Nephrotoxicity in advanced thyroid cancer treated with tyrosine kinase inhibitors: An update

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Highlights

- Tyrosine kinase inhibitors (TKIs) are employed in advanced thyroid cancer patients
- Renal adverse events (RAEs), especially proteinuria, are frequently reported
- VEGF pathway inhibition seems to be involved in the development of RAEs
- TKIs-treated patients should be monitored with serum creatinine and urine dipstick
- In case of RAEs from TKIs a multidisciplinary approach is recommended

ABSTRACT
Over the past decade, the prognosis of advanced thyroid cancer (TC) patients has dramatically improved thanks to the introduction of tyrosine kinase inhibitors (TKIs). Despite their effectiveness, these drugs are burdened with several side effects that can negatively affect quality of life and compromise therapy continuation. Among renal adverse events (RAEs), proteinuria is the most frequently reported in clinical trials and real-life experiences, especially during treatment with lenvatinib or cabozantinib. This peculiar toxicity is commonly associated with targeted therapies with anti-angiogenic activity, even if the mechanisms underlying its onset and progression are not entirely clear. RAEs should be early recognized and properly managed to avoid renal function worsening and life-threatening consequences. Aiming at providing a comprehensive summary that can help clinicians to identify and manage TKIs-related RAEs in TC patients, we reviewed the current evidence about this topic, from pathogenesis and potential risk factors to diagnosis and treatment.

KEY-WORDS: thyroid carcinoma, targeted therapy, adverse event, proteinuria, renal injury

Introduction

In recent years, the increasing knowledge of the molecular pathways implicated in tumorigenesis has led to several anticancer targeted therapies. Tyrosine kinase inhibitors (TKIs) have been successfully employed for the treatment of progressive metastatic thyroid cancer (TC) in phase II and III clinical trials [1-4]. The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved vandetanib and cabozantinib for the treatment of medullary thyroid cancer (MTC), while sorafenib, lenvatinib and cabozantinib were approved for the management of radioiodine-refractory (RAI-R) differentiated thyroid cancer (DTC). More recently, a second generation of TKIs targeting specific altered oncogenes has been introduced and approved by FDA and EMA also in TC setting, two

selective tropomyosin receptor kinase (TRK) inhibitors (larotrectinib and entrectinib) and two selective rearranged during transfection (RET) inhibitors (selpercatinib and pralsetinib) [5].

One of the main target molecules of the first generation of TKIs employed for the management of TC (TC-TKIs) is the vascular endothelial growth factor receptor (VEGF-R) [6]. The VEGF pathway inhibition confers a strong anticancer efficacy to these agents, but it also seems to contribute to their multiple toxic profile [7].

Among the renal adverse events (RAEs) during TC-TKIs, proteinuria is the most frequently reported in clinical trial and real-life experience [8]. This toxicity is also associated with other targeted therapies with anti-angiogenic activity, thus suggesting a drug class effect [9].

Conversely, no remarkable nephrotoxicity with RET inhibitors and TRK inhibitors has been reported so far.

Proteinuria, in particular albuminuria, is an early and sensitive marker of glomerular disease and kidney damage. Furthermore, it is a critical prognostic factor for a further decline in renal function and progression to end-stage kidney disease, as well as an independent and significant risk factor for cardiovascular disease and all-cause mortality [8]. Whether proteinuria might represent an on-target side effect is still unknown, since results about targeted agents used in various neoplasms are conflicting [9].

Some reviews about anti-VEGF kidney toxicity are available in the literature; however, none is focused explicitly on the renal effects of TC-TKIs. Aiming at providing a comprehensive summary that can help clinicians identify and manage TC-TKIs-related RAEs, we reviewed the current evidence about this topic, from pathogenesis to diagnosis and treatment.

Pathophysiology

The mechanisms underlying proteinuria induced by TC-TKIs are not still thoroughly understood.

During anti-angiogenic therapies, proteinuria commonly occurs with hypertension. It has been hypothesized that VEGF pathway inhibition leads to a decreased vascular production of nitric oxide (NO), which causes systemic and intraglomerular hypertension leading to proteinuria [10]. After cessation of an anti-VEGF drug, a consensual decrease of blood pressure (BP) and proteinuria is usually observed [11]. However, it is not clear if a causal relationship exists or if both AEs are independently caused by VEGF blockade. Renal alterations can also occur in the absence of increased BP in anti-VEGF-treated patients. Furthermore, in murine models, glomerular injury has been detected even before the onset of hypertension [10, 12]. Hence, additional mechanisms are likely to be involved in the pathogenesis of proteinuria.

The glomerular filtration barrier is composed by fenestrated endothelium, structurally supported by the glomerular basement membrane, and podocytes, with their slit diaphragm. Podocytes secrete VEGF and VEGF-Rs are expressed on podocytes and glomerular capillary endothelial cells. This interplay is critical in maintaining the integrity of the filtration barrier: VEGF exerts a paracrine effect on endothelial structures helping to maintain fenestrations, together with an autocrine regulation of the podocyte cytoskeleton and slit membrane [10, 13].

Pharmacological inhibition of the VEGF axis can cause a perturbation of endothelial-podocyte signaling and lead to kidney damage (**Figure 1**) [9]. Treatment with anti-VEGF TKIs induces the podocyte cytoplasmatic retention of RelA, a subunit of the transcription factor NF-κB, and overexpression of C-Maf-inducing protein (c-mip), causing cytoskeleton alteration and apoptosis [14, 15]. During treatment with these agents, a podocyte injury might also be mediated by the inhibition of tyrosine phosphorylation of nephrin. This slit-diaphragm protein junction is essential to maintain the filtration barrier's integrity and selective glomerular permeability [11, 16]. According with these data, in the majority of patients on TKIs targeting the VEGF-R tyrosine kinase domain, renal biopsy specimens exhibited podocytopathies, including minimal change disease (MCD) and collapsing focal segmental glomerulosclerosis (FSGS) [14]. FSGS was identified in both MTC and DTC patients during TC-TKIs [10, 15].

Despite pathognomonic features of thrombotic microangiopathy (TMA) are more frequently observed during VEGF direct ligand therapy (e.g., bevacizumab) [15], TMA has also been described during treatment with VEGF-R inhibitors, including lenvatinib [13], cabozantinib [8, 17] and sorafenib [18]. TMA is under-diagnosed in anti-VEGF treated patients since renal biopsy is rarely performed. Additionally, the histological findings are not usually related to the degree of proteinuria and are not accompanied by severe hypertension, renal failure, hemolytic anemia, or thrombocytopenia [19].

Beyond the crucial role of the inhibition of VEGF signaling in inducing renal damage in patients on TC-TKIs, it has been claimed that the blockade of other pathways might also mediate the worsening of renal injury, such as fibroblast

growth factor (FGF) axis, which is implicated in podocyte differentiation and recovery after injury [20, 21]. Recently, the demonstration that TRKC is expressed in podocytes and is directly involved in actin cytoskeleton stability and glomerular integrity [22] paved the way to a possible direct TKI-mediated effect in proteinuria development. However, data are controversial and additional research is needed to draw definite conclusions, especially in the human setting.
In TC-TKIs-treated patients, renal failure has anecdotally been reported, even in absence of proteinuria. In this case, direct tubule-interstitial damage without glomerular involvement has been hypothesized, although the specific molecular mechanisms are still unknown [21]. TKIs may also impair tubular function, causing hypocalcemia [23] and hypophosphatemia through a direct effect on proximal tubular cells receptors [24].
Tubular damage was also reported during treatment with other small molecules inhibitors employed in TC patients. Vemurafenib and dabrafenib are inhibitors of advanced v-Raf murine sarcoma viral oncogene homolog B (BRAF), a serine/threonine-kinase part of the mitogen-activated protein kinase (MAPK) pathway. The renal toxicities commonly noted with BRAF inhibitors included an allergic interstitial nephritis or acute tubular toxicity in the early phase of treatment. In some cases, Fanconi's syndrome, isolated electrolyte disorders (hypophosphatemia, hyponatremia, hypokalemia) and subnephrotic-range proteinuria have also been reported [25]. Analysis of kidney biopsies revealed tubular injury as the major histopathologic lesion. In a murine model, vemurafenib showed that the off-target inhibition of ferrochelatase, an enzyme involved in heme biosynthesis, significantly contributes to kidney tubular epithelial cell dysfunction. However, the mechanisms underlying the nephrotoxicity of BRAF inhibitors remain mostly unclear [26].

Risk factors

So far, no focused evaluation has been performed to identify the patients at higher risk of developing RAEs during treatment with TC-TKIs. Still, some data are available for other anti-angiogenic therapies.
Age could be considered a risk factor, with an increased risk detected among elderly patients [9].
Diabetes was independently associated with a higher incidence of severe proteinuria and, similarly, a direct correlation between baseline high systolic BP and proteinuria onset has been observed [27].
A higher frequency of proteinuria during TKI was recently found in TC patients previously exposed to other nephrotoxic drugs [8].
Several data suggested that a pre-existing grade (G)1 proteinuria correlates to a higher risk of any G and G ≥3 proteinuria while conflicting and more puzzling results have been reported about the relationship between baseline estimated glomerular filtration rate (eGFR) and proteinuria on-therapy [27, 28].
The use of zoledronate has been associated with both dose-dependent and infusion time-dependent acute and chronic renal failure [6]. In anti-VEGF treated patients, there is no sufficient evidence to indicate that baseline use of bisphosphonates significantly alters the risk of proteinuria. However, a study reported that the use of pamidronate was associated with an increased risk of proteinuria during treatment with bevacizumab [27, 29].
Iodine-containing contrast media are frequently employed in patients treated with TC-TKIs, mainly on the occasion of the computed tomography (CT) tumor assessments. These agents may induce kidney dysfunction due to several factors, including the formation of reactive oxygen species (ROS), reduction of NO production, endothelial injury and renal ischemia [30]. However, recent observational studies have questioned the prevalence and severity of contrast-induced nephropathy (CIN) and the following risk classification was recommended: patients with eGFR ≥ 45 mL/min/1.73 m^2 are at negligible risk for CIN, those with eGFR < 30 mL/min/1.73 m^2 are at high risk, while patients with eGFR between 30 and 44 mL/min/1.73 m^2 have an intermediate risk, unless DM is present [31].
It has been reported a case of a lenvatinib-treated patient who underwent three coronarographic procedures and showed a steady increase in serum creatinine. In this case, the cumulative nephrotoxic effect of the concomitant application of imeron and ultravist together with lenvatinib could not be excluded [6]. However, there is no clear evidence to support the need for additional preparation or TKI interruption prior to the contrast administration to prevent RAEs in TC-TKIs-treated patients with normal eGFR.

