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RESEARCH

Management of hypertension during lenvatinib for advanced thyroid cancer: a suggested diagnostic and therapeutic algorithm

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Abstract

Background: Hypertension (HTN) is the most frequent adverse event during treatment with lenvatinib (LEN), but data on its best management are limited.
Aim: The objective of this study was to assess incidence, features and best management of LEN-related HTN in a consecutive single tertiary-care centre cohort.
Methods: Twenty-nine patients were followed up for a mean time of 29.8 months (6–77 months).
Results: After a mean follow-up of 6.8 months, HTN was recorded in 76% of cases, as a *de novo* occurrence in half of them. HTN significantly correlated with LEN dose and was of grade 1, grade 2 and grade 3 in 5%, 50% and 45% of patients, respectively. The majority (77%) of patients with HTN developed proteinuria. There was no correlation between HTN and proteinuria or clinical features or best morphological response or any other adverse event (AE), with the exception of diarrhoea. Patients with or without pre-existing HTN or any other cardiovascular disease had a similar incidence of HTN during LEN, thus excluding the impact of this potential predisposing factor. After evaluation by a dedicated cardiologist, medical treatment was introduced in 21/22 patients (polytherapy in 20 of them). The most frequently used drugs were calcium channel blockers (CCBs) due to their effect on vasodilation. In case of poor control, CCBs were associated with one or more anti-hypertensive drug.
Conclusion: HTN is a frequent and early AE in patients on LEN treatment. We suggest a diagnostic and therapeutic algorithm to be applied in clinical practice to allow efficient HTN control and improve patient compliance, reducing LEN discontinuation.

Key Words

- thyroid cancer
- lenvatinib
- hypertension
- adverse event
- treatment

Introduction

Multikinase inhibitors (MKIs) with strong anti-angiogenetic action are frequently used for the treatment of advanced radioiodine-refractory differentiated thyroid cancer (RAI-R DTC) or medullary thyroid cancers (MTCs) (1, 2, 3). In particular, in Europe, sorafenib and lenvatinib (LEN) can be used as-first line and cabozantinib as second-line treatment for RAI-R DTCs, while vandetanib and cabozantinib are first-line compounds for MTCs. In phase

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III trials, these drugs demonstrated significantly prolonged progression-free survival (PFS) (4, 5, 6, 7, 8).

The occurrence of several adverse events (AEs) has been reported, particularly during treatment with anti-angiogenic drugs: hypertension (HTN), diarrhoea, decreased appetite, decreased weight, fatigue, proteinuria and others. These AEs virtually affect all patients and usually occur during the first months of treatment, often requiring dose reduction and/or drug discontinuation.

HTN represents one of the most frequent toxicities recorded during both clinical trials and real-life (RL) studies and has a high incidence during LEN treatment (reviewed in Table 1). Indeed, in the LEN registration trial SELECT, it was recorded in 67.8% of cases, and 41.8% of patients experienced grade ≥ 3 HTN according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (2). A similar incidence (72%) has been confirmed in RL studies, with 20.8% of patients experiencing a grade ≥ 3 HTN (9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22). Interestingly, LEN dose was found to correlate, though not significantly, with HTN incidence (23). Consistently, patients with unresectable hepatocarcinoma treated with lower LEN doses (8-12 mg/day) experienced HTN in only 25% of cases (10.4% grade ≥3) (24, 25, 26). As for the other toxicities developing during these chronic treatments, careful management should be adopted, with the final aim not to either reduce the drug dose or discontinue it (27, 28, 29). HTN is usually initially managed using compounds commonly suggested for HTN, by the endocrinologist or oncologist, and a cardiologist's advice is required in more complicated or resistant cases. No specific clinical trial has ever been conducted to assess the best management of LEN-induced HTN. Capdevila *et al.* gave specific recommendations to reduce the incidence and severity of LEN-induced AEs (including HTN), suggesting to use, as a first line treatment, angiotensin-converting enzyme inhibitors (ACE-i) followed by calcium channel blockers (CCBs) and beta-blockers (BBs) (27). In addition, some information on anti-hypertensive drugs and LEN reduction/interruption comes from a study on 25 patients on MKI treatment developing persistent grade 2 HTN (11).

In order to get more insights into HTN during LEN, we performed careful specialist evaluations at baseline and during treatment in our cohort of patients with RAI-R DTC and here suggest a protocol indicating the best management strategies according to the different clinical conditions.

