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RESEARCH

Use of lenvatinib in the treatment of radioiodine-refractory differentiated thyroid cancer: a multidisciplinary perspective for daily practice

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Abstract

Background: Most thyroid cancers of follicular origin have a favorable outcome. Only a small percentage of patients will develop metastatic disease, some of which will become radioiodine refractory (RAI-R). Important challenges to ensure the best therapeutic outcomes include proper, timely, and appropriate diagnosis; decisions on local, systemic treatments; management of side effects of therapies; and a good relationship between the specialist, patients, and caregivers.

Methods: With the aim of providing suggestions that can be useful in everyday practice, a multidisciplinary group of experts organized the following document, based on their shared clinical experience with patients with RAI-R differentiated thyroid cancer (DTC) undergoing treatment with lenvatinib. The main areas covered are patient selection, initiation of therapy, follow-up, and management of adverse events.

Conclusions: It is essential to provide guidance for the management of RAI-R DTC patients with systemic therapies, and especially lenvatinib, since compliance and adherence to treatment are fundamental to achieve the best outcomes. While the therapeutic landscape in RAI-R DTC is evolving, with new targeted therapies, immunotherapy, etc., lenvatinib is expected to remain a first-line treatment and mainstay of therapy for several years in the vast majority of patients and settings. The guidance herein covers baseline work-up and initiation of systemic therapy, relevance of symptoms, multidisciplinary assessment, and patient education. Practical information based on expert experience

Key Words

- differentiated thyroid cancer
- lenvatinib
- radioiodine refractory
- toxicity
- management

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is also given for the starting dose of lenvatinib, follow-up and monitoring, as well as the management of adverse events and discontinuation and reinitiating of therapy. The importance of patient engagement is also stressed.

Introduction

The incidence of thyroid cancer (TC) has steadily increased by 20% from 1990 to 2013 and is now predicted to be the fourth leading type of cancer globally (1). The increase has been ascribed primarily to the ability to detect early tumors as well as to the overdiagnosis of clinically indolent tumors (1, 2). Differentiated thyroid cancer (DTC) accounts for the vast majority of cases, of which papillary thyroid cancer is the most common subtype (3). Other forms of TC, such as anaplastic thyroid cancer and medullary thyroid cancer (MTC), account for only a small percentage of cases (<1% and 1–2%, respectively), and no increase in incidence has been reported in recent years (3).

The majority of TCs have aberrations in the mitogen-activated kinase pathway (3). In non-MTC, *BRAF* c.1799 T>A is the most common mutation, seen in 50–70% of cases, which leads to the production of a BRAF p.V600E mutant protein (4, 5). However, mutations in the RAS family of oncogenes as well as genomic rearrangements involving various fusion partners (e.g. *RET; NTRK, ALK*) have also been observed (3). Treatment for DTC is normally based on the results of ultrasound (US) evaluation and US-guided fine-needle aspiration cytology, according to which patients are assigned to surveillance or surgery. Many patients who undergo surgery will receive post-surgical therapy with radioactive iodine (RAI) and thyroid-stimulating hormone (TSH) suppression, which can improve long-term outcomes by eliminating/reducing foci of neoplastic cells in the neck and in distant metastases. Local recurrence occurs in about 20% of patients with the presence of distant metastasis, either synchronous or metachronous, in about 10–15% of cases (6). In roughly one-third of advanced DTC, metastatic lesions have lost the ability to take up iodine (RAI-refractory (RAI-R) DTC) with an associated decrease in overall survival (7). The standard definition for refractoriness to RAI is the absence of RAI uptake in all metastatic lesions (initially or during treatment), or progression of lesions within 12 months after the last therapeutic RAI, even if more complex situations can occur (8). In addition, a tumor might be considered at risk to be refractory to additional RAI therapy in case of persistence of disease after a cumulative activity of 22.2 GBq (600 mCi) of ^{131}I. It is, however, known that RAI refractoriness is associated with poor prognosis, with 5-year disease-specific survival of 66% and a 10-year survival of only 10% (7, 9, 10).