Evidence from clinical trials

RAEs have often been reported in clinical trials of anti-VEGF TKIs. **Table 1** summarizes data about nephrotoxicity of TKIs with anti-VEGF activity registered in phase II and III trials involving TC patients [1-4, 32-43].

According to a recent meta-analysis regarding the newly approved anti-VEGF TKIs, lenvatinib is one of the most frequently associated with any-G and high-G proteinuria [9]. In the phase III trial SELECT, proteinuria of any grade was one of the most common AEs among lenvatinib-treated patients, reported in 31% of cases versus 1.5% of patients in the placebo group. It was the second most common G ≥3 AE (10% of lenvatinib-treated patients) and it was the third most frequent cause of dose interruption or reduction (18.8% of cases) [4]. Like other AEs, it generally occurred in the early phase of treatment: the median time of onset was 6.1 weeks. Drug interruption and dosage tapering were often appropriate to resolve proteinuria, with a median time to resolution of 8.8 weeks; permanent drug discontinuation was necessary only in 1% of patients [44]. Some subgroup-analysis of the SELECT population showed a higher incidence of proteinuria (any-G 63.3%; G ≥3 20%) in Japanese patients [45] and a more common G ≥3 proteinuria in older patients (>65 years) versus the younger ones (13.2 vs. 7.7%) [46].
Preliminary data from a phase II trial investigating the safety and the efficacy of different starting doses of lenvatinib (24 versus 18 mg/day) showed a similar incidence of G ≥3 proteinuria in the two groups, while any-G proteinuria resulted slightly higher in the 24 mg/day arm (44 vs. 31.2%) [47].
Less frequent RAEs reported in the SELECT trial were renal failure (4.2% of lenvatinib-treated patients) and renal tubular necrosis (one patient, 0.4%). No association between the development of RAEs and progression-free survival (PFS) or overall survival (OS) has been demonstrated so far [44].
Lenvatinib was also evaluated for the treatment of advanced MTC and anaplastic thyroid cancer (ATC): again, in these settings, proteinuria was reported among the most common AEs [35, 36].
Besides TC, lenvatinib is FDA-approved also as a first-line treatment for patients with unresectable hepatocellular carcinoma (HCC) and, in combination with everolimus, with advanced renal cell carcinoma (RCC) following prior anti-angiogenic therapy. In the REFLECT study regarding unresectable HCC, rates of any-G and G ≥3 proteinuria in lenvatinib-treated patients were 25% and 6%, respectively [48]. In patients with advanced RCC, proteinuria was found in 31% of patients treated with lenvatinib alone; it was the most common G ≥3 AE (19%). Among serious RAEs, acute renal failure and haematuria were also reported in 8% and 2% of patients, respectively [49].
Regarding sorafenib, no RAEs were reported in the DECISION study in patients with RAI-R DTC [3]. Similarly, drug-related nephrotoxicity was not registered in the phase II trial evaluating sorafenib in an advanced MTC setting [40]. Among patients with unresectable HCC in the REFLECT study, sorafenib-treated cases experienced any-G and G3 proteinuria in 11% and 2% of cases, respectively [48]. These rates were inferior to those observed in the lenvatinib-treated group of the same study and similar to safety data of another phase III trial regarding sorafenib in RCC patients [50].
In the phase III trial ZETA, 10% of MTC patients treated with vandetanib developed proteinuria (G 1-2 in all cases) [1]. At the same time, no RAEs were reported in the phase II trial of vandetanib in DTC [43].
Among patients with MTC in the phase III study EXAM, the patients treated with cabozantinib showed a very low proteinuria rate (1.9%) [2]. However, a subgroup of MTC patients enrolled in the EXAM trial in an Italian center showed a high incidence of proteinuria (22.2% of treated patients) during long-term treatment, after a mean time of 38 months. Proteinuria was significantly related to previous exposure to other potentially nephrotoxic drugs (TKIs or traditional chemotherapy), suggesting that a pre-existing drug-induced renal damage could represent a predisposing factor. In this cohort, a positive correlation between the onset of proteinuria and a better drug response was observed. However, the relationship between this AE and response to therapy is difficult to establish, due to a possible selection bias discussed by the authors: well-responder patients have long-term exposure to the drug and, thus, a higher probability of developing proteinuria [8].
Outside the context of MTC, proteinuria incidence during cabozantinib was high (32%) in a phase II trial including DTC patients [33], but the rate of patients with nephrotoxicity was lower according to a more recent phase III trial [34] . The reported proteinuria rates were variable in other clinical trials regarding HCC or RCC patients (range 0-11%) [51, 52].
The higher rate of renal damage and proteinuria reported for lenvatinib and cabozantinib when compared to vandetanib and sorafenib could be partly explained by their different anti-VEGFR activity [8].

Data from the real-life setting

To our knowledge, no prospective study regarding FDA-approved TC-TKIs with a focused evaluation on RAEs has been conducted in a real-life setting.

The only retrospective analysis specifically addressing RAEs during TKI treatment for advanced DTC was conducted in a single center in Japan; 73 patients with normal renal function before TKI therapy were divided into two groups, on the basis of lenvatinib or sorafenib treatment. The incidence of proteinuria was higher in the lenvatinib group (60.8 vs 27.8%), and a slight reduction in eGFR and serum albumin was noted only in patients on lenvatinib; more than 20% of patients in the lenvatinib group underwent dose reduction or drug withdrawal for RAEs [53].

In the last years, various real-life retrospective studies regarding the efficacy and safety of lenvatinib treatment for RAI-R TC have been published, with heterogeneous findings regarding proteinuria [54-68] (**Figure 2**). The higher percentages were found in Japanese real-life studies (78.6% reported by *Masaki et al* [63]; 61.5% observed by *Suzuki et al* [60]), suggesting a different ethnic susceptibility to develop proteinuria [69]. A similar heterogeneity in the incidence of proteinuria during this TKI has also been reported in other malignancies: although in a small cohort, almost 80% of the patients with ATC showed some degree of this AE [70], while the incidence was relatively low in HCC [71]. Lenvatinib-induced renal failure was rarely reported and seldom severe [57, 66].

In most real-life cohorts, no RAEs were reported during sorafenib [72-74]. Conversely, some reports of proteinuria [53, 67, 75, 76] and renal failure [67, 77] can be found in the literature.

Few real-life data have also been gathered for vandetanib. In a retrospective French cohort, the use of vandetanib was associated with both proteinuria and renal impairment, especially in the case of long-term treatment (>4 years) [78]. These findings have not been confirmed by another recent multicentre experience [79].

RAEs were not described during treatment with cabozantinib in TC patients not enrolled in clinical trials, apart from single case reports [6]. Many studies focusing on cabozantinib's real-world efficacy in RCC are available and reports of RAEs seem relatively uncommon [80, 81].

Diagnosis

The best overall index of kidney function is generally considered the eGFR. A level <60 ml/min/1.73 m^2 for at least three months defines a chronic kidney disease (CKD); eGFR is mildly to moderately decreased (45-59 ml/min/1.73 m^2) in G3a stage, moderately to severely decreased (30-44 ml/min/1.73 m^2) in G3b stage; severely decreased (15-29 ml/min/1.73 m^2) in G4 stage; <15 ml/min/1.73 m^2 in G5 stage. CKD could also be present in patients with conserved eGFR; other kidney damage markers include albuminuria, abnormalities detected by imaging or histology, urine sediment alterations, or electrolyte disorders derived from tubular diseases [82].

The recommended method for the initial assessment of eGFR is the dosage of serum creatinine and a GFR estimating equation. The Modification of Diet in Renal Disease (MDRD) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations are based on standardized creatinine assay and, therefore, should be used for estimating GFR. The Cockcroft and Gault formula was developed before the standardization of creatinine assays but cannot be re-expressed for use with standardized creatinine assays [82].

Proteinuria is a term that, generally speaking, includes albuminuria, increased urinary excretion of other specific proteins, and increased excretion of total urine protein. Higher proteinuria degrees are associated with a more rapid progression to kidney failure, without any clear threshold value. However, nephrotic range proteinuria confers unique additional risks. Albuminuria and proteinuria categories are summarized in **Table 2**.

Urine protein excretion is increased by physiological variables, such as upright posture, strenuous physical activity, pregnancy, menstruation, urinary tract infection, and fever.

The methods for detecting urinary proteins and urine specimen collection timing are essential issues [82]. Semiquantitative proteinuria measurement, such as the standard urine dipstick, may not detect moderately increased albuminuria (formerly called "microalbuminuria") unless the urine is highly concentrated. However, screening with urine dipsticks is deemed acceptable for detecting severely increased albuminuria (formerly called "macroalbuminuria") or proteinuria in cancer patients treated with TKIs. In any case, patients with a dipstick test positive for albuminuria/proteinuria (≥1+) should be confirmed by quantitative measurement, the 24-hour urine protein test.

Timed overnight collections or shorter timed daytime collections may reduce the inconvenience and difficulties of a 24-h collection but are associated with significant errors (under- or over-collections). An acceptable alternative for quantitative evaluation, as well as for correcting for hydration-induced variations in urinary concentration, is the measurement of the protein-to-creatinine ratio (PCR) or the albumin-to-creatinine ratio (ACR) in an untimed "spot"

urine specimen. Protein excretion varies throughout the day, and the ratio in mid-morning specimen has been suggested to correlate most closely with the 24-h protein excretion rate.