Patients and methods

This is a retrospective, cohort study. We evaluated 29 consecutive patients with progressive, locally advanced or metastatic differentiated and poorly differentiated thyroid cancer who received LEN treatment during the period July 2016–November 2022, for an average time of 29.8 months (6–77 months) and were followed-up at our tertiary centre. All patients were MKI naïve, and the clinico-pathological features and treatment details are reported in Table 2. All patients were followed up according to Italian and International guidelines, and the functional status of patients was assessed by the Eastern Cooperative Oncology Group (ECOG) performance status scale (30, 31, 32). Tumour response rate (defined as the objective response rate, complete or partial, ORR) was evaluated according to the revised RECIST (Response Evaluation Criteria in Solid Tumours) criteria guidelines version 1.1 (33). All patients were submitted to surgery followed by levothyroxine thyroid-stimulating hormone-suppressive therapy, except two (#21 and #26) who are receiving LEN in a neo-adjuvant setting.

AEs were recorded on Electronic Hospital Records and were classified according to CTCAE version 5.0 (HTN, diarrhoea, fatigue, proteinuria, weight loss, anorexia and

Table 1 Hypertension prevalence and CTCAE grade developed during MKI treatment in clinical trials and real-life studies

	Hypertension prevalence developed during MKI treatment (%)	Hypertension grade ≥3 CTCAE v 5.0 (%)	Patients (*n*)	Evaluation of hypertension medical treatment
DECISION (4)	40.6	9.7	207	No
SELECT (5)	67.8	41.8	261	No
ZETA (6)	32	9	231	No
EXAM (7)	32.7	8.9	214	No
COSMIC-311 (23)	28	8.8	125	No
LIBRETTO-001 (8)	30	12	162	No
LEN real-life studies (#9–22) mean (range)	72.4 (15–100)	20.8 (0–74)	1045	Only #11
Present study: LEN	76	45	29	Yes

CTCAE v 5.0, Common Terminology Criteria for Adverse Events version 5.0; LEN, lenvatinib; MKI, multikinase inhibitor.

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Table 2 Clinical features of the series of 29 patients treated with lenvatinib.

Patient ID/ gender	Age at diagnosis/ age at LEN start (years)	Tumor histotype	pTNM/ AJCC Stage	Metastases (site)	LEN starting dose (mg)	ECOG status	BMR	Follow-up from LEN start (months)	Time to HTN worsening or onset (months)	HTN grade (CTCAE)	HTN medical treatment, number (drug)
#1/female	36/39	FTC	T3bNXMX/I	LN, lung	20	0	PR	32	1	3	4 (ARB, CCB, BB, AB)
#2/female	79/79	PTC	T3bNXMX/II	LN	10	1	PR	17	6	2	2 (CCB, ACE-i)
#3/female	33/75	PTC	T2N1aMX/I	LN	10	1	PR	68	1	2	2 (ACE-i, CCB)
#4/female	42/58	FTC	T2NXM0 /I	Lung, vertebrae	20	0	PR	77	12	2	3 (CCB, D, ACE-i)
#5/female	57/73	PTC	T3bNXMX/II	LN, lung	14	1	SD	23	3	2	2 (ACE-i, CCB)
#6/female	71/72	PTC	T4aNXMX/II	LN, vertebrae	10	0	PR	29	15	2	5 (AB, D, D, D, BB)
#7/male	65/65	FTC	M1[a]/IVb	LN, trachea, lung, sternum	24	0	SD	26	12	3	2 (ARB, BB)
#8/female	63/74	PDTC	T3NXM0/II	LN, lung	20	0	PR	38	15	2	3 (CCB, ARB, D)
#9/male	50/66	PTC	T2NXMX/I	LN, lung	20	1	SD	47	4	2	3 (BB, CCB, ACE-i)
#10/male	67/68	FTC	T4bNXM1/IVb	LN, lung, bone	20	0	PR	64	24	3	3 (ARB, D, CCB)
#11/male	58/60	HCC	T3aNXMX/II	LN, neck, skin	20	0	PD	38	1	3	3 (ARB, CCB, AB)
#12/male	60/73	PTC	T3bN1aMX/II	LN, lung, pleura	12	0	PR	14	1.5	2	1 (CCB)
#13/female	79/84	FTC	T3aNXMX/II	LN, lung, clavicle	4	1	PR	50	1	3	3 (ARB, BB, D)
#14/male	19/21	FTC	T3N1bM0/I	LN, skin	18	0	PR	45	32	1	0
#15/female	71/71	PTC	T3bNXMX/II	LN, neck, mediastinum, vertebrae	20	1	PD	2	1	2	2 (ACE-i, BB)
#16/female	74/76	PDTC	T3bN1aMX/II	LN, neck	10	0	PR	32	12	2	3 (ARB, D, CCB)
#17/male	71/73	PTC	T3bN1bMX/II	LN, lung	20	0	PR	13	1	3	4 (AB, BB, ARB, CCB)
#18/male	56/71	PTC	T3NXM0/II	LN, trachea, lung	20	1	PR	7	4	3	5 (CCB, AB, BB, ARB, D)
#19/male	76/79	HCC	T4aNXMX/III	LN, multiple bones	20	1	PD	2	1	3	2 (BB, ACE-i)
#20/female	77/77	PDTC	T4bNXM1/IVb	LN, neck, lung	24	1	PD	5	2	2	3 (ARB, CCB, BB)
#21/female	49/55	FTC	M1[a]/II	LN, multiple bones	24	1	SD	29	1	3	5 (CCB, BB, AB, ARB, D)
#22/male	51/59	PDTC	T1aNXMX/I	LN	24	0	PR	3	3	3	3 (ACE-i, CCB, BB)
#23/female	45/65	PTC	T3bN1aMX/I	LN, lung	4	1	PR	5	/	/	/
#24/male	64/67	PTC	T3bN1bMX/II	LN, lung	14	0	PR	14	/	/	/
#25/female	78/90	PTC	T4aN1bMX/III	LN, vertebrae	4	0	PR	5	/	/	/
#26/male	85/85	PTC	M1[a]/IVb	LN, sternum, lung	4	1	PR	5	/	/	/
#27/male	54/66	PTC	T4aN1MX/I	LN, lung, neck	20	0	PR	59	/	/	/
#28/female	73/80	FTC	T4aN1aMX/III	LN, lung, bone	6	1	SD	16	/	/	/
#29/male	51/58	PDTC	T4aN1aM0/I	LN, skull, vertebra	24	1	PR	68	/	/	/