Systemic therapies are an important treatment option for RAI refractoriness DTC. Among these, multikinase inhibitors (MKIs) are most frequently used, and lenvatinib, sorafenib, and cabozantinib have been approved for the treatment of advanced RAI-resistant DTC by the FDA and EMA given their antiangiogenic activity. More recently, new agents have been approved. We have two different scenarios for RET inhibitors, one for the US (FDA) and one for Europe (EMA): selpercatinib and pralsetinib have been approved by the FDA to treat RET-altered TC regardless of whether or not they have received previous MKI therapy; selpercatinib is the only RET inhibitor approved up to now by the EMA to treat RET-altered DTC that was previously been treated with lenvatinib and/or sorafenib in adult and adolescent (≥12 years) patients with RET-mutant MTC.

Tailored agents such as entrectinib and larotrectinib obtained an agnostic approval in the presence of an *NTRK* rearrangement, while no BRAF/MEK inhibitors have been approved up to now in Europe. Since MKIs are associated with substantial adverse events (AEs) such as hypertension, diarrhea, fatigue, and weight loss, and since they are expected to be administered on a long-term term (i.e. as long as the patient does not progress under treatment and as long as tolerance is acceptable), careful assessment of the risk–benefit profile is warranted prior to initiation of an MKI. This evaluation is made based on tumor load, symptoms, location of metastases, and clinical status (8).

A number of societies have issued guidance for the initiation of MKIs; however, their recommendations are not totally uniform. For example, the National Comprehensive Cancer Network guidelines recommend that patients with progressive and/or symptomatic disease should be considered as candidates for an MKI (11), while the American Thyroid Association guidelines state that MKIs should be considered in patients with life-threatening lesions, as well as in the presence of diffuse disease progression and symptomatic disease (12). The European Society for Medical Oncology (ESMO) guidelines recommend MKIs for patients with symptomatic

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disease and multiple lesions or in those with progressive asymptomatic disease and multiple lesions (13). In addition, the European Thyroid Association guidelines recommend that patient-related factors and preferences should be considered in a multidisciplinary context (8). In the first-line setting of RAI-R DTC, in the ESMO guidelines, it is stated that lenvatinib should be generally preferred over sorafenib based on activity and prolonged progression-free survival (PFS), even if the choice should be personalized according to the likelihood of response and comorbidities (13). While different guidelines provide general indications for starting therapy with an MKI, there is still controversy over the precise criteria to use, the optimal timing, dose and dose adjustments, and follow-up criteria (14).

Because patient compliance and adherence to treatment are essential to achieve the best possible outcomes, the present article summarizes the perspectives of a group of experts who virtually met to discuss the optimal management of patients with RAI-resistant DTC under consideration for treatment with lenvatinib, with the aim of providing guidance that can be useful in daily practice. In this context, experts agree that patient engagement is essential to improve treatment outcomes, increase satisfaction with the care experience, and provide a better therapeutic alliance with physicians.

The guidance covers a wide range of areas, from initiating systemic therapy and baseline work-up, relevance of symptoms, multidisciplinary assessment, and role of patient education, with specific focus on lenvatinib, from a European perspective. Practical information is also given for the starting dose, follow-up, and monitoring, as well as management of AEs and discontinuation of therapy.

Materials and methods

The experts involved were recruited for participation in the present project by the corresponding author to form a group with broad clinical expertise in RAI-R DTC. The group is a self-referential group and is not a committee of a European scientific society. The experts involved were sent a survey designed by the corresponding author that contained 18 questions that were to be answered in an open format and limiting the response to 150 words (Supplementary Table 1, see section on supplementary materials given at the end of this article). The guidance provided is based on the clinical experience and opinion of the participants. The survey was divided into four main areas: patient selection, initiation of therapy, follow-up, and management of AEs. The answers were meant to facilitate an open discussion. The results were then collated and discussed in an online meeting, with an open format, on November 29, 2021, during which the group shared experiences and knowledge on various topics, addressing their individual experiences and reviewing the survey results, in order to find shared agreement. The group, consisting of a multidisciplinary board (i.e. three medical oncologists, four endocrinologists, two nuclear medicine physicians, and one epidemiologist) of ten experts in management of RAI-R DTC patients from different European countries, was also joined by representatives from two patient associations in France and UK. As patient association members, KF and BB did not attend the meeting but did revise the present document.