It should be considered that elderly and/or cachectic people (such as many of those treated for an advanced TC) display a reduced urinary creatinine excretion due to a fall in muscle mass. Consequently, the accuracy of the ratio can be significantly diminished, with PCR overestimating proteinuria. Given these limitations of ACR/PCR measurements, alternative calculations for estimated albumin/protein excretion rate have been developed [83].

Patients with persistent proteinuria on more than two quantitative laboratory measurements (adequately spaced 1-2 weeks apart) should undergo further evaluation.

In oncological clinical trials, RAEs during TKIs are generally defined according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) [84] (**Table 3**).

Figure 3 summarises the proper workup of TC-TKIs-related RAEs. Pre-existing renal dysfunction should be investigated by dipstick test and eGFR assessment in all cases [19, 20]. If the baseline dipstick urinalysis detects proteinuria, a quantitative measurement must be performed. In selected cases, the nephrologist consultation could help analysing the potential risks linked to the start of an anti-VEGF-therapy and achieving optimal pre-TKI management of the kidney disease [8].

During treatment with anti-VEGF agents, all patients should be regularly monitored using a urine sample dipstick [20]. Since proteinuria occurs in the early phase of treatment in most cases, it has been suggested to control the onset of this AE once a month for the first three months of therapy [85]. Afterward, checks can be performed less frequently, every 2–3 months, even if RAE's long-term monitoring is required [8].

If a dipstick proteinuria ≥1+ is detected, a 24-hour urine collection is required [86]. Spot urine PCR determination can be considered a valuable alternative: a statistically significant correlation between assessment by PCR and 24-hour urine protein was found in patients receiving lenvatinib for HCC in the REFLECT study. The optimal cut-off to discriminate G1 from G2 proteinuria by PCR resulted in 1.02 (mg/mg), while the optimal cut-off to distinguish G2 from G3 proteinuria was 2.43 (mg/mg) [87]. These thresholds remain to be validated also for other TKIs.

Referral to the nephrologist for further analysis (e.g., kidney ultrasound, evaluation of the urine sediment, renal biopsy) should be considered in G2 proteinuria and it is recommended in G ≥3 proteinuria [88]. Since there is no clear correlation between the degree of proteinuria and the severity of the renal injury, renal biopsy should be considered in subjects with progressive proteinuria, especially in simultaneous unexplained renal function decline. Patient's life expectancy should always be taken into account [19].

Changes in albuminuria/proteinuria provide important prognostic information and may reflect antiproteinuric agents' response; hence, quantitative measurements are strongly recommended for their monitoring.

Management

Regarding TC-TKIs-related RAEs management, no evidence-based guidelines or interventional studies are available.

The current approach is mainly based on standardized protocols employed in oncological clinical trials or follows indications provided by nephrologists in other settings.

In TC patients on TKIs, proteinuria is generally manageable and usually it does not progress to life-threatening consequences if appropriately monitored and treated.

Before the start of TKI therapy, a detailed record of the patient's clinical data and medical history is essential to detect specific risk factors for RAE, including the presence of uncontrolled hypertension and DM: optimization of BP levels and a good glycemic control are recommended before starting therapy [8].

According to the summary of product characteristics (SPC), in case of severe renal impairment the recommended starting dose of lenvatinib is 14 mg/daily (instead of 24 mg/daily) [89], due to the higher incidence of G3 and 4 toxicities in subjects with baseline renal injury compared to patients with normal renal function [90]. In contrast, no dose adjustment is suggested for patients with CKD starting sorafenib [91]. However, a reduced starting dose seems reasonable with the possibility of a dose escalation in relation to tolerance and clinical effectiveness [90]. Due to limited efficacy and safety data, vandetanib and cabozantinib are not recommended in case of severely impaired renal function. Cabozantinib should be used with caution in subjects with mild or moderate CKD, while a reduced starting dose of 200 mg/daily might be indicated for vandetanib in case of moderately impaired renal function [92, 93]. No data regarding the use of these agents in patients on hemodialysis are available **(Supplementary Table 1)**.

The new onset of hypertension or the worsening of BP control is a frequent TKI-related AE. Most patients with high BP levels on treatment are prone to develop proteinuria. In uncontrolled BP, antihypertensive medications should be prescribed, together with a low salt intake [19]. KDIGO guidelines recommend that BP targets consistently ≤130/80 mmHg should be maintained in adults with CKD and moderately increased albuminuria (AER >30 mg/24 hours) [82].

Among antihypertensive drugs, angiotensin-converting enzyme (ACE) inhibitors or angiotensin 2-receptor blockers (ARBs) represent the first choice since they lower intraglomerular pressure, diminishing protein excretion. In refractory patients, other antihypertensive molecules can be added (e.g., calcium channel blockers) [85]. There is insufficient evidence to recommend combining ACE inhibitors with ARBs to prevent CKD progression [82].

For their antiproteinuric and renoprotective effect, ACE inhibitors or ARBs can be employed in proteinuria regardless of blood pressure. The recommended dose in normotensive subjects remains unclear since no controlled trials are available in these patients [19].

In nephropathic adults, it is generally recommended to avoid high protein intake; in case of severe CKD, a low protein intake (<0.8 g/kg/day) is suggested [82]. Conversely, recent guidelines suggest a higher range of protein intake (1.2–1.5 g/kg/day) in patients with cancer, because of the potential positive effects of protein balancing and avoiding sarcopenia [94]. Frequently, oncologic patient's nutritional intake might be significantly reduced as a consequence of treatment-related AEs, such as anorexia, nausea, and vomiting, leading to weight loss and sarcopenia in most cases. Therefore, in case of TKIs-related RAEs, there is not enough evidence to support a protein intake restriction, favoring the loss of lean tissue and negatively affecting the patient's general well-being.

In most patients with DM, the ideal target for hemoglobin A1c (HbA1c) is ≤7.0% (≤53 mmol/mol), even if the optimal range must also be chosen taking into account patients' comorbidities and life expectancy [95]. In the last years, sodium-glucose co-trasporter-2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists have shown a consistent benefit in terms of the renal outcome of type 2 DM patients [96]. In the absence of studies exploring such agents' role in patients with DM and CKD on treatment with TKIs, no strong recommendation can be formulated. However, the introduction of one of these drugs in DM patients who experienced RAEs on anti-VEGF treatment, in the absence of contraindication, seems advisable.

Proteinuria generally improves when the TKI is interrupted, or its dosage is reduced, suggesting a dose-dependent relationship [85].

In the absence of edema or elevated serum creatinine, TKI may be continued when urinary protein levels are <2 g/24 h. Conversely, it is recommended to temporarily interrupt the treatment in case of confirmed proteinuria ≥2g/24 h, before further renal deterioration ensues [20, 88]. The drug can be resumed at a reduced dose in case of improvement (<2g/24 h), with subsequent quantitative monitoring of urine protein levels [19]. Treatment should be permanently discontinued in case of nephrotic syndrome [86].

Since TKIs dramatically improve the outcome of most advanced TC patients, the withdrawal of TKI treatment always needs to be discussed in a multidisciplinary team: the risk to continue the drug, that could definitively damage the kidney, and the risk to interrupt therapy, that might let the tumor to progress, should be carefully weighted in a case-by-case discussion [19].

Proteinuria can be considered a VEGF-class effect; hence, it could be argued that switching a patient to another anti-angiogenic TKI may not be of any benefit [88]. However, various incidences of proteinuria are reported for each anti-VEGF TKIs. For example, it has been suggested that sorafenib has no other detrimental effect on proteinuria or renal impairment induced by lenvatinib, so it may represent an effective treatment option for patients who cannot tolerate lenvatinib for RAEs [97, 98].

The selective TRK inhibitors showed remarkable results in solid cancers (including TC) harboring neurotrophic tyrosine kinase receptor (NTRK) gene fusions, while selective RET inhibitors demonstrated high efficacy in the setting of advanced RET-mutated MTC or RET fusion-positive RAI-R TC [5]. The high specificity of these new classes of drugs limits their off-targeted activities and the number of AEs, including renal events. Therefore, when a renal damage is developed using a multitargeted-TKI therapy, the use of mutation-specific kinase inhibitors targeting NTRK or RET might be considered in patients harbouring such mutations or gene fusions. Hence, the role of genomic sequencing appears crucial in the selection of the most appropriate anticancer therapy in these cases.

Although kidney failure on TKIs is less frequently described than proteinuria, progressive renal function deterioration has been reported, particularly in long-term treatment [53]. Moreover, TC patients on TKIs may experience gastro-intestinal AEs, such as diarrhea or anorexia, accompanied by an important reduction in the intake of fluids, leading to

dehydration and further reducing the eGFR [85]. Close monitoring of serum creatinine and eGFR is mandatory; in some cases, nutritional counseling about proper fluid intake can be helpful. In case of the progressive decline of renal function, TKI treatment withdrawn must be considered [8].

As mentioned above, also iodinated contrast media, needed for a proper imaging definition by CT, can worsen kidney function, causing CIN in some cases. Both reduced eGFR and proteinuria (>1 g/day) are risk factors for CIN [31, 99]. Therefore, it is reasonable to pay special attention to CIN development and prevent its harmful effects also in TC patients with TKI-related RAEs. Where clinically possible, the use of nephrotoxic drugs should be minimized. Volume supplementation is the cornerstone for CIN prevention: it suppresses the renin-angiotensin cascade, reduces renal vasoconstriction and hypoperfusion, and lowers the contrast medium's concentration within the tubule lumen. A low infusion rate (e.g., physiological saline solution 1 mL/kg per hour before and after contrast administration) is generally employed in clinical practice to reduce the risk of volume overload and pulmonary edema, especially in the case of heart disease. Sodium bicarbonate administration (e.g., 3 mL/kg per hour for 1 hour before the exam, followed by 1 mL/kg per hour for 6 hours after the procedure) can be employed to decrease the acidification of urine and increase the neutralization of ROS, considering their essential role in the development of CIN.