*Patients with unresectable tumor

AB, alpha-blocker; ACE-i, angiotensin-converting enzyme inhibitor; AJCC, American Joint Committee on Cancer eighth edition staging system; ARB, angiotensin receptor blocker; BB, beta-blocker; BMR, best morphological response; CCB, calcium channel blocker; CTCAE, Common Terminology Criteria for Adverse Events; D, diuretic; ECOG, Eastern Cooperative Oncology Group; FTC, follicular thyroid cancer; HCC, Hürtle cell carcinoma; HTN, hypertension; LEN, lenvatinib; LN, lymph node; PD, progressive disease; PDTC, poorly differentiated thyroid cancer; pTNM, pathological tumor-node-metastasis; PR, partial response; PTC, papillary thyroid cancer; SD, stable disease.

nausea, palmar–plantar erythrodysesthesia syndrome, stomatitis and other uncommon AEs).

At baseline, before starting LEN therapy, a dedicated cardiologist evaluated all patients, and HTN was scored by the CTCAE version v 5.0. During treatment, blood pressure (BP) values were checked daily at home and reported to the team by a dedicated Telegram account with titration of the anti-hypertensive treatment when needed (29). Moreover, BP was measured monthly during follow-up visits and, in some cases, with 24-h continuous pressure monitoring test. To note, the titration of the anti-hypertensive drugs and the variation of the therapeutic scheme, including the addition of other compound/s, were managed by the dedicated cardiologist with the aim to control BP without reducing the LEN dose. All patients underwent a follow-up electrocardiogram at baseline and every 1–3 months. If needed, additional tests were performed (echocardiogram, electrocardiogram and renal artery ultrasound). In all patients, proteinuria levels, creatinine clearance, electrolytes and thyroid function were assessed every 1–2 months.

Importantly, other potential causes of secondary HTN (pheochromocytoma, hyperaldosteronism, Cushing's syndrome and renovascular diseases) were always excluded.

Statistical analysis

We described quantitative data as mean ± standard deviation and median with range, depending on the normality of distribution (according to Shapiro–Wilk test). Categorical variables were expressed by the absolute number and percentage.

Statistical group comparisons were performed using the Mann–Whitney *U*-test and the Student's *t*-test for respective nonparametric and parametric continuous variables. Categorical variables were compared using the χ^2 test or the Fisher's exact test. We defined the *P*-value for statistical significance as <0.05.

