline or Minocycline 100 mg bid in case of folliculitis (doxycycline might increase photo sensitivation) Use perfume free soap and loose natural fabric clothing Avoid hot and cold water

Continued

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Table 4 Continued

Adverse events	Frequency (any grade)	Frequency (grade ≥3)	Management
Hand and foot syndrome	Lenvatinib 32% Sorafenib 76% Pazopanib 8.6%	Lenvatinib 3.4% Sorafenib 20%	Prevention: Removal of hyperkeratotic lesions from hands and feet Avoid traumatism (also using comfortable clothing and shoes), avoid hot and cold water Urea creams 5–10% Moisturizing creams Treatment: Urea creams 30%; topic steroid creams (hydrocortisone 1%) and pain killers Withold TKI treatment and resume it when grade <1
Skin tumors	Sorafenib Vemurafenib (4–46%)		Surgical resection. Does not imply TKI termination
Arthralgias and myalgias	Lenvatinib 18% Pazopanib 9% Sorafenib 9% Sunitinib 43% Vemurafenib 59%	Lenvatinib 2% Sorafenib 9%	Pain killers Corticosteroid therapy Dose reduction
Venous or arterial thrombosis		Lenvatinib 3%	Low-molecular-weight heparin
Hemorrhage	Pazopanib 13% Sorafenib 15% Sunitinib 30%	Lenvatinib 1% Pazopanib 2% Sorafenib 3% Sunitinib 3%	Consider airway invasion assessment (with direct fibroscopy or imaging revision)
QTc prolongation	Vandetanib 23%		Electrocardiogram and electrolytes assessment before TKI start, 1–2 weeks after start, monthly for 3 months and then periodically Correct any electrolyte abnormality Avoid concomitant use of drugs that lead to QT prolongation or monitor carefully (a comprehensive list of drugs that prolong QT can be found at www.crediblemeds.org) TKI withdrawal in case of QTc >500 ms or >60 ms above baseline Minor prolongation with sorafenib and lenvatinib

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CrCl, creatinine clearance.

progression has been reported after discontinuation of TKI treatment (Yun *et al.* 2014), and patients with progressive disease should not be left untreated for long periods of time. In patients who progress slowly during TKI treatment, the treatment may be maintained as long as there is evidence of clinical benefits. Alternatively, patients may benefit from another anti-angiogenic medication: after a first line with sorafenib, cabozantinib or lenvatinib given as second line was effective (Dadu *et al.* 2014, Massicotte *et al.* 2014, Schlumberger *et al.* 2015, Cabanillas *et al.* 2017), but benefits with another anti-angiogenic drug are questionable, and future studies should test cross-resistance between drugs. Alternatively, drugs targeted at genetic abnormalities that are present in the tumor tissue may be used, as well as immunotherapy. There is a need for trials, and recent trials performed in the frame of clinical networks have shown that inclusion of the expected number of thyroid cancer patients to reach statistically significant conclusions is possible in a limited period of time.

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