N-acetylcysteine administration's additional benefit has been investigated in high-risk patients, showing conflicting results [100, 101]. In any case, each center should define a standardized protocol after a multidisciplinary discussion.

Conclusions

Currently, due to the promising results obtained by phase II/III clinical trials and real-life studies, lenvatinib and sorafenib are commonly used for patients with advanced RAI-R DTC. Lenvatinib, in particular, is often used as a first-choice drug in this setting due to its better efficacy and higher tolerability compared to sorafenib, as well as to greater ease of prescription (at least in some countries). However, it has been associated with a high incidence of any-G and high-G proteinuria, that can be severe enough to compromise renal function and therapy continuation [9]. Among MTC patients, also cabozantinib determined proteinuria in a significant number of cases, especially during long-term treatment.

Many questions regarding TC-TKI-associated nephrotoxicity are still unanswered and many critical issues remain to be clarified.

First of all, the mechanisms underlying the onset and progression of proteinuria are not entirely clear. Hopefully, more in-depth studies will clarify if the VEGF pathway's inhibition is responsible for hypertension and increased intraglomerular pressure leading to proteinuria, or if glomerular injury (e.g., collapsing FSGS and TMA) and/or tubule-interstitial damage may happen regardless of VEGF-blockade.

Secondly, contradictory evidence exists about the possibility that the onset or worsening of proteinuria may represent a surrogate marker of a better antitumor response, similar to what has been hypothesized for other TKIs-associated AEs [102].

Moreover, it is still to be clarified if proteinuria is an independent and relevant risk factor for cardiovascular disease and overall mortality in this setting, similar to what is observed in people with DM and/or hypertension. SGLT2 inhibitors and GLP-1 receptor agonists have been demonstrated to prevent the worsening of albuminuria and reduce the decline of GFR in patients with DM, with effects supposed to be independent of the actions on glycemic control [96]. In particular, SGLT2 inhibitors have been shown to offer cardiovascular and renal protection without differences based on the presence of DM or baseline eGFR, potentially making them first-line therapy for CKD regardless of DM [103]. If this was the case, they could be effective also for the management of TKIs-induced proteinuria.

More evidence is required on the better screening test for starting (or continuing) TKI therapy. The need to interrupt TKIs as proteinuria worsens or temporarily suspend them before contrast-administration for CT assessments remains to be assessed.

Renal biopsy plays a crucial role in subsequent therapeutic decisions because proteinuria may imply the occurrence of various conditions (MCD, FSGS, and TMA) with different clinical and renal prognoses. Noteworthy, TMA may appear in a subclinical form without the classic presentation (severe hypertension, hemolytic anemia, thrombocytopenia) and could be underestimated.

In each patient, both the risk of progression of cancer in case of interruption of treatment and the risk of progression of renal damage in case of continuation of the same, must be carefully weighed. In this sense, some good results were obtained on both fronts after replacing the more nephrotoxic TKIs (lenvatinib, cabozantinib) with more neutral ones (sorafenib, vandetanib). Moreover, the use of mutation-specific kinase inhibitors targeting NTRK or RET might be considered in elegible patients.

Finally, a multidisciplinary approach, which necessarily involves the endocrinologist, the oncologist, the cardiologist, and the nephrologist, is strongly recommended for managing patients with advanced TC treated with TKIs.

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Conflict of interest
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References

[1] Wells SA, Robinson BG, Gagel RF, Dralle H, Fagin JA, Santoro M, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol 2012;30:134–41. https://doi.org/10.1200/JCO.2011.35.5040.

[2] Elisei R, Schlumberger MJ, Muller SP, Schoffski P, Brose MS, Shah MH, et al. Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol 2013;31:3639–46. https://doi.org/10.1200/JCO.2012.48.4659.

[3] Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet 2014;384(9940):319-28. https://doi.org/10.1016/S0140-6736(14)60421-9.

[4] Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med 2015;372(7):621-30. https://doi.org/10.1056/NEJMoa1406470.

[5] Lorusso L, Cappagli V, Valerio L, Giani C, Viola D, Puleo L, et al. Thyroid Cancers: From Surgery to Current and Future Systemic Therapies through Their Molecular Identities. Int J Mol Sci 2021; 18;22(6):3117. https://doi.org/10.3390/ijms22063117.

[6] Paschke L, Lincke T, Mühlberg KS, Jabs WJ, Lindner TH, Paschke R. Anti VEGF-TKI Treatment and New Renal Adverse Events Not Reported in Phase III Trials. Eur Thyroid J 2018; 7(6):308-12. https://doi.org/10.1159/000491387.

[7] Rosner MH, Jhaveri KD, McMahon BA, Perazzella MA. Onconephrology: The Intersections Between the Kidney and Cancer. CA Cancer J Clin 2021;71: 47-77. https://doi.org/10.3322/caac.21636.

[8] Cappagli V, Moriconi D, Bonadio AG, Giannese D, La Manna G, Egidi MF, et al. Proteinuria is a late-onset adverse event in patients treated with cabozantinib. J Endocrinol Invest 2021; 44:95-103. https://doi.org/10.1007/s40618-020-01272-y.

[9] Zhang W, Feng LJ, Teng F, Li YH, Zhang X, Ran YG. Incidence and risk of proteinuria associated with newly approved vascular endothelial growth factor receptor tyrosine kinase inhibitors in cancer patients: an up-to-date meta-analysis of randomized controlled trials. Expert Rev Clin Pharmacol 2020; 13(3):311-20. https://doi.org/10.1080/17512433.2020.1734450.

[10] Fleming K, McGuinness J, Kipgen D, Glen H, Spiliopoulou P. A Case of Lenvatinib-Induced Focal Segmental Glomerulosclerosis (FSGS) in Metastatic Medullary Thyroid Cancer. Case Rep Oncol Med 2018; 2018:6927639. https://doi.org/10.1155/2018/6927639.

[11] Izzedine H, Massard C, Spano JP, Goldwasser F, Khayat D, Soria JC. VEGF signalling inhibition-induced proteinuria: Mechanisms, significance and management. Eur J Cancer 2010; 46(2):439-48. https://doi.org/10.1016/j.ejca.2009.11.001.

[12] Eremina V, Jefferson JA, Kowalewska J, Hochster H, Haas M, Weisstuch J, et al. VEGF inhibition and renal thrombotic microangiopathy. N Engl J Med 2008; 358(11):1129-36. https://doi.org/10.1056/NEJMoa0707330.

[13] Hyogo Y, Kiyota N, Otsuki N, Goto S, Imamura Y, Chayahara N, et al. Thrombotic Microangiopathy with Severe Proteinuria Induced by Lenvatinib for Radioactive Iodine-Refractory Papillary Thyroid Carcinoma. Case Rep Oncol 2018; 11(3):735-41. https://doi.org/10.1159/000494080.

[14] Estrada CC, Maldonado A, Mallipattu SK. Therapeutic Inhibition of VEGF Signaling and Associated Nephrotoxicities. Review J Am Soc Nephrol 2019; 30(2):187-200. https://doi.org/10.1681/ASN.2018080853.

[15] Furuto Y, Hashimoto H, Namikawa A, Outi H, Takahashi H, Horiuti H, et al. Focal segmental glomerulosclerosis lesion associated with inhibition of tyrosine kinases by lenvatinib: a case report. Case Reports BMC Nephrol 2018; 19(1):273. https://doi.org/10.1186/s12882-018-1074-3.

[16] Stavniichuk A, Savchuk O, Khan AK, Jankiewicz WK, Imig JD. A sorafenib induced model of glomerular kidney disease. Visnyk Kyivskoho Natsionalnoho Universytetu Imeni Tarasa Shevchenka Biolohiia 2020; 81(2) 25-31. https://doi.org/10.17721/1728_2748.2020.81.25-31.

[17] La Manna G, Baraldi O, Corradetti V, Comai G. Cabozantinib-induced renal thrombotic microangiopathy. Nephrology (Carlton) 2018; 23(1):96-7. https://doi.org/10.1111/nep.13086.

[18] Usui J, Glezerman IG, Salvatore SP, Chandran CB, Flombaum CD, Seshan SV. Clinicopathological spectrum of kidney diseases in cancer patients treated with vascular endothelial growth factor inhibitors: a report of 5 cases and review of literature. Hum Pathol 2014; 45(9):1918-27. https://doi.org/10.1016/j.humpath.2014.05.015.

[19] Tesařová P, Tesar V. Proteinuria and hypertension in patients treated with inhibitors of the VEGF signalling pathway--incidence, mechanisms and management. Folia Biol Czech Repub 2013; 59(1):15–25.

[20] Takahashi S, Kiyota N, Tahara M. Optimal use of lenvatinib in the treatment of advanced thyroid cancer. Cancers Head Neck 2017; 2:7. https://doi.org/10.1186/s41199-017-0026-0.

[21] Cavalieri S, Cosmai L, Genderini A, Nebuloni M, Tosoni A, Favales F, et al. Lenvatinib-induced renal failure: two first-time case reports and review of literature. Review Expert Opin Drug Metab Toxicol 2018; 14(4):379-85. https://doi.org/10.1080/17425255.2018.1461839.

[22] Lepa C, Hoppe S, Stöber A, Skryabin BV, Sievers LK, Heitplatz B, et al. TrkC Is Essential for Nephron Function and Trans-Activates Igf1R Signaling. J Am Soc Nephrol 2021; 32(2):357-74. https://doi.org/10.1681/ASN.2020040424.

[23] Cataldi M, Gaudino A, Lariccia V, Russo M, Amoroso S, di Renzo G, et al. Imatinib-mesylate blocks recombinant T-type calcium channels expressed in human embryonic kidney-293 cells by a protein tyrosine kinase-independent mechanism. J Pharmacol Exp Ther 2004; 309(1):208-15. https://doi.org/10.1124/jpet.103.061184.

[24] François H, Daugas E, Bensman A, Ronco P. Unexpected efficacy of rituximab in multirelapsing minimal change nephrotic syndrome in the adult: first case report and pathophysiological considerations. Am J Kidney Dis 2007; 49(1):158-61. https://doi.org/10.1053/j.ajkd.2006.10.015.