Results

Patient selection: when and how should systemic treatment be initiated?

Factors to consider at baseline work-up

Baseline work-up should minimally consist of medical history, clinical parameters (body weight, blood pressure, heart rate, Eastern Cooperative Oncology Group (ECOG) status, symptoms, comorbidities, concomitant medications), blood test assessment (electrolytes, liver function, renal function, TSH and thyroglobulin levels, proteinuria), and cardiac function evaluation (left ventricular function and ECG). It is also important to quantify tumor burden by morphological and functional imaging.

Evaluation of the tumor for somatic mutations and gene rearrangement by next-generation sequencing (NGS) was suggested, whenever possible, in each individual with RAI-R DTC, since it can provide information that can be valuable considering the availability of several new treatments, even if many are not currently reimbursed by most healthcare systems in Europe. A new biopsy of the relapse/metastatic lesion would be advisable, especially when the primary tumor sample dates to earlier than 2000. Nevertheless, it was acknowledged that lenvatinib can currently be used as first-line treatment independently of the tumor's mutational profile (15).

Eligibility criteria

Some experts mentioned that in their daily practice, systemic therapy with lenvatinib is felt to be indicated, outside of the standard recommendations of disease

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progression according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 criteria, or symptomatic disease, for example, in patients with lesions at high risk of progression (e.g. for histotype and/or site of the lesion) and/or high tumor burden. Others mentioned that the presence of a *BRAF* mutation, *RET*, or *NTRK* fusion gene could be a criterion to initiate therapy with newer targeted agents other than with lenvatinib (i.e. with dabrafenib and trametinib for *BRAF*-mutated tumors, selpercatinib or pralsetinib for *RET*-altered tumors, or with entrectinib or larotrectinib for *NTRK*-rearranged tumors). However, there was some controversy regarding this later point, citing the lack of long-term clinical experience, lack of randomized trials and regulatory issues. Accordingly, patients with progressive, locally advanced, or metastatic, RAI-R DTC (papillary/follicular/oncocyte cell), who meet disease progression according to RECIST version 1.1 criteria (16) should be considered for treatment with lenvatinib (Table 1). In the SELECT trial, patients were considered eligible if they were progressing within 14 months prior to inclusion and were considered RAI-R based on the following definition: had at least one measurable lesion without iodine uptake on any ^{131}I scan, at least one measurable lesion that had progressed according to the RECIST criteria within 12 months after ^{131}I therapy despite ^{131}I avidity at the time of treatment, or cumulative activity of ^{131}I >22.2 GBq (600 mCi) (17). Different approaches may be considered on a case-by-case basis in real-life practice. For example, potentially high-risk or life-threatening lesions (e.g. lesion close to cavitate organs or encasing blood vessels) may require local treatment or the start of MKI therapy, even if other criteria are not met.

Contraindications

The patient's overall status and comorbidities should be carefully assessed before starting treatment to predict and avoid serious AEs and to modulate the treatment dose. Most of the experts would not initiate lenvatinib in a patient with an ECOG performance status higher than 2. Several conditions were considered by the experts to be relative contraindications (Table 1). These include all severe cardiac, renal, and hepatic comorbidities, as well as all contraindications reported in the exclusion criteria of the SELECT trial: any other malignancy within the past 24 months, any anticancer treatment 21 days before randomization, proteinuria ≥ 1 g/24 h, or significant cardiovascular or gastrointestinal dysfunction (17). For example, in patients with uncontrolled hypertension, initiation of treatment should be delayed until blood pressure is controlled (<140/90 mmHg) with specific drugs and cardiologic evaluation plus ECG has been done.

