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RESEARCH

Impact of systemic treatments for advanced thyroid cancer on the adrenal cortex

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Abstract

Background: Fatigue is a frequent adverse event during systemic treatments for advanced thyroid cancer, often leading to reduction, interruption, or discontinuation. We were the first group to demonstrate a correlation between fatigue and primary adrenal insufficiency (PAI).

Aim: The objective was to assess the entire adrenal function in patients on systemic treatments.

Methods: ACTH, cortisol and all the hormones produced by the adrenal gland were evaluated monthly in 36 patients (25 on lenvatinib, six on vandetanib, and five on selpercatinib). ACTH stimulation tests were performed in 26 cases.

Results: After a median treatment period of 7 months, we observed an increase in ACTH values in 80–100% of patients and an impaired cortisol response to the ACTH test in 19% of cases. Additionally, dehydroepiandrosterone sulphate, Δ-4-androstenedione and 17-OH progesterone levels were below the median of normal values in the majority of patients regardless of the drug used. Testosterone in females and oestradiol in males were below the median of normal values in the majority of patients on lenvatinib and vandetanib. Finally, aldosterone was below the median of the normal values in most cases, whilst renin levels were normal. Metanephrines and normetanephrines were always within the normal range. Replacement therapy with cortisone acetate improved fatigue in 14/17 (82%) patients with PAI.

Conclusion: Our data confirm that systemic treatments for advanced thyroid cancer can lead to impaired cortisol secretion. A reduction in the other hormones secreted by the adrenal cortex has been first reported and should be considered in the more appropriate management of these fragile patients.

Keywords: adrenal; aldosterone; hypoadrenalism; MKIs; thyroid cancer

Introduction

Tyrosine kinase inhibitors (TKIs) and target therapies are efficiently used in the treatment of progressive radioiodine-refractory differentiated thyroid cancer (RAI-R DTC) and advanced medullary thyroid cancer (MTC) (1).

In Europe, the multikinase inhibitors sorafenib, lenvatinib (LEN) and cabozantinib have been approved for RAI-R DTC, vandetanib (VAN) and cabozantinib for MTC, and the gene-targeted selpercatinib (SELP) and larotrectinib for cancers harbouring rearranged during

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transfection (RET) proto-oncogene alterations and neurotrophic tyrosine receptor kinase (NTRK) fusions, respectively (2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12).

These drugs, along with remarkable efficacy, display several adverse events (AEs) (13), including fatigue and its related significant impact on quality of life being one of the most frequent. Notably, fatigue has been reported in the registration studies in 59%, 24% and 25% of patients treated with LEN, VAN and SELP, respectively, and often leads to treatment discontinuation or withdrawal with a possible reduction in efficacy and in progression-free survival (PFS) (14, 15).

In 2018, for the first time, we demonstrated a correlation between fatigue and primary adrenal insufficiency (PAI) in 12 patients treated with LEN and VAN (16). Specifically, we showed a progressive increase in ACTH with normal cortisol levels and an impaired response to the ACTH stimulation test. In those patients, cortisone acetate (CA) replacement therapy was able to significantly improve fatigue and quality of life. Our data were further confirmed by two other Italian studies and by a real-world post-marketing analysis based on the Food and Drug Administration Adverse Event Reporting System (FAERS) (17, 18, 19). However, to date, no clinical trials or real-life studies have confirmed these findings in patients treated with targeted therapies (20).

Our aim was to get more insights into adrenal toxicity induced by systemic treatments, extending the evaluation to the entire hormonal production of the adrenal glands (both cortex and medulla) in a monocentric series of patients treated with LEN and VAN and with RET-targeted drug, SELP.

Methods

Patients

The study was performed in accordance with the ethical standards of the Institutional Research Committee and with the 1964 Helsinki Declaration. All patients were enroled 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).

In particular, written consent was obtained from each patient after a full explanation of the purpose and nature of all procedures used.

We enroled 36 consecutive patients with advanced RAI-R DTC and MTC treated with LEN ($n = 25$), VAN ($n = 6$) and SELP ($n = 5$) and followed up for a mean time of 43.2 months (range: 6–180) at a single tertiary institution. The 12 patients reported in our previous study (16) are included in the present series.

Thirty-one out of 36 patients were MKIs-naive, and 5 out of 36 were on second-line treatment, as patients on SELP were previously treated with VAN. The clinical–pathological features and treatment details are reported in Table 1. Eastern Cooperative Oncology Group (ECOG) performance status was assessed at the start of treatment with LEN, VAN or SELP. AEs, including fatigue, were scored by the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. During follow-up, for each AE, we considered the worst CTCAE grade developed by patients during treatment.