PFS and overall survival (OS) were defined as the time between the date of LEN initiation and either progression disease, or death, or the date of the last follow-up visit. PFS and OS were evaluated using Kaplan–Meier curves with 95% confidence interval (CI). All statistical analyses were performed using MedCalc Statistical Software version 19.2.0 (MedCalc Software bvba, Ostend, Belgium).

The study was performed in accordance with the ethical standards of the Institutional Research Committee and with the 1964 Helsinki Declaration. All patients were enrolled in a protocol approved by the Ethical Committee of the Istituto Auxologico Italiano and provided informed consent to the use of their anonymised clinical data for research purposes (study code approval: 2022_03_08_03).

Results

Prevalence, timing and grade of HTN in patients treated with LEN

After a mean follow-up of 6.8 months (1–32 months), 22/29 patients developed HTN (76%): *de novo* occurrence in 14 and worsening of pre-existing HTN in 8 of them. According to CTCAE v.5.0, 1/22 (5%) had HTN of grade 1, 11/22 (50%) of grade 2 and 10/22 (45%) of grade 3 (Fig. 1, Table 2).

HTN was more frequent in patients treated with LEN doses >14 mg (89% vs 54%, $P=0.035$); linear regression analysis showed that the grade of HTN positively correlated with LEN dose ($P=0.011$) (Fig. 2A). To note, none of the patients developed ECG variations with respect to baseline during LEN treatment, with the exception of two patients who developed a grade 1 QTc elongation.

Correlation between HTN and other AEs

Among the 22 patients with LEN-induced HTN, 17 (77%) also had proteinuria (7/17 grade 1, 6/17 grade 2 and 4/17 grade 3). Nevertheless, no correlation was found between HTN grade and proteinuria grade ($P=0.187$) (Table 2, Fig. 2B). In particular, among the ten patients who developed a grade 3 HTN, four had grade 2, four had grade 1 proteinuria and two patients had no proteinuria Among the 11 patients who developed a grade 2 HTN, three had grade 1, two had grade 2, three had grade 3 proteinuria and three had no proteinuria. Finally, the only patient who developed grade 1 HTN had a grade 3 proteinuria. On the other hand, three of seven patients without HTN developed proteinuria (two grade 2 and one grade 1). Interestingly, 13/17 patients with proteinuria showed an improvement in the proteinuria grade during follow-up probably due to the effect of the anti-hypertensive medical drug used, such as ACE-i or angiotensin receptor blocker (ARB) (data not shown).

Among other LEN-related AEs, only diarrhoea correlated with the development of HTN ($P=0.025$) (Fig. 2B).

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Correlation between HTN, clinico-pathological features and tumour response to LEN

No significant differences were found between patients who developed or did not develop HTN as far as some clinical features such as gender, age at LEN start, ECOG status and American Joint Committee on Cancer (eighth edition)stage are concerned (Fig. 3). Interestingly, patients who developed HTN during LEN treatment did not have a significantly higher incidence of cardiovascular disease (pre-existing HTN and/or myocardial infarction and/or valvulopathies) prior to the start of the drug compared with patients who did not develop HTN (8 out of 22, 36% vs 5 out of 7, 71%; $P=0.104$) (Fig. 3). The best ORR to LEN treatment was not different between patients who developed or did not develop HTN. In particular, complete response, partial response and stable disease were observed in 0%, 64% and 18% of patients with HTN and in 0%, 86% and 14% of patients without HTN, respectively ($P=0.84$) (Fig. 3). To note, progressive disease was observed (18% of cases) only in the group of patients developing HTN. In addition, PFS was similar in patients developing or not developing HTN (hazard ratio, 0.43; 95% CI, 0.11–1.64; log-rank $P=0.2175$). Similarly, OS was not different among the two groups (log-rank $P=0.150$).