In patients with tracheal and/or esophageal invasion, the high risk of fistula should be considered, especially in the case of papillary histotype (18). If treatment is initiated in such a patient, accurate initial evaluation and close monitoring should be carried out. The same considerations should apply to patients with a high risk of hemorrhage (e.g. blood vessel encasement). In these cases, caution is mandatory and a lower starting dose of lenvatinib should be considered, to mitigate the potential complications associated with rapid tumor shrinkage. This suggestion is based on case reports and small case series, highlighting the association between lenvatinib and bleeding events (19, 20, 21).

Brain metastases were not thought to be an *a priori* reason to exclude a patient from initiating lenvatinib. Brain MRI with contrast to exclude active bleeding or signs of recent bleeding should always be performed. However, in the case of brain metastases, systemic treatment can be delayed until loco-regional treatment as stereotactic radiosurgery (if feasible), or external beam radiotherapy (EBRT) is delivered in cases with symptomatic and/or large lesions. However, some experts mentioned that they do not routinely screen for the presence of brain metastases.

Elderly patients are progressively increasing due to the aging of population, especially in Western European countries. The utility of the G8 score in elderly patients with cancer has already been reported (22). In elderly patients (>75 years old) with unresectable hepatocellular carcinoma, receiving sorafenib or lenvatinib, the modified G8 score contributed to elaborate a therapeutic strategy in these patients (23). Despite the significant benefits of lenvatinib in outcomes of RAI-R DTC patients >_65 years old (24), particular caution is needed in the very elderly (>75 years), for whom very limited data are available regards the use of lenvatinib and a shared decision should always be made with the patient. Moreover, in complex cases, geriatric evaluation with a specific instrument such as the G8 Health Status Screening Tool can help with treatment decisions in elderly patients. Frail patients should be managed with extreme care.

Relevance of symptoms

While all asymptomatic patients should be evaluated on an individual basis, systemic treatment should ideally be started before the patient becomes symptomatic (Table 1). If the decision is made to treat, whichever drug is chosen, starting therapy at full dose is recommended.

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Table 1 Summary of investigations to perform at baseline, eligibility criteria, relative contraindications, and relevance of symptoms when initiating lenvatinib.

Investigations to perform at baseline
Medical history
Clinical parameters (body weight, blood pressure, heart rate, ECOG status, symptoms, concomitant diseases, and treatment)
Functional assessment (electrolytes, liver function, renal function, TSH, Tg and anti-Tg antibody levels, proteinuria)
Cardiac assessment (left ventricular function and ECG)
Clinical parameters (body weight, blood pressure, heart rate, ECOG status, symptoms, concomitant diseases, and treatment)
Eligibility criteria
RAI-R DTC[a]
Progressive, locally advanced, or metastatic, poorly differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma according to RECIST version 1.1 criteria
Symptoms
High tumor burden evaluated by imaging (CT and/or ^{18}F-FDG PET/CT)
High risk of progression (e.g. for histotype or site of neoplastic lesion)
Relative contraindications to be considered on a case-by-case basis
Severe cardiac, renal, and hepatic comorbidities
Fistula and organ perforation
Hypertension should be controlled prior to treatment
Tracheal and/or esophageal invasion
High risk of hemorrhage
Brain metastases
ECOG PS $\geq$ 2
Relevance of symptoms
Treatment should ideally be started before the patient becomes symptomatic
24 mg/day should be used whenever possible
A lower starting dose may be warranted in selected patients (e.g. frail)
Presence of symptoms requires careful choice of starting dose

[a]Patients with locally advanced disease might be considered for systemic therapy in case of unresectable tumor, regardless of RAI-avidity status.

A full dose of lenvatinib at 24 mg/day has been shown to be associated with an improvement in the overall response rate compared to 18 mg/day (25). The dosage of 24 mg/day can lead to more substantial tumor reduction and may help to obtain a rapid tumor shrinkage, which is often clinically relevant, for example, to avoid infiltration of vital structures by the tumor.