[25] Wanchoo R, Jhaveri KD, Deray G, Launay-Vacher V. Renal effects of BRAF inhibitors: a systematic review by the Cancer and the Kidney International Network. Clin Kidney J 2016;9(2):245-51. https://doi.org/10.1093/ckj/sfv149.

[26] Bai Y, Kim JY, Bisunke B, Jayne LA, Silvaroli JA, Balzer MS, et al. Kidney toxicity of the BRAF-kinase inhibitor vemurafenib is driven by off-target ferrochelatase inhibition. Kidney Int 2021; 15:S0085-2538(21)00855-3. https://doi.org/10.1016/j.kint.2021.08.022.

[27] Sorich MJ, Rowland A, Kichenadasse G, Woodman RJ, Mangoni AA. Risk factors of proteinuria in renal cell carcinoma patients treated with VEGF inhibitors: a secondary analysis of pooled clinical trial data. Br J Cancer 2016; 114(12):1313-7. https://doi.org/10.1038/bjc.2016.147.

[28] Tomita Y, Uemura H, Fujimoto H, Kanayama H-o, Shinohara N, Nakazawa H, et al. Key predictive factors of axitinib (AG-013736)-induced proteinuria and efficacy: A phase II study in Japanese patients with cytokine-refractory metastatic renal cell Carcinoma. Eur J Cancer 2011; 47: 2592–602. https://doi.org/ 10.1016/j.ejca.2011.07.014.

[29] Miller KD, Chap LI, Holmes FA, Cobleigh MA, Marcom PK, Fehrenbacher L, et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol 2005; 23: 792–9. https://doi.org/ 10.1200/JCO.2005.05.098.

[30] Andreucci M, Faga T, Pisani A, Sabbatini M, Michael A. Acute kidney injury by radiographic contrast media: pathogenesis and prevention. Biomed Res Int 2014; 2014:362725. https://doi.org/10.1155/2014/362725.

[31] Rudnick MR, Leonberg-Yoo AK, Litt HI, Cohen RM, Hilton S, Reese PP. The Controversy of Contrast-Induced Nephropathy With Intravenous Contrast: What Is the Risk? Am J Kidney Dis 2020; 75(1):105-13. https://doi: 10.1053/j.ajkd.2019.05.022.

[32] Cohen EE, Rosen LS, Vokes EE, Kies MS, Forastiere AA, Worden FP, et al. Axitinib is an active treatment for all histologic subtypes of advanced thyroid cancer: results from a phase II study. J Clin Oncol 2008; 26(29):4708-13. https://doi.org/10.1200/JCO.2007.15.9566.

[33] Cabanillas ME, de Souza JA, Geyer S, Wirth LJ, Menefee ME, Liu SV, et al. Cabozantinib As Salvage Therapy for Patients With Tyrosine Kinase Inhibitor-Refractory Differentiated Thyroid Cancer: Results of a Multicenter Phase II International Thyroid Oncology Group Trial. J Clin Oncol 2017; 35(29):3315-21. https://doi.org/10.1200/JCO.2017.73.0226.

[34] Brose MS, Robinson B, Sherman SI, Krajewska J, Lin CC, Vaisman F, et al. Cabozantinib for radioiodine-refractory differentiated thyroid cancer (COSMIC-311): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2021; 22(8):1126-1138. https://doi.org/10.1016/S1470-2045(21)00332-6.

[35] Schlumberger M, Jarzab B, Cabanillas ME, Robinson B, Pacini F, Ball DW, et al. A Phase II Trial of the Multitargeted Tyrosine Kinase Inhibitor Lenvatinib (E7080) in Advanced Medullary Thyroid Cancer. Clin Cancer Res 2016; 22(1):44-53. https://doi.org/10.1158/1078-0432.CCR-15-1127.

[36] Tahara M, Kiyota N, Yamazaki T, Chayahara N, Nakano K, Inagaki L, et al. Lenvatinib for Anaplastic Thyroid Cancer. Front Oncol 2017;7:25. https://doi.org/10.3389/fonc.2017.00025.

[37] Bible KC, Suman VJ, Molina JR, Smallridge RC, Maples WJ, Menefee ME, et al. Efficacy of pazopanib in progressive, radioiodine-refractory, metastatic differentiated thyroid cancers: results of a phase 2 consortium study. Lancet Oncol 2010; 11(10):962-72. https://doi.org/10.1016/S1470-2045(10)70203-5.

[38] Bible KC, Suman VJ, Menefee ME, Smallridge RC, Molina JR, Maples WJ, et al. A multiinstitutional phase 2 trial of pazopanib monotherapy in advanced anaplastic thyroid cancer. J Clin Endocrinol Metab 2012; 97(9):3179-84. https://doi.org/10.1210/jc.2012-1520.

[39] Bible KC, Suman VJ, Molina JR, Smallridge RC, Maples WJ, Menefee ME, et al. A multicenter phase 2 trial of pazopanib in metastatic and progressive medullary thyroid carcinoma: MC057H. J Clin Endocrinol Metab 2014; 99(5):1687-93. https://doi.org/10.1210/jc.2013-3713.

[40] Lam ET, Ringel MD, Kloos RT, Prior TW, Knopp MV, Liang J, et al. Phase II clinical trial of sorafenib in metastatic medullary thyroid cancer. J Clin Oncol 2010;28(14):2323-30.

[41] Bikas A, Kundra P, Desale S, Mete M, O'Keefe K, Clark BG, et al. Phase 2 clinical trial of sunitinib as adjunctive treatment in patients with advanced differentiated thyroid cancer. Eur J Endocrinol 2016; 174(3):373-80. https://doi.org/10.1530/EJE-15-0930.

[42] Ravaud A, de la Fouchardière C, Caron P, Doussau A, Do Cao C, Asselineau J, et al. A multicenter phase II study of sunitinib in patients with locally advanced or metastatic differentiated, anaplastic or medullary thyroid carcinomas: mature data from the THYSU study. Eur J Cancer 2017; 76:110-17. https://doi.org/10.1016/j.ejca.2017.01.029.

[43] Leboulleux S, Bastholt L, Krause T, de la Fouchardiere C, Tennvall J, Awada A, et al. Vandetanib in locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 2 trial. Lancet Oncol 2012; 13(9):897-905. https://doi.org/10.1016/S1470-2045(12)70335-2.

[44] Haddad RI, Schlumberger M, Wirth LJ, Sherman EJ, Shah MH, Robinson B, et al. Incidence and timing of common adverse events in Lenvatinib-treated patients from the SELECT trial and their association with survival outcomes. Endocrine 2017; 56(1):121-8. https://doi.org/10.1007/s12020-017-1233-5.

[45] Kiyota N, Schlumberger M, Muro K, Ando Y, Takahashi S, Kawai Y, et al. Subgroup analysis of Japanese patients in a phase 3 study of lenvatinib in radioiodine-refractory differentiated thyroid cancer. Cancer Sci 2015; 106(12):1714-21. https://doi.org/10.1111/cas.12826

[46] Brose MS, Worden FP, Newbold KL, Guo M, Hurria A. Effect of Age on the Efficacy and Safety of Lenvatinib in Radioiodine-Refractory Differentiated Thyroid Cancer in the Phase III SELECT Trial. J Clin Oncol 2017; 35(23):2692-9. https://doi.org/10.1200/JCO.2016.71.6472.

[47] Brose MS, Panaseykin Y, Konda B, de la Fouchardiere C, Hughes BGM, Gianoukakis AG, et al. A multicenter, randomized, double-blind, phase II study of Lenvatinib (LEN) in patients (pts) with radioiodine-refractory differentiated thyroid cancer (RR-DTC) to evaluate the safety and efficacy of a daily oral starting dose of 18 mg vs 24 mg. Annals of Oncology 2020; 31 (suppl_6): S1407-S1415. https://doi.org/10.1016/annonc/annonc368.

[48] Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018; 391(10126):1163-73. https://doi.org/10.1016/S0140-6736(18)30207-1.

[49] Motzer RJ, Hutson TE, Glen H, Michaelson MD, Molina A, Eisen T, et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. Lancet Oncol 2015; 16(15):1473-82. https://doi.org/10.1016/S1470-2045(15)00290-9.

[50] Motzer RJ, Escudier B, Tomczak P, Hutson TE, Michaelson MD, Negrier S, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. Lancet Oncol 2013; 14(6):552-62. https://doi.org/10.1016/S1470-2045(13)70093-7.

[51] Abou-Alfa GK, Meyer T, Cheng AL, El-Khoueiry AB, Rimassa L, Ryoo BY, et al. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. N Engl J Med 2018;379(1):54-63. https://doi.org/10.1056/NEJMoa1717002.

[52] Choueiri TK, Escudier B, Powles T, Tannir NM, Mainwaring PN, Rini BI, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Oncol 2016; 17(7):917-27. https://doi.org/10.1016/S1470-2045(16)30107-3.

[53] Iwasaki H, Yamazaki H, Takasaki H, Suganuma N, Sakai R, Nakayama H, et al. Renal dysfunction in patients with radioactive iodine-refractory thyroid cancer treated with tyrosine kinase inhibitors: A retrospective study. Medicine (Baltimore) 2019; 98(42):e17588. https://doi.org/10.1097/MD.0000000000017588.

[54] Balmelli C, Railic N, Siano M, Feuerlein K, Cathomas R, Cristina V, et al. Lenvatinib in Advanced Radioiodine-Refractory Thyroid Cancer - A Retrospective Analysis of the Swiss Lenvatinib Named Patient Program. J Cancer 2018; 9(2):250-5. https://doi.org/10.7150/jca.22318.

[55] Nervo A, Gallo M, Samà MT, Felicetti F, Alfano M, Migliore E, et al. Lenvatinib in Advanced Radioiodine-refractory Thyroid Cancer: A Snapshot of Real-life Clinical Practice. Anticancer Res 2018; 38(3):1643-9. https://doi.org/10.21873/anticanres.12396.