None of the patients reported fatigue before treatment and/or had potentially fatigue-determining comorbidities (anaemia, renal or liver failure, other malignancies, depressive syndrome, etc.) and/or were on treatment with drugs potentially leading to fatigue (e.g. antipsychotics). L-thyroxine dosage was titrated to maintain TSH levels below the normal limit (0.01–0.1 mU/L) in patients treated for RAI-R DTC either before or during antineoplastic treatment. In patients with advanced MTC, TSH levels were maintained in the normal range (0.5–2 mU/L).

Whole-body CT scan and/or whole-body 18F-fluorodeoxy-glucose (FDG) or 18F-dihydroxyphenylalanine (DOPA) PET/CT were performed to assess disease response to treatment. Tumour response (defined as the best morphological response (BMR)) was evaluated according to the revised Response Evaluation Criteria in Solid Tumours (RECIST) guidelines version 1.1 (21).

With the aim to find possible alterations leading to adrenal glands impairment (such as adrenal haemorrhage), the revision of the CT scans performed during the follow-up was done by expert radiologists in all patients who developed PAI. Finally, adrenal autoantibodies were tested in all patients to exclude autoimmune adrenal insufficiency.

Adrenal function evaluation

All patients were submitted to a fasting ACTH and cortisol evaluation at 8:00–9:00 h, both before starting treatment with LEN/VAN/SELP in 13/36 (basal evaluation) and during the follow-up (36/36). No patient received glucocorticoids before and during the study, and patients on replacement treatment took CA after blood sampling. In order to confirm a possible PAI, patients who developed an ACTH elevation during treatment were submitted to a 250 µg ACTH stimulation test (synacthen test), which is considered the gold standard for establishing the diagnosis of PAI (22).

Current guidelines consider a peak cortisol level > 18.1 µg/dL (500 nmol/L) at 30 or 60 min after ACTH injection as appropriate, allowing for the exclusion of PAI (22). Nevertheless, since cortisol assays have recently become more sensitive and a new cutoff of 15 µg/dL has been proposed (23, 24, 25), we calculated the prevalence of PAI accordingly.

To avoid false-positive and/or false-negative results for renin and aldosterone measurement, patients withdrew any anti-hypertensive drugs before being tested. Aldosterone antagonists, other potassium-sparing

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Table 1 Clinical features of the 36 patients treated with lenvatinib, vandetanib, selpercatinib, evaluated for adrenal function.

Patient		Age (years)				ECOG	TKI treatment				
ID	M/F	Diagnosis	TKI start	Histotype	TNM/AJCC stage	status	TKI	Dose, mg	Duration, months	Adverse events (CTCAE v 5.0 grade)	BMR
#1	F	36	39	FTC	pT3bNXMX/I	1	LEN	20 → 14	36	Fatigue (2), weight loss (3), hypertension (3), diarrhoea (3), anorexia (3), stomatitis (2), nausea (3), proteinuria (2)	PD
#2	F	21	28	sMTC	pT3N1bM1/II	0	VAN	300	70	Rash maculo-papular (1), fatigue (1), diarrhoea (1)	PR
#3	F	79	79	PTC	pT3bNXMX/II	1	LEN	10	22	Fatigue (3), weight loss (3), hypertension (3), diarrhoea (1), anorexia (3), stomatitis (1), nausea (3), proteinuria (3)	PR
#4	F	33	75	CPTC	T2N1aMX/I	1	LEN	10	74	Hypertension (3), diarrhoea (2), stomatitis (3), fatigue (1), nausea (1), haemorrhoids (2)	PR
#5	F	42	58	FTC	pT2NXM0/I	0	LEN	17	82	Hypertension (3), fatigue (2), diarrhoea (2), anorexia (1), palmar-plantar erythrodysesthesia syndrome (1), stomatitis (1), haemorrhoids (3)	PR
#6	F	45	65	PTC	pT3bN1aMX/I	1	LEN	4	11	Fatigue (1), hypertension (3), diarrhoea (1), stomatitis (1), proteinuria (1)	SD
#7	F	57	73	PTC	pT3bNXMX/II	1	LEN	10	29	Fatigue (2), weight loss (3), hypertension (3), diarrhoea (1), anorexia (3), stomatitis (2), proteinuria (3)	SD
#8	M	64	67	PTC	pT3bN1bMX/II	0	LEN	14	20	Fatigue (2), stomatits (1)	PR
#9	F	8	9	MTC/MEN2B	pT4aN1bM1/II	0	VAN	300 → 200	180	Fatigue (2), weight loss (1)	SD
#10	F	78	90	PTC	pT4aN1bMX/III	1	LEN	4	11	Fatigue (1)	PR
#11	M	65	65	FTC	M1/IVb	1	LEN	20 → 10	32	Fatigue (2), weight loss (3), diarrhoea (2), anorexia (2), palmar-plantar erythrodysesthesia syndrome (2), stomatitis (1), nausea (2)	SD
#12	M	85	85	NA	[a]M1/IVb	1	LEN	4 → 10	11	Fatigue (1), anorexia (1)	PR
#13	F	67	69	sMTC	pT2N0MX/I	1	VAN	300	23	Fatigue (2), nausea (1), diarrhoea (1), proteinuria (1), hypertension (2)	PR
#14	M	50	66	PTC	pT2NXMX/I	1	LEN	20 → 14	48	Fatigue (1), weight loss (2), hypertension (2), diarrhoea (2), anorexia (1), nausea (1), cholecystitis, dysphonia	SD
#15	M	67	68	FTC	pT4bNXM1/IVb	0	LEN	20	70	Hypertension (3), stomatitis (2), dysgeusia (1), weight loss (1)	PR
#16	M	58	60	HCC	pT3aNXMX/II	1	LEN	20 → 10	43	Fatigue (1), weight loss (3), hypertension (2), diarrhoea (1), anorexia (1), nausea (1), proteinuria (2), cholecystitis	PD
#17	M	60	73	PTC	pT3bN1aMX/II	0	LEN	12	19	Fatigue (2), hypertension (1), diarrhoea (1/2), anorexia (2), palmar-plantar erythrodysesthesia syndrome (3), stomatitis (2), proteinuria (1)	PR
#18	F	79	84	FTC	pT3aNXMX/II	1	LEN	4	58	Fatigue (2), weight loss (2), hypertension (2), anorexia (1), proteinuria (1)	PR
#19	M	19	21	FTC	pT3N1bM0/I	0	LEN	18	65	Fatigue (1), hypertension (1), diarrhoea (1)	PR