On the other hand, the presence of specific symptoms and site(s) of tumor mandate caution in choosing the starting dose, and the type of symptoms might influence the decision; lower starting doses (14 mg) might be considered especially for frail patients, based on their individual profiles and symptoms.

Multidisciplinary evaluation

The experts agreed that whenever possible all patients should be discussed in a multidisciplinary tumor board prior to initiating any systemic therapy, including lenvatinib (11). Even though RAI-R DTC represents a rare tumor entity, referral of these tumors to dedicated centers has been recommended to ensure patient access to expertise, to multidisciplinary approaches and to innovation (26, 27). The board should ideally include a medical oncologist, endocrinologist, radiologist, pathologist, surgeon, radiation oncologist, nuclear medicine specialist, and other specialists as needed (e.g. orthopedic surgeon, psychologist, palliative care, etc.). According to the experts, it is not necessary to systematically re-discuss the patient's evolution during treatment in the tumor board, except when complications have occurred and/or treatment modification appears necessary.

Role of patient information and education

The experts noted that side effects are the strongest predictors for non-adherence to therapy with an MKI, and thus it is important to prevent AEs in order to optimize adherence to a potentially lifelong treatment. It was noted that specific tools to improve potential adherence prior to therapy are of definite benefit.

Before initiation, educational materials such as brochures and instructional cards were considered to be very helpful for patients. These materials should clearly explain not only the benefits of treatment but what AEs may occur and how they can be managed. Such materials may often be available from patient associations and clinicians, and these latter should make sure that the patient has understood their content. Indeed, the role of patients in reading, understanding, and approving the information materials is fundamental in the process of patient empowerment; involvement of patient associations in the creation and evaluation of any new information material is strongly recommended. The experts also suggested to use a daily diary where the patient can register the occurrence and severity of any side effects as well as any missed doses. Lastly, specialist nurses can play a critical role in the patient journey by helping to ensure that patients are aware of the benefits and possible side effects, as well as by assisting and/or guiding patients regarding practical and social issues. Patients must be given a contact telephone to use should they have concerns or worries (28).

Quality of life (QoL) must also be considered; currently, there are limited data on QoL patients with RAI-R TC.

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Interestingly, health-related QoL (HRQoL) seems to be not influenced by the starting dose of lenvatinib (18 mg vs 24 mg), contrary to common opinion. In addition, time to treatment deterioration (defined as the time between randomization and the first detrimental change in HRQoL score relative to baseline during the treatment period) has been influenced by the objective radiological response, being longer in those subjects with a tumor shrinkage compared to those without volume reduction (29). The group discussed the use of QoL measurements with specific tools (e.g. EORTC QLQ-THY34) on a regular basis, at baseline and during treatment (30).

Initiation of therapy: what is crucial for the patient to know? How will the patient be informed and educated?

Patient education

As mentioned earlier, when starting therapy with lenvatinib, it is important that the patient understands the nature of the disease, its progression, and the need to start systemic therapy with an MKI. The patient should be reminded that lenvatinib will hopefully aid in reducing tumor burden and/or stabilize the disease, with the aim of achieving prolonged PFS. Concerns about safety, tolerance, and the strategy used to prevent and manage AEs must be discussed in advance with the patient.

Initiation of therapy: how to choose an effective and safe starting dose?

Starting dose

As a standard of care, the recommended starting dose of lenvatinib is 24 mg/day, which can maximize the chances of a rapid response to therapy and should be used whenever clinically feasible (31) (Table 2). In the opinion of the panel, based on their clinical experience and as recommended by others, the starting dose of lenvatinib could be lowered to 14 mg/day, even if not evidence-based: (i) in patients with a high risk of fistula (tumor related or not); (ii) in those with a high risk of bleeding; and (iii) in patients with poor ECOG performance status (ECOG > 2), depending on the physician's clinical judgment (31). It was noted that the dosage is often widely variable in routine practice among centers, including doses lower than 14 mg/day. The experts mentioned that they do not use a planned individualized dose management plan; rather, the dose is adapted based on response and tolerance. Planned drug holidays seemed to be feasible and associated with a better outcome in 73 RAI-R DTC patients out of 262 RAI-R DTC, managed with planned drug holidays (32). However, this strategy should not be recommended in this setting in the lack of prospective data, since clinical evidence suggests that the dose affects treatment effectiveness (31, 33).