Treatment management of HTN during LEN

After evaluation by a dedicated cardiologist, medical therapy was introduced in the 13/14 patients who developed a *de novo* HTN. One patient has a grade 1 HTN (#14, Table 2), and no treatment has been started to date. In seven cases, the first drug was a CCB, alone (four cases) or in combination with an ACE-i (two cases) or with a BB (one case). HTN was well controlled with CCB alone (one case), CCB+BB (one case) or after the introduction of other drugs such as ARB+diuretic (D) (two cases),

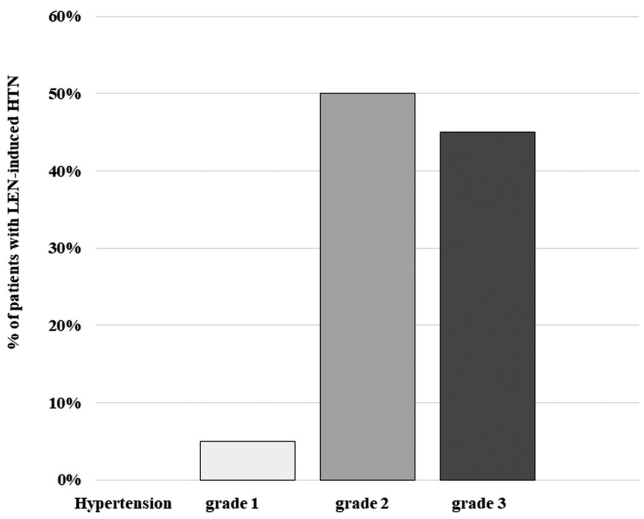

Figure 1
Prevalence and grade of hypertension (HTN) in patients treated with lenvatinib (LEN). 22/29 patients developed HTN during treatment. Considering severity according to Common Terminology Criteria for Adverse Events (CTCAE) v.5.0, 1/22 (5%) had HTN of grade 1, 11/22 (50%) of grade 2 and 10/22 (45%) of grade 3.

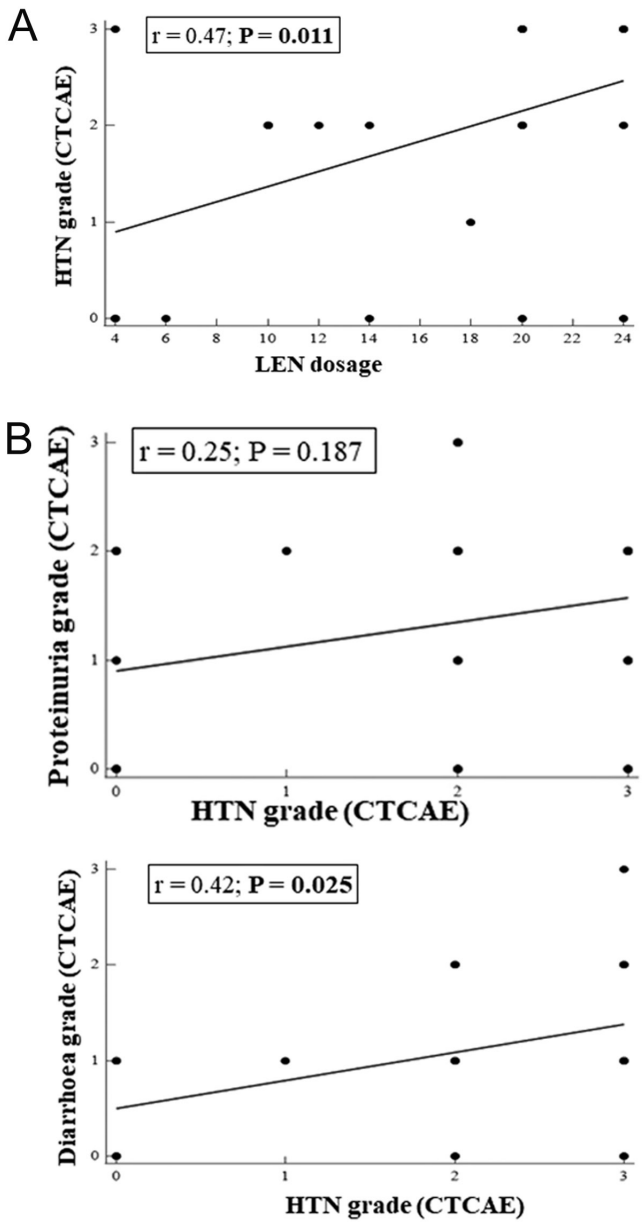

Figure 2
(A) Correlation between hypertension (HTN) and lenvatinib (LEN) dosage. Linear regression analysis showed that the grade of HTN positively correlated with LEN dose ($P=0.011$). (B) Correlation between HTN, proteinuria and diarrhoea during treatment with LEN. There was no significant correlation between HTN and proteinuria ($P=0.187$), while LEN-induced HTN had a significant positive correlation with diarrhoea ($P=0.025$).