[56] Sugino K, Nagahma M, Kitagawa W, Ohkuwa K, Uruno T, Matsuzu K, et al. Clinical factors related to the efficacy of tyrosine kinase inhibitor therapy in radioactive iodine refractory recurrent differentiated thyroid cancer patients. Endocr J 2018; 65(3):299-306. https://doi.org/10.1507/endocrj.EJ17-0365

[57] Kim SY, Kim SM, Chang H, Kim BW, Lee YS, Chang HS, et al. Safety of Tyrosine Kinase Inhibitors in Patients With Differentiated Thyroid Cancer: Real-World Use of Lenvatinib and Sorafenib in Korea. Front Endocrinol (Lausanne) 2019; 10:384. https://doi.org/10.3389/fendo.2019.00384.

[58] Lee EK, Kim SM, Kim BH, Kim MJ, Lim DJ, Kim MH, et al. Lesion-Based Evaluation Predicts Treatment Response to Lenvatinib for Radioactive Iodine-Refractory Differentiated Thyroid Cancer: A Korean Multicenter Retrospective Study. Thyroid 2019; 29(12):1811-9. https://doi.org/10.1089/thy.2019.0022.

[59] Locati LD, Piovesan A, Durante C, Bregni M, Castagna MG, Zovato S, et al. Real-world efficacy and safety of lenvatinib: data from a compassionate use in the treatment of radioactive iodine-refractory differentiated thyroid cancer patients in Italy. Eur J Cancer 2019; 118:35-40. https://doi.org/10.1016/j.ejca.2019.05.031.

[60] Suzuki C, Kiyota N, Imamura Y, Goto H, Suto H, Chayahara N, et al. Exploratory analysis of prognostic factors for lenvatinib in radioiodine-refractory differentiated thyroid cancer. Head Neck 2019; 41(9):3023-32. https://doi.org/10.1002/hed.25784.

[61] De Leo S, Di Stefano M, Persani L, Fugazzola L, Colombo C. Lenvatinib as first-line treatment for advanced thyroid cancer: long progression-free survival. Endocrine 2020. https://doi.org/10.1007/s12020-020-02477-0.

[62] Jerkovich F, Califano I, Bueno F, Carrera JM, Giglio R, Abelleira E, et al. Real-life use of lenvatinib in patients with differentiated thyroid cancer: experience from Argentina. Endocrine 2020; 69(1):142-8. https://doi.org/10.1007/s12020-020-02290-9.

[63] Masaki C, Sugino K, Saito N, Akaishi J, Hames KY, Tomoda C, et al. Efficacy and Limitations of Lenvatinib Therapy for Radioiodine-Refractory Differentiated Thyroid Cancer: Real-World Experiences. Thyroid 2020; 30(2):214-21. https://doi.org/10.1089/thy.2019.0221.

[64] Song E, Kim M, Kim EY, Kim BH, Shin DY, Kang HC, et al. Lenvatinib for Radioactive Iodine-Refractory Differentiated Thyroid Carcinoma and Candidate Biomarkers Associated with Survival: A Multicenter Study in Korea. Thyroid 2020; 30(5):732-8. https://doi.org/10.1089/thy.2019.0476.

[65] Rendl G, Sipos B, Becherer A, Sorko S, Trummer C, Raderer M, et al. Real-world data for Lenvatinib in radioiodine-refractory differentiated thyroid cancer (RELEVANT): a retrospective multicentric analysis of clinical practice in Austria. Int J Endocrinol 2020; 2020:8834148. https://doi.org/10.1155/2020/8834148

[66] Giani C, Valerio L, Bongiovanni A, Durante C, Grani G, Ibrahim T, et al. Safety and Quality-of-Life Data from an Italian Expanded Access Program of Lenvatinib for Treatment of Thyroid Cancer. Thyroid 2021; 31(2):224-32. https://doi.org/10.1089/thy.2020.0276.

[67] Ito Y, Onoda N, Kudo T, Masuoka H, Higashiyama T, Kihara M, et al. Sorafenib and Lenvatinib treatment for metastases/recurrence of radioactive iodine-refractory differentiated thyroid carcinoma. In Vivo 2021; 35:1057-64. https://doi.org/10.21873/invivo.12350

[68] Porcelli T, Luongo C, Sessa F, Klain M, Masone S, Troncone G, et al. Long-term management of lenvatinib-treated thyroid cancer patients: a real-life experience at a single institution. Endocrine 2021; online ahead of print. http://doi.org/10.1007/s12020-021-02634-z

[69] Kiyota N, Schlumberger M, Muro K, Ando Y, Takahashi S, Kawai Y, et al. Subgroup analysis of Japanese patients in a phase 3 study of lenvatinib in radioiodine-refractory differentiated thyroid cancer. Cancer Sci 2015; 106(12):1714-21. https://doi.org/10.1111/cas.12826.

[70] Kim M, Ahn J, Song DE, Yoon JH, Kang HC, Lim DJ, et al. Real-world experience of lenvatinib in patients with advanced anaplastic thyroid cancer. Endocrine 2021; 71(2):427-33. https://doi.org/10.1007/s12020-020-02425-y.

[71] Hiraoka A, Kumada T, Kariyama K, Takaguchi K, Atsukawa M, Itobayashi E, et al. Clinical features of lenvatinib for unresectable hepatocellular carcinoma in real-world conditions: Multicenter analysis. Cancer Med. 2019; 8(1):137-46. https://doi.org/10.1002/cam4.1909.

[72] Gallo M, Michelon F, Castiglione A, Felicetti F, Viansone AA, Nervo A, et al. Sorafenib treatment of radioiodine-refractory advanced thyroid cancer in daily clinical practice: a cohort study from a single center. Endocrine 2015; 49(3):726-34. https://doi.org/10.1007/s12020-014-0481-x.

[73] Kim M, Kim TH, Shin DY, Lim DJ, Kim EY, Kim WB, et al. Tertiary Care Experience of Sorafenib in the Treatment of Progressive Radioiodine-Refractory Differentiated Thyroid Carcinoma: A Korean Multicenter Study. Thyroid 2018; 28(3):340-8. https://doi.org/10.1089/thy.2017.0356.

[74] Longo L, de Freitas LBR, Santos D, Grivicich I, Álvares-da-Silva MR. Sorafenib for Advanced Hepatocellular Carcinoma: A Real-Life Experience. Dig Dis 2018; 36(5):377-84. https://doi.org/10.1159/000490378.

[75] Kim MJ, Kim SM, Lee EK, Hwangbo Y, Lee YJ, Cho SW, et al. Tumor doubling time predicts response to sorafenib in radioactive iodine-refractory differentiated thyroid cancer. Endocr J 2019; 66(7):597-604. https://doi.org/10.1507/endocrj.EJ18-0488.

[76] Ito Y, Onoda N, Ito KI, Sugitani I, Takahashi S, Yamaguchi I, et al. Sorafenib in Japanese Patients with Locally Advanced or Metastatic Medullary Thyroid Carcinoma and Anaplastic Thyroid Carcinoma. Thyroid 2017; 27(9):1142-8. https://doi.org/10.1089/thy.2016.0621.

[77] Kim SY, Kim SM, Chang H, Kim BW, Lee YS, Chang HS, et al. Safety of Tyrosine Kinase Inhibitors in Patients With Differentiated Thyroid Cancer: Real-World Use of Lenvatinib and Sorafenib in Korea. Front Endocrinol (Lausanne). 2019; 10:384. https://doi.org/10.3389/fendo.2019.00384.

[78] Ramos HE, Hecht F, Berdelou A, Borget I, Leboulleux S, Baudin E, et al. Long-term follow-up and safety of vandetanib for advanced medullary thyroid cancer. Endocrine 2020; https://doi.org/10.1007/s12020-020-02426-x.

[79] Kim M, Yoon JH, Ahn J, Jeon MJ, Kim HK, Lim DJ, et al. Vandetanib for the Management of Advanced Medullary Thyroid Cancer: A Real-World Multicenter Experience. Endocrinol Metab (Seoul) 2020; 35(3):587-94. https://doi.org/10.3803/EnM.2020.687.

[80] Procopio G, Prisciandaro M, Iacovelli R, Cortesi E, Fornarini G, Facchini G, et al. Safety and Efficacy of Cabozantinib in Metastatic Renal-Cell Carcinoma: Real-World Data From an Italian Managed Access Program. Clin Genitourin Cancer. 2018; 16(4):e945-e951. https://doi.org/10.1016/j.clgc.2018.03.014.

[81] Martínez Chanzá N, Xie W, Asim Bilen M, Dzimitrowicz H, Burkart J, Geynisman DM, et al. Cabozantinib in advanced non-clear-cell renal cell carcinoma: a multicentre, retrospective, cohort study. Lancet Oncol 2019;20(4):581-90. https://doi.org/10.1016/S1470-2045(18)30907-0.

[82] Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013; 3: 1-150.

[83] Fotheringham J, Campbell MJ, Fogarty DG, El Nahas M, Timothy Ellam T. Estimated albumin excretion rate versus urine albumin-creatinine ratio for the estimation of measured albumin excretion rate: derivation and validation of an estimated albumin excretion rate equation. Am J Kidney Dis 2014; 63:405. https://doi.org/10.1053/j.ajkd.2013.08.009.

[84] Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf [accessed March 8, 2021]

[85] Capdevila J, Newbold K, Licitra L, Popovtzer A, Moreso F, Zamorano J, et al. Optimisation of treatment with lenvatinib in radioactive iodine-refractory differentiated thyroid cancer. Cancer Treat Rev 2018; 69:164-76. https://doi.org/10.1016/j.ctrv.2018.06.019.

[86] Resteghini C, Cavalieri S, D Galbiati D, Granata R, Alfieri S, Bergamini C, et al. Management of tyrosine kinase inhibitors (TKI) side effects in differentiated and medullary thyroid cancer patients. Best Pract Res Clin Endocrinol Metab 2017; 31(3):349-61. https://doi.org/10.1016/j.beem.2017.04.012. Epub 2017 May 10.