Follow-up

During therapy: how to schedule follow-up?

Frequency of follow-up

It was completely agreed that the first year of treatment with lenvatinib is the most critical period. It was proposed that follow-up visits should be scheduled every 2 weeks for the first month, mainly in order to check for drug toxicity, and then monthly for the first year of therapy (Table 3). After 12 months on the drug, many of the experts stated that follow-up visits should take place every 2 months. Patients should always be given the opportunity to contact medical staff. Some experts noted that the frequency of follow-up could be discussed with the patient on an individual basis, particularly relevant for patients living far away from the clinic, in addition to difficulties with clinical visits during the current coronavirus disease 2019 pandemic. During therapy, it is recommended to discuss the case with a multidisciplinary board if complications or new events occur and/or if a change in therapy appears indicated.

During therapy: how to monitor outcomes and adherence?

Monitoring

Regarding monitoring needed during follow-up, the experts recommended that blood pressure should be monitored daily for the first 2 months, and thereafter at least once a month. Laboratory parameters (blood chemistry, TSH, free thyroxine, and calcium), and urinalysis can be performed monthly for the first year, after which the time interval

Table 2 Starting doses recommended for patients initiating lenvatinib.

Dose of lenvatinib	Patient group
24 mg/day	Standard of care dose to be used in all patients whenever feasible
18–10 mg/day	To be considered for frail patients with ECOG ≥ 2, and patients with a high risk of fistula/bleeding

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can be increased (Table 3). Cortisol levels and ACTH do not need to be measured routinely, but only in case of severe/unexplained/unexpected fatigue. In ambiguous cases, an ACTH stimulation test can be performed (34). It is mandatory to monitor cardiac function by ECG with a frequency that is decided upon based on the patient's medical history, given the risk of cardiac AEs in the long term (35). Echocardiogram should be done at baseline and once a year during treatment, since the decline in left ventricular ejection fraction has been reported in 10% of patients during antiangiogenic treatment (36).

Morphological imaging (CT scan) is the gold standard for monitoring response and should be repeated every 3–4 months, but most experts carry out ^{18}F-fluorodeoxyglucose (FDG) PET/CT during follow-up, especially in case of suspicion of disease progression. To properly evaluate response, all experts agreed on the fact that for follow-up imaging the same image technique used at baseline should be carried out.

Biomarkers

Biomarkers must be checked at baseline, before starting any systemic therapy, which also helps to predict the outcome. Thyroglobulin (Tg) was considered to be a key indicator for clinical outcomes. Tg can be used as a marker for progression, and when a constant increase is observed and the CT scan does not show tumor progression, ^{18}F-FDG PET/CT should be performed and brain MRI should be considered. Measurement of both Tg and antibodies should be tested as standard protocol to optimize the management of patients and assessed every 4–6 months (Table 3).

Adherence

As mentioned, at the beginning of therapy, a good relationship must be established between medical staff and the patient to ensure adherence to treatment. According to the tools described in the patient education paragraph, the patient should be asked to record any intentional or unintentional changes in therapy (i.e. reporting if the drug is sometimes skipped, side effects, etc.) in a diary. The patient should also be advised to regularly monitor blood pressure and to report any changes in body weight and intake of food and fluid. As mentioned earlier, patients should also be counseled that a 'weekend-off' strategy is not routinely recommended.

Response to therapy

In evaluation of response to therapy, Tg levels should be monitored to detect variations during follow-up as mentioned earlier. To assess the response, RECIST version 1.1 criteria (16) should be applied. With this intent, strict collaboration with radiologist should be planned.

Management of AEs: how to manage AEs? How to manage therapy discontinuation?