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ACE-i (two cases) or more than three compounds (one case). In four cases, the first drug introduced was an ACE-i associated or not with BB, in one case the first drug was a BB and in the remaining case the initial treatment was ARB + D. In these last six cases, HTN was not controlled and CCB was always introduced, alone or in combination with other compounds.

The eight patients who had HTN before the start of LEN treatment were on anti-hypertensive treatment with different drugs in monotherapy or polytherapy. One patient remained well controlled without changing treatment (#4, Table 2), while in seven cases CCB was introduced or increased alone or in association with other compounds such as BB, ARB, alpha-blockers and D, obtaining HTN control in all but one case (#21, Table 2).

Considering the whole cohort of 22 cases who developed HTN or experienced a worsening of a pre-existing HTN, we can summarise as follows: (a) 21/22 (95%) patients were on anti-hypertensive treatment: 1/21 in monotherapy and 20/21 in polytherapy; (b) the only patient in monotherapy was on CCB; (c) four of five patients treated with two drugs were well controlled with CCB + ACE-i/BB (three cases) or with ACE-i/BB (one case); (d) nine of ten patients controlled with three drugs were on CCB + ARB/ACE-i + and other drug; (e) only three of five patients treated with more than four drugs were controlled (Fig. 4, panel A). We recorded an adequate BP response in 18/21 patients (86%) and an improvement of proteinuria in 12/17 (71%). No patient had to reduce or discontinue LEN treatment due to HTN.

CCBs were the most common drugs, used in 17/21 patients, either in monotherapy (5% of cases) or, in case of poor BP control, in association with other anti-hypertensive drugs as ACE-i or BB (14%), with ARB/ACE-i + other anti-hypertensive drug (43%) or with a total of four anti-hypertensive drugs in 24% of patients (Fig. 4, panel B). We preferred to use dihydropyridine CCB (e.g. amlodipine), rather than non-dihydropyridine CCB (e.g. verapamil), considering the high risk of drug interaction of the latter.

Based on the data above reported, we have drawn a flow chart for the strategic management of HTN during LEN (Fig. 5). In particular, CCB is suggested as first-line treatment. In case of proteinuria, ACE-i or ARB can be the first choice or the drugs to be added to CCB.

Discussion

In the present RL series of patients with advanced thyroid cancer on LEN treatment, a 76% incidence of HTN was recorded with a mean onset of 6.8 months (range 1–32 months) after the start of treatment. These data are in accordance with the average HTN incidence of 72.4% reported in the RL studies available to date (10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23). HTN is the most common AE observed during treatment with MKIs and is frequently of grade ≥3 (45% of patients in the present series and 41.8% in the SELECT trial), warranting a prompt treatment in order not to worsen possible underlying

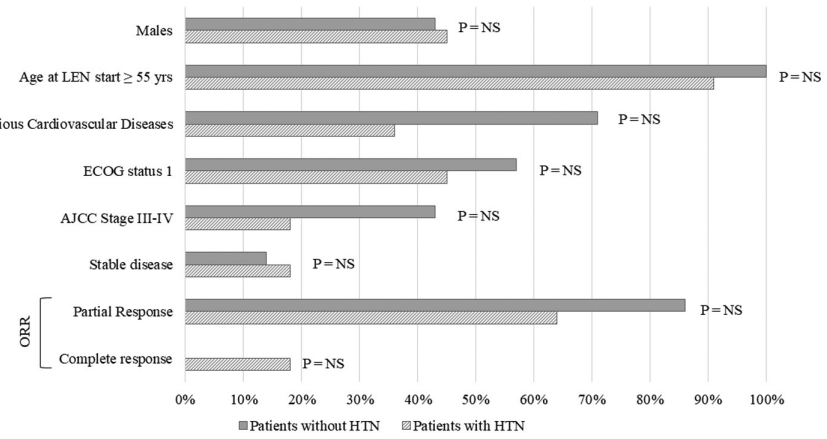

Figure 3
Patients who developed hypertension (HTN) during lenvatinib (LEN) treatment did not have a significant higher prevalence of cardiovascular disease (pre-existing HTN and/or myocardial infarction and/or valvulopathies) prior to the start of the drug compared with patients who did not develop HTN (8 out of 22, 36% vs 5 out of 7, 71%; $P = 0.104$). A response to LEN treatment (measured according to RECIST criteria) was not different between patients who developed or did not develop HTN (82% and 100%, respectively). In particular, complete response, partial response and stable disease were observed in 0%, 64% and 18% of patients with HTN and in 0%, 86% and 14% of patients without HTN, respectively ($P = $ NS). In addition, there was no significant correlation between HTN and other clinico-pathological features analysed. AJCC, American Joint Committee on Cancer eighth edition staging system; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; NS, not significant.