[87] Evans TRJ, Kudo M, Finn RS, Han K, Cheng A, Ikeda M, et al. Urine protein:creatinine ratio vs 24-hour urine protein for proteinuria management: analysis from the phase 3 REFLECT study of lenvatinib vs sorafenib in hepatocellular carcinoma. Br J Cancer 2019; 121(3):218-21. https://doi.org/10.1038/s41416-019-0506-6.

[88] Cabanillas ME, Takahashi S. Managing the adverse events associated with lenvatinib therapy in radioiodine-refractory differentiated thyroid cancer. Semin Oncol 2019; 46(1):57-64. https://doi.org/10.1053/j.seminoncol.2018.11.004.

[89] INN-lenvatinib - European Medicines Agency - Europa EU - Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/lenvima-epar-product-information_en.pdf. [accessed March 8, 2021]

[90] Silvestris N, Argentiero A, Cosmai L, Porta C, Gesualdo L, Brunori G, et al. Management of targeted therapies in cancer patients with chronic kidney disease, or on haemodialysis: An Associazione Italiana di Oncologia Medica (AIOM)/Societa' Italiana di Nefrologia (SIN) multidisciplinary consensus position paper. Crit Rev Oncol Hematol 2019; 140:39-51. https://doi.org/10.1016/j.critrevonc.2019.05.016.

[91] INN-sorafenib - European Medicines Agency - Europa EU - Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/nexavar-epar-product-information_en.pdf. [accessed March 8, 2021]

[92] INN-vandetanib - European Medicines Agency - Europa EU - Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/caprelsa-epar-product-information_en.pdf. [accessed March 8, 2021]

[93] INN-cabozantinib - European Medicines Agency - Europa EU - Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/cometriq-epar-product-information_en.pdf. [accessed March 8, 2021]

[94] Ravasco P. Nutrition in Cancer Patients. J Clin Med 2019; 8(8): 1211. https://doi.org/10.3390/jcm8081211.

[95] Gallo M, Muscogiuri G, Felicetti F, Faggiano A, Trimarchi F, Arvat E, et al. Adverse glycaemic effects of cancer therapy: indications for a rational approach to cancer patients with diabetes. Metabolism 2018; 78:141–54. https://doi.org/10.1016/j.metabol.2017.09.013.

[96] Palmer SC, Tendal B, Mustafa RA, Vandvik PO, Li S, Hao Q, et al. Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. BMJ. 2021 Jan 13;372:m4573. https://doi.org/10.1136/bmj.m4573.

[97] Goto H, Kiyota N, Otsuki N, Imamura Y, Chayahara N, Suto H, et al. Successful treatment switch from lenvatinib to sorafenib in a patient with radioactive iodine-refractory differentiated thyroid cancer intolerant to lenvatinib due to severe proteinuria. Auris Nasus Larynx 2018; 45(6):1249-52. https://doi.org/10.1016/j.anl.2018.05.003.

[98] Yang CH, Chen KT, Lin YS, HSU CY, Ou YC, Tung MC. Improvement of lenvatinib-induced nephrotic syndrome after adaptation to sorafenib in thyroid cancer: A case report. World J Clin Cases 2020; 8(20):4883-94. https://doi.org/10.12998/wjcc.v8.i20.4883.

[99] Piskinpasa S, Altun B, Akoglu H, Yildirim T, Agbaht K, Yilmaz R, et al. An uninvestigated risk factor for contrast-induced nephropathy in chronic kidney disease: proteinuria. Ren Fail 2013; 35(1):62-5. https://doi.org/10.3109/0886022X.2012.741646.

[100] Van der Molen AJ, Reimer P, Dekkers IA, Bongartz G, Bellin MF, Bertolotto M, et al. Post-contrast acute kidney injury – Part 1: Definition, clinical features, incidence, role of contrast medium and risk factors. European Radiology 2018; 28:2845–55. https://doi.org/10.1007/s00330-017-5246-5.

[101] Van der Molen AJ, Reimer P, Dekkers IA, Bongartz G, Bellin MF, Bertolotto M, et al. Post-contrast acute kidney injury. Part 2: risk stratification, role of hydration and other prophylactic measures, patients taking metformin and chronic dialysis patients. European Radiology 2018; 28:2856–69. https://doi.org/10.1007/s00330-017-5247-4.

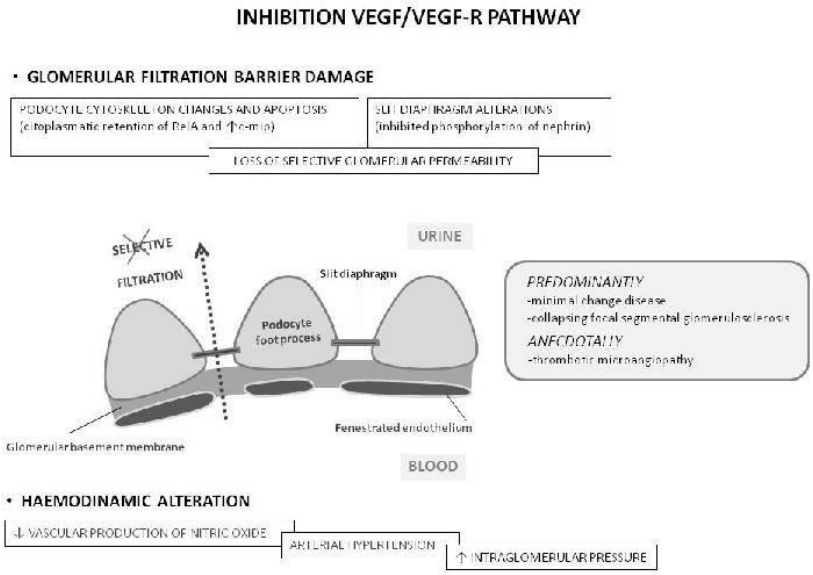
[102] Wirth LJ, Tahara M, Robinson B, Francis S, Brose MS, Habra MA, et al. Treatment-emergent hypertension and efficacy in the phase 3 Study of (E7080) lenvatinib in differentiated cancer of the thyroid (SELECT). Cancer 2018; 124(11):2365-2372. https://doi.org/10.1002/cncr.31344.

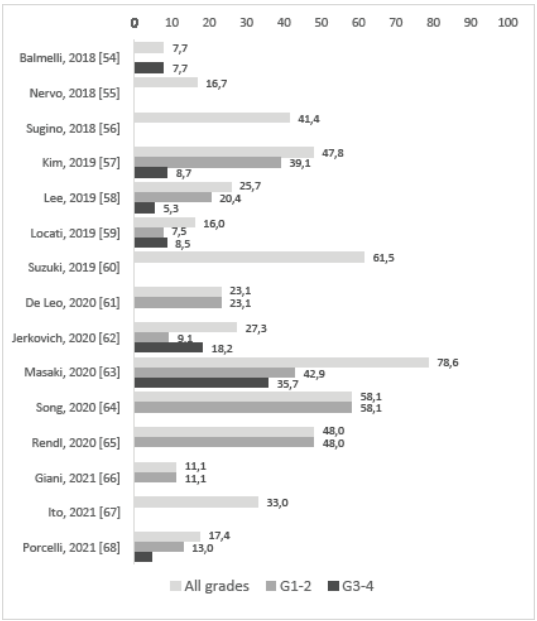
[103] Fernandez-Fernandez B, Sarafidis P, Kanbay M, Navarro-González JF, Soler MJ, Górriz JL, Ortiz A. SGLT2 inhibitors for non-diabetic kidney disease: drugs to treat CKD that also improve glycaemia. Clin Kidney J 2020;13(5):728-733. https://doi.org/10.1093/ckj/sfaa198.

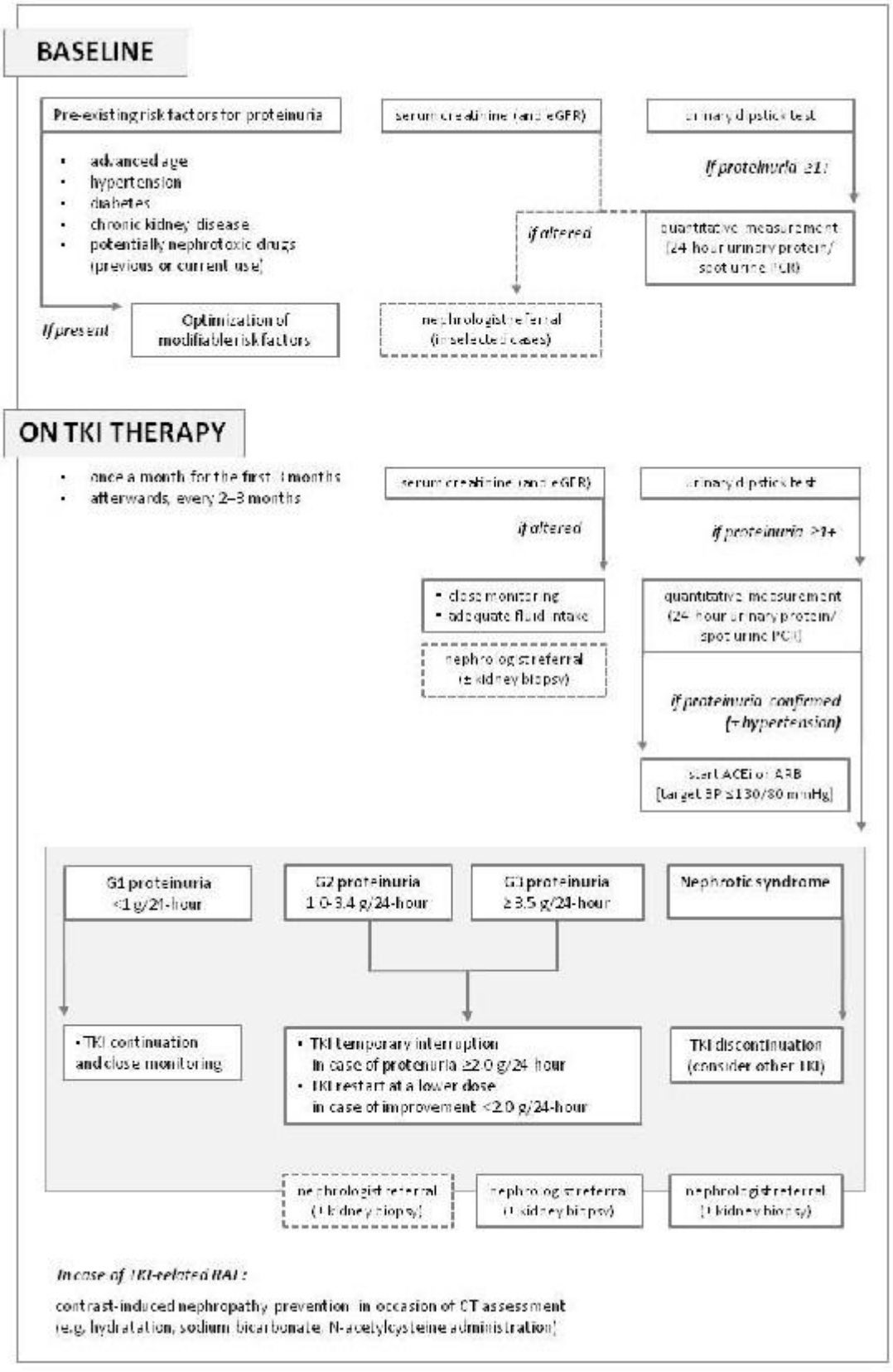
Figure 1. Potential mechanisms underlying the onset of proteinuria induced by TC-TKIs targeting the VEGF axis.
c-mip: C-Maf-inducing protein, VEGF: vascular endothelial growth factor, VEGFR: vascular endothelial growth factor receptor