Adverse events

In the phase III SELECT trial, the most common AEs (any grade) considered to be related to treatment were hypertension (68%), diarrhea (59%), fatigue (59%), and decreased appetite (50% of patients) (17). Management of adverse reactions may require temporary interruption, dose adjustment, or permanent discontinuation of lenvatinib therapy. Mild to moderate adverse reactions (e.g. grade 1 or 2) generally do not warrant interruption of lenvatinib, unless intolerable to the patient despite optimal management. Severe (e.g. grade 3 or higher than grade 3) or intolerable adverse reactions require interruption of lenvatinib until improvement to grade 0 to 1 or baseline (37, 38). As previously mentioned, blood pressure should be well controlled prior to initiating lenvatinib. Moreover, longer treatment with lenvatinib is also associated with an increased risk of hypertension (39). Hypertensive AEs should involve consultation with a cardiologist. In treating hypertension, angiotensin-

Table 3 Follow-up schedule suggested.

Exam/test	Suggested frequency
Clinical exam	Every 2 weeks for the first month, monthly for the first 12 months; every 2 months could be considered after the first year
Blood chemistry, TSH, free T4, calcium, urine analysis	
Tg, anti-Tg antibodies	4–6 months
ECG/echocardiogram	At baseline and once a year or based on the individual medical history
Imaging	Morphological Imaging (CT scan) every 4 months
	^{18}F-FDG -PET/CT optional, recommended in case of suspicion of clinical and biochemical progression. If used to monitor disease response, also perform ^{18}F-FDG PET/CT at baseline

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Table 4 Management of adverse events with lenvatinib.

Adverse event	Severity and action	Management
Hypertension	Grade 3 → interrupt Grade 4 → discontinuation	ACE inhibitors preferred, multiple antihypertensive drugs if necessary
Diarrhea	Grade 3 → interrupt Grade 4 → discontinuation	Antidiarrheal drugs with loperamide 2 mg after the first discharge up to a maximum of 16 mg/day, increase fluid intake, and nutrition counseling (e.g. avoid high-fiber foods)
Nausea/vomiting	Grade 3 → interrupt Grade 4 → discontinuation	Metoclopramide 10 mg/8 h; ondansetron (attention to QTc prolongation); neurokinin-1 receptor antagonist if necessary; hospitalization and parenteral nutrition in severe case
Weight loss	Grade 3 → interrupt Grade 4 → discontinuation	Dietary counseling and physical exercise to maintain muscular mass
Proteinuria	>2 g/24 h →interrupt until <2 g/24 hours	ACE inhibitors or angiotensin II receptor blockers; consult nephrologist
Dermatological	Grade 3 → interrupt Grade 4 → discontinuation	Topical treatments; moisturizing creams, creams with urea; corticosteroids
Fatigue	Grade 3 → interrupt Grade 4 → discontinuation	Medications, physical exercise, and dietary counseling; specific therapy in case of adrenal failure

Data from (41).

converting enzyme (ACE) inhibitors are preferred, based on preliminary data suggesting that inhibition of ACE prevents adverse hemodynamic effects and left ventricular remodeling (40).

Diarrhea is a common AE and can be adequately controlled with antidiarrheal drugs and nutritional counseling in most cases. Nausea/vomiting can be managed with specific anti-nausea/vomiting agents, as well as with nutritional counseling (37, 38). In patients with weight loss, dietary counseling with a nutritionist and physical exercise to prevent loss of muscle mass even prior to treatment initiation should be recommended and individualized to the patient's characteristics. Renal AEs should be closely monitored by following estimated glomerular filtration rate and proteinuria, and nephrologist should be consulted if there is a deterioration in either. It is essential that renal function be assessed at baseline in order to have a reference value. Lastly, dermatological AEs can usually be managed with moisturizing creams, creams with urea, and corticoids, if necessary, as previously noted (37).

Fatigue of any grade is also one of the AEs associated with lenvatinib that can limit its clinical application. Unfortunately, fatigue is difficult to manage because, unlike other common side effects, there are no effective treatments. It is mandatory to investigate and rule out any causes of fatigue distinct from lenvatinib, such as hypothyroidism, anemia, psychological distress (e.g. anxiety and depression), sleep disturbance, or adrenal failure (34). In some patients, fatigue may improve with medications, physical exercise, or nutritional support (37, 38). In case of serious and persistent fatigue, dosage of ACTH is recommended (34).