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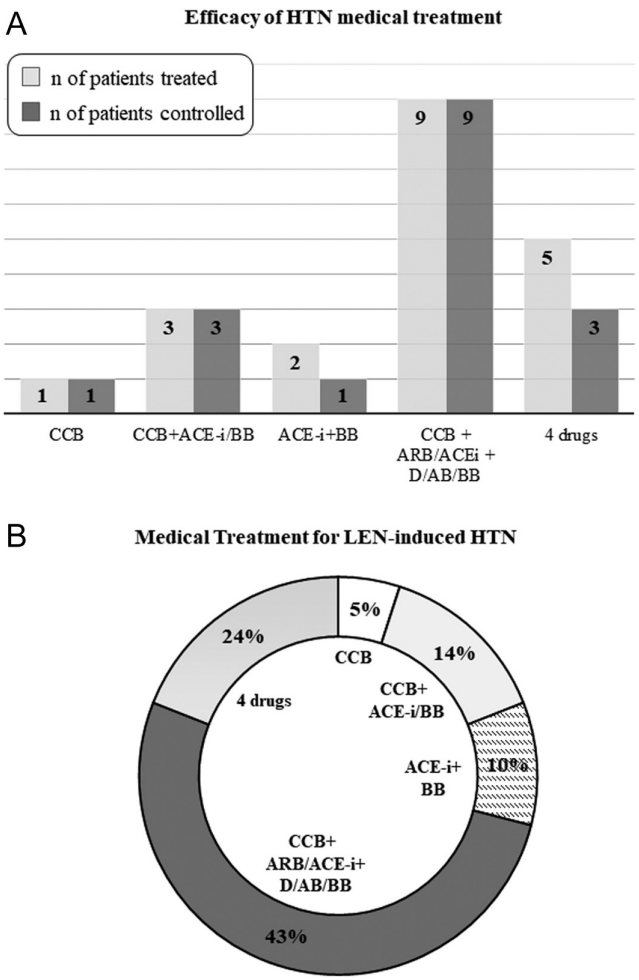

Figure 4
Panel A: (a) 21/22 (95%) patients were on anti-hypertensive treatment: 1/21 in monotherapy and 20/21 in polytherapy; (b) the only patient in monotherapy was on calcium channel blocker (CCB); (c) four of five patients treated with two drugs were well controlled with CCB + angiotensin-converting inhibitor (ACE-i)/beta-blocker (BB) (three cases) or with ACE-i/BB (one case); (d) nine of ten patients controlled with three drugs were on CCB + angiotensin receptor blocker (ARB)/ACE-i and other drug; (e) only three of five patients treated with more than four drugs were controlled. Panel B: CCBs were the most common drugs, used in 17/21 patients, either in monotherapy (5% of cases) or, in case of poor pressure control, in association with other anti-hypertensive drugs as ACE-i or BB (14%), with ARB/ACE-i + other anti-hypertensive drug (43%) or with a total of four anti-hypertensive drugs in 24% of patients.

cardiovascular disease and not to reduce or discontinue the anti-tumoural treatment (1, 2, 3). Interestingly, in our series of patients treated with doses ranging 4–24 mg/day, HTN incidence and grade were positively correlated to LEN dosage. A similar result, though not reaching statistical significance, was found in the randomised study aimed to compare the efficacy and safety of LEN 24 mg vs 18 mg/day (23). On the other hand, no correlation was found with ORR or PFS or OS, differently from previous data reporting a better ORR and PFS in patients developing HTN, included in the SELECT trial (34). The reasons for these discrepancies may lie in the different characteristics of the two cohorts. In particular, the present study has a lower number of patients but is RL and monocentric, with patients starting with different LEN dosages and followed by a dedicated cardiologist.