Figure 2. All grades, G1-2 and G≥3 proteinuria reported in the real-life studies of lenvatinib in TC patients.

Figure 3. Suggested algorithm for the management of TKI-related RAEs.
ACEi: angiotensin-converting enzyme inhibitor, ARB: angiotensin 2-receptor blocker, BP: blood pressure, CT: computed tomography, eGFR: estimated glomerular filtration rate, G: grade, PCR: protein-to-creatinine ratio, RAE: renal adverse event, TKI: tyrosine kinase inhibitor.






BASELINE
Pre-existing risk factors for proteinuria
advanced age
hypertension
diabetes
chronic kidney disease
potentially nephrotoxic drugs (previous or current use)
If present
Optimization of modifiable risk factors
serum creatinine (and eGFR)
if altered
nephrologist referral (in selected cases)
urinary dipstick test
If proteinuria ≥1+
quantitative measurement (24-hour urinary protein/ spot urine PCR)
ON TKI THERAPY
once a month for the first 3 months
afterwards, every 2–3 months
serum creatinine (and eGFR)
if altered
close monitoring
adequate fluid intake
nephrologist referral (± kidney biopsy)
urinary dipstick test
if proteinuria >1+
quantitative measurement (24-hour urinary protein/ spot urine PCR)
if proteinuria confirmed (+hypertension)
start ACEi or ARB (target BP ≤130/80 mmHg)
G1 proteinuria <1 g/24-hour
G2 proteinuria 1.0-3.4 g/24-hour
G3 proteinuria ≥3.5 g/24-hour
Nephrotic syndrome
• TKI continuation and close monitoring
• TKI temporary interruption in case of proteinuria ≥2.0 g/24-hour
• TKI restart at a lower dose in case of improvement <2.0 g/24-hour
TKI discontinuation (consider other TKI)
nephrologist referral (± kidney biopsy)
nephrologist referral (± kidney biopsy)
nephrologist referral (± kidney biopsy)
In case of TKI-related IRAI:
contrast-induced nephropathy prevention in occasion of CT assessment (e.g. hydratation, sodium bicarbonate, N-acetylcysteine administration)

Drug	Molecular target	Study phase	TC subgroup	FDA approval	RAEs
Axitinib	VEGFR1–3	II [32]	DTC ATC MTC	No	Proteinuria: 18% (any G), 5% (G ≥ 3)
Cabozantinib	VEGFR2 MET FLT3 RET c-kit	III (EXAM study) [2]	MTC	Yes	Proteinuria: 1.9% (any G), 0.9% (G ≥ 3)
		II [33]	DTC	No	Proteinuria: 32% (any G), 0% (G ≥ 3)
		III (COSMIC study) III [34]	DTC	Yes	Proteinuria: 15% (any G), 1% (G ≥ 3) Renal failure: 1% (G ≥ 3) Acute kidney injury: 1% (G ≥ 3)
Lenvatinib	VEGFR1–3 FGFR1–4 PDGFRα RET c-kit	III (SELECT study) [4]	DTC	Yes	Proteinuria: 31% (any G), 10% (G ≥ 3) Renal failure: 4.2% (any G), 1.9% (G ≥ 3)
		II [35]	MTC	No	Proteinuria: 59% (any G), 2% (G ≥ 3)
		II [36]	ATC	No*	Proteinuria: 59% (any G), 6% (G ≥ 3)
Pazopanib	VEGFR1–3 PDGFR FGFR1/2 c- kit	II [37]	DTC	No	Proteinuria: 20% (any G), 0% (G ≥ 3) Raised creatinine: 5% (any G), 2.5% (G ≥ 3)
		II [38]	ATC	No	Proteinuria: 33% (any G), 0% (G ≥ 3)
		II [39]	MTC	No	Proteinuria: 37% (any G), 0% (G ≥ 3)
Sorafenib	VEGFR1–3 PDGFRβ RET c-kit BRAF	III (DECISION study) [3]	DTC	Yes	N.R.
		II [40]	MTC	No	N.R.
Sunitinib	VEGFR1–3 PDGFR RET c-kit CSF-1R Flt-3	II [41]	DTC	No	Proteinuria: 22% (any G), 0% (G ≥ 3) Raised creatinine: 43% (any G), 0% (G ≥ 3)
		II [42]	DTC, ATC, MTC	No	Renal failure: 1.4% (G ≥ 3)
Vandetanib	VEGFR2-3 EGFR RET	III (ZETA study) [1]	MTC	Yes	Proteinuria: 10% (any G), 0% (G ≥ 3) Renal failure: <1% (G ≥ 3)
		II [43]	DTC	No	N.R.

Table 1. RAEs of TKIs with anti-VEGF activity from the main phase II and III clinical trials in the TC setting.

Abbreviations: ATC, anaplastic thyroid cancer; N.R., not reported; DTC, differentiated thyroid cancer; G, grade; MTC, medullary thyroid cancer; TC, thyroid cancer

** From 2015, Lenvatinib is approved in Japan for the treatment of ATC and DTC patients*

	Normal to mildly increased albuminuria	Moderately increased albuminuria ("microalbuminuria")	Severely increased albuminuria ("macroalbuminuria")	Nephrotic syndrome
Urine dipstick	Negative to trace	Trace to +	+ or greater	+++/++++
AER (mg/24-h)	<30	30-300 [20-200 µg/min]	>300	>2200
ACR (mg/g; mg/mmol)	<30; <3	30-300; 3-30	>300; >30	>2200; >220
PER (mg/24-h)	<150	150-500	>500	>3500
PCR (mg/g; mg/mmol)	<150; <15	150-500; 15-50	>500; >50	>3500; >350

Table 2. Albuminuria and proteinuria categories (modified from KDIGO 2012 [82]).

Relationships are based on the assumption of an average creatinine excretion rate ~1.0 g/24-h, but creatinine excretions varies with age, sex, race, diet, and muscle mass. The relationship between urine dipstick and quantitative measurements depends on urine concentrations.

Abbreviations: AER, albumin excretion rate; PER, protein excretion rate; ACR, albumin-to-creatinine ratio; PCR, protein-to-creatinine ratio

		G1	G2	G3	G4	G5
Proteinuria	proteinuria (urine dipstick)	1+	2+ and 3+	4+	-	-
	urinary protein (24-hour urine collection; g/24h)	≥ULN <1.0	1.0-3.4	≥3.5	-	-
Chronic kidney disease	eGFR or ClCr (ml/min/1.73m)	<LLN – 60	59 – 30	29 – 15	<15	-
	proteinuria (urine dipstick)	2+	-	-	-	-
	PCR (spot urine sample; mg/mg)	>0.5	-	-	-	-
		-	-	-	dialysis or renal transplant indicated	death

Table 3. Proteinuria and CKD as an adverse event according to CTCAE (Renal and urinary disorders; adults) [84].

Abbreviations: ClCr, creatinine clearance; CTCAE, Common Terminology Criteria for Adverse Events; eGFR, estimated Glomerular Filtration Rate; G, grade; LLN, lower limit of normal; PCR, protein-to-creatinine ratio; ULN, upper limit of normal

DRUG	DOSE ADJUSTMENT IN CASE OF RENAL IMPAIRMENT
CABOZANTINIB	Mild or moderate CKD (ClCr 30-59 ml/min/1.73 m^2): use with caution Severe CKD (ClCr 15-29 ml/min/1.73 m^2): not recommended - insufficient data
LENVATINIB	Mild or moderate CKD (ClCr 30-59 ml/min/1.73 m^2): initial dose adjustment not required Severe CKD (ClCr 15-29 ml/min/1.73 m^2): initial dose adjustment (14 mg/daily) End-stage kidney disease: not recommended - insufficient data
SORAFENIB	Mild, moderate or severe CKD (ClCr 15-59 ml/min/1.73 m^2): dose adjustment not required Dialysis: no available data
VANDETANIB	Mild CKD (ClCr 50-59 ml/min/1.73 m^2): dose adjustment not required Moderate CKD (ClCr 30-50 ml/min/1.73 m^2): initial dose adjustment (200 mg/daily) Severe CKD (ClCr 15-29 ml/min/1.73 m^2): not recommended - insufficient data

Supplementary Table 1. Suggested management of the TKIs with anti-VEGF activity approved in TC in case of renal impairment (adapted from the summary of product characteristics) [89, 91, 92, 93].

Abbreviations: CKD, chronic kidney disease, ClCr, creatinine clearance