(Continued)

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Table 1 Continued.

Patient		Age (years)				ECOG	TKI treatment				
ID	M/F	Diagnosis	TKI start	Histotype	TNM/AJCC stage	status	TKI	Dose, mg	Duration, months	Adverse events (CTCAE v 5.0 grade)	BMR
#20	F	74	76	PDTC	pT3bN1aMX/II	1	LEN	10	39	Fatigue (2), weight loss (2), hypertension (2), stomatitis (2)	PR
#21	M	58	60	HCC	pT3aNXMX/II	1	LEN	20 → 10	64	Fatigue (1), weight loss (3), hypertension (2), diarrhoea (1), anorexia (1), nausea (1), proteinuria (2), cholecystitis	SD
#22	M	71	73	PTC	pT3bN1bMX/II	1	LEN	20 → 14	19	Fatigue (1), weight loss (1), hypertension (3), anorexia (1), proteinuria (1)	PR
#23	M	84	85	sMTC	[a]M1/IVb	1	SELP	120 → 80	14	Hypertension (1), proteinuria (1)	SD
#24	M	51	58	PTC	pT4aN1aM0/I	0	LEN	24	74	Fatigue (2), diarrhoea (1), weight loss (1), anorexia (1), proteinuria (1), palmar-plantar erythrodysesthesia syndrome (1)	PR
#25	M	9	20	MTC/MEN2B	pT4N1bM0/II	0	VAN	300 → 200 → 100	103	Fatigue (1), diarrhoea (1), QTc prolongation (2)	SD
#26	F	72	76	sMTC	pT2N1bMX/II	1	VAN	300 → 200 → 100	97	Fatigue (1), anorexia (1), QTc prolongation (2)	PR
#27	F	49	55	FTC	TXNXM1/II	0	LEN	24	65	Hypertension (3), fatigue (2), weight loss (3), diarrhoea (1), anorexia (1), stomatitis (3), nausea (1), proteinuria (1), cholecystitis	SD
#28	M	51	58	PDTC	pT1bNXMX/I	0	LEN	24	8	Hypertension (1)	PR
#29	M	46	63	sMTC	pT4N1bM1/II	1	VAN	100	44	Fatigue (2), diarrhoea (3), anorexia (1)	SD
#30	F	63	74	PDTC	pT3NXM0/II	1	LEN	20 → 10	39	Hypertension (3), fatigue (2), diarrhoea (1), weight loss (1), anorexia (1), proteinuria (2), reversible posterior leukoencephalopathy (3)	PR
#31	F	71	72	CPTC	pT3NXM0/II	1	LEN	10	25	Hypertension (2), fatigue (3), diarrhoea (2), Anorexia (1), Skin ulceration (2), arthralgia (1), hoarseness (1), dysgeusia (1)	PR
#32	F	75	75	PDTC	pT4aN1bM1/IVb	1	LEN	20 → 10	6	Hypertension (3), fatigue (1)	PD
#33	F	49	49	MTC/MEN2A	pT3aN1bMX/II	0	SELP	80	10	Diarrhoea (1), rash (1), fatigue (1), AST/ALT increase (1), nausea (1), vomiting (1), hypertension (2), weight loss (2), anaemia (1), constipation (1), proteinuria (1)	CR
#34	M	55	56	sMTC	pT4aN1bM0/III	0	SELP	320	24	Haemoglobin increase (3), ALP increase (1), diarrhoea (2), fatigue (1), hypothyroidism (2), weight loss (1)	CR
#35	F	56	60	sMTC	pT2N1aMX/II	0	SELP	320 → 80	18	Hypertension (2), ALP increase (2), AST/ALT increase (3), blood bilirubin increase (1), hypothyroidism (2)	PR
#36	F	45	45	sMTC	[a]M1/IVb	0	SELP	320	6	Hypertension (2), ALP increase (1)	PR

[a]Patients with unresectable tumour.