Although the majority of our patients also developed proteinuria during LEN treatment, no correlation was found between its grade and that of HTN, confirming that the mechanisms by which MKI induce HTN and proteinuria are different, as hypothesised in a recent review which evaluated literature data regarding MKI treatment and nephrotoxicity (35). Moreover, it is interesting to note that patients with or without pre-existing HTN or any other cardiovascular disease (including myocardial infarction and valvulopathies) had a similar incidence of HTN during LEN, confirming that the underlying mechanisms are probably related exclusively to the anti-angiogenic drug. The causes of MKI-induced HTN are still unknown, but some hypotheses pointed to the fact that MKIs, through the inhibition of VEGF-R, reduce the synthesis of nitric oxide, leading to vasoconstriction and, hence, HTN (36). Interestingly, the inhibition of microcirculation in the gastrointestinal tract seems to contribute to the development of diarrhoea (37), which is the only AE correlated with HTN in the present series, suggesting a possible common pathogenesis. Based on the above-mentioned hypothesis, CCB, whose effect on vascular smooth muscle leads to vasodilation, was the most frequently used drug, alone (5% of cases) or in combination with one or two additional drugs (15% and 49%, respectively). The most frequent association was with ACE-i or ARB, due to the effect of these drugs on proteinuria, which was frequent in our cohort. The lack of correlation with HTN seems to indicate that proteinuria is directly induced by LEN treatment through a still unknown mechanism.

The accurate cardiological evaluation, both at baseline and during LEN treatment, was crucial in assessing HTN and in choosing the best personalised medical therapy, as reported in our flow chart for the strategic management of HTN during LEN. Although four different drugs were needed in 20% of cases, up to 75% of patients reached the BP control with the administration of two or three compounds. As a whole, we had adequate control of HTN in 19/22 patients (86%), improving compliance to LEN treatment, avoiding

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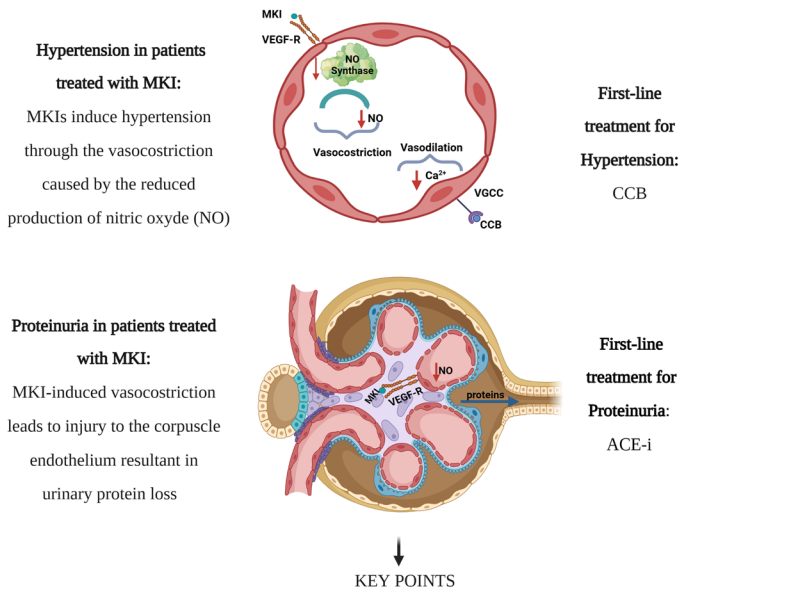

Figure 5
Graphical illustrations of the potential mechanisms underlying multityrosine kinase inhibitor (MKI)-induced hypertension (HTN) and proteinuria and the deriving suggested treatments in patients developing these adverse events. In addition, a diagnostic and therapeutic algorithm is suggested to be applied in clinical practice in the management of patients with MKI-induced HTN. AB, alpha-blockers; ACE-i, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BP, blood pressure; Ca, calcium; CCB, calcium channel blockers; D, diuretics; NO, nitric oxide; VEGF, vascular endothelial growth factor; VGCC, voltage-gated calcium channels.

dosage reductions or drug discontinuation and reducing patients' cardiovascular risk.

Conclusions

HTN is the most frequent AE in patients treated with LEN, and in the present series its incidence and grade correlated with LEN dosage. An accurate cardiological evaluation and optimised medical therapy are crucial for the best management of this AE. CCBs should be always included in the therapeutic scheme, due to the vasodilation effect, and the association with ACE-i/ARBs has been shown to be frequently effective.

Declaration of interest
LF is a consultant for Eisai, Ipsen and Lilly. The remaining authors have nothing to disclose.

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Author contribution statement
CC, DC: Conceptualisation, data collection, formal analysis, writing and editing; SDL, MT, NG, CM: Data collection, formal analysis and editing; GB: Data collection and editing; GP, LP: supervision; LF: Conceptualisation, supervision and writing. All the authors were responsible for the final approval of the article.

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