Supplementation with nutrients, often lost due to malnutrition related to the tumor, is necessary; a nutritionist can be valuable in managing the patient's diet. Table 4 summarizes the actions to be taken in the case of AEs.

Discontinuation of therapy and rechallenge

Major organ failure, fistula, active bleeding, and acute cardiovascular events (e.g. thromboembolic events) are AEs that require discontinuation of therapy (temporary or definitive). The clinician should also consider the possibility that the patient may refuse to continue treatment given its impact on QoL. In case of therapy discontinuation for disease progression, resumption of lenvatinib can be considered based on the type of progression (i.e. local progression vs multi-organ progression) and parallel treatment options for the progressing lesions (e.g. surgery, EBRT, thermoablation etc.). Depending on the tumor's molecular profile and the regulatory setting in each country, the clinician can consider prescribing a second-line treatment, including cabozantinib or new tailored agents (e.g. BRAF, RET, or NTRK inhibitors, etc.).

Conclusions and perspectives

It is essential to provide guidance for the management of RAI-R DTC patients with systemic therapies, and especially lenvatinib, since compliance and adherence to treatment are fundamental in order to achieve the best possible outcomes (Fig. 1). The present publication provides expert multidisciplinary perspectives that can serve as a practical

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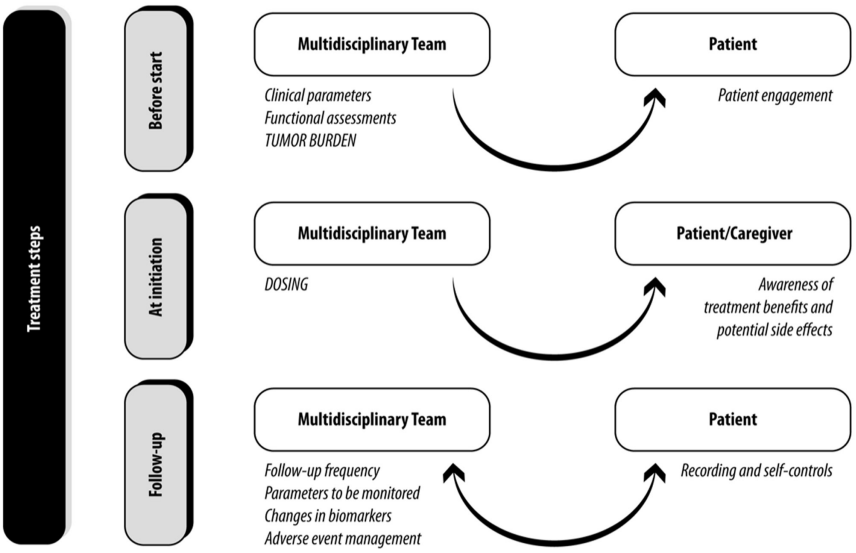

Figure 1
Actions to be taken before, at the beginning, and during therapy with lenvatinib, in RAI-R-DTC patients.

guide for the daily management of patients with DTC treated with lenvatinib. Even though the therapeutic landscape in RAI-R DTC is evolving, with new targeted therapies, immunotherapy, etc., lenvatinib is expected to remain a first-line treatment and mainstay of therapy for several years in the vast majority of patients and countries. The guidance herein covers a wide range of areas, from initiating systemic therapy and baseline work-up, relevance of symptoms, multidisciplinary assessment, and role of patient education. Practical information based on expert experience is also given for the starting dose of lenvatinib, follow-up, and monitoring, as well as management of AEs and discontinuation and restart of therapy. The experts stress the importance of patient engagement in the pathway for RAI-R DTC.

Supplementary materials
This is linked to the online version of the paper at https://doi.org/10.1530/ETJ-23-0068.

Declaration of interest
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