AJCC 8th edition staging system; BMR, best morphological response; CPTC, papillary thyroid cancer classic variant; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; FTC, follicular thyroid cancer; HCC, Hürthle cell carcinoma; LN, lymph nodes; LEN, lenvatinib; M/F, male/female; MEN, multiple endocrine neoplasia syndromes; PDTC, poorly differentiated thyroid cancer; PTC, papillary thyroid cancer; PR, partial response; PD, progressive disease; SELP, selpercatinib; SD, stable disease; sMTC, sporadic medullary thyroid carcinoma; VAN, vandetanib.

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diuretics and potassium-wasting diuretics were withdrawn for at least 4 weeks, while beta-blockers, angiotensin-converting inhibitors, angiotensin receptor blockers, and dihydropyridine calcium antagonists for at least 2 weeks (26, 27). To maintain proper blood pressure control, all interfering antihypertensive drugs were replaced with those that do not interfere with the secretion of renin and aldosterone, such as non-dihydropyridine calcium channel antagonists (e.g. verapamil) and α-adrenergic blockers (e.g. doxazosin) (26). Patients with uncontrolled and severe hypertension (CTCAE grade >3) were not tested (27).

Given the differential production of sex hormones by the adrenals and gonads in both sexes, and to minimise hormonal secretion due to the gonads, we evaluated Δ4 androstenedione (Δ4) and dehydroepiandrosterone sulphate (DHEA-S) in both females and males, 17-hydroxyprogesterone (17-OHP) in males and post-menopausal women, estradiol (E2) in men and testosterone in postmenopausal women.

Before urine collection for the assessment of 24-h urinary fractionated metanephrines, all patients avoided catecholamine-rich foods and interfering drugs (proton pump inhibitors, diuretics, etc.) for at least 3 days (28).

Analytical methods

Serum cortisol (normal value (NV): 5–25 µg/dL), ACTH (NV: 8–50 ng/L), DHEA-S (NV – males: 0.8–5.6 mg/L; females: 0.35–4.30 mg/L), E2 (NV – males: 41.4–159 pmol/L; post-menopause females: 18.4–505 pmol/L; females during fertile age: 45.8–854 pmol/L) and testosterone (NV – males: 9.9–27.8 nmol/L; females: 0.2–2.86 nmol/L) were assayed respectively with Elecsys® cortisol II, ACTH, DHEA-S, oestradiol III and testosterone II ECLIA immunoassays (Roche Diagnostics). Serum 17-OHP (NV – males: 0.32–3.32 µg/L; females during menopause: 0.32–2.72 µg/L; females during fertile age: 0.65–1.91 µg/L), aldosterone (NV: 3.7–21.4 ng/dL) and renin (NV: 4.4–46.1 mU/L) were assayed respectively with IDS-iSYS 17-OHP, aldosterone and renin CLIA immunoassays (Immunodiagnostic Systems, IDS®). Serum Δ4 (NV – males: 0.2–3.10 µg/L; females: 0.3–1.8 µg/L) was assayed with LIAISON® Androstenedione CLIA immunoassays (DiaSorin Inc. 1951, MN, USA). Measurement of 24-h urinary fractionated metanephrines was done by HPLC (Agilent Technologies). Adrenal autoantibodies were determined by an indirect immunofluorescence assay targeted on adrenal tissue (Werfen, Le Pré-Saint-Gervais, France).

For all the analytes, along with the normal values, the median and 5th percentile levels were considered, as reported in the data sheets.

Statistical analysis

We described quantitative data as mean ± S.D. and median with range, depending on 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. Continuous variable associations were assessed by Pearson correlation test and rank correlation tests for respective parametric and nonparametric data. We defined the *P*-value for statistical significance as <0.05.

All statistical analyses were performed using MedCalc Statistical Software version 19.2.0 (MedCalc Software bvba, Ostend, Belgium).

Results

Primary adrenal insufficiency during LEN, VAN and SELP treatment

Thirty-one out of 36 patients (86%) developed fatigue during systemic treatment: 15 of grade 1, 14 of grade 2 and two patients of grade 3 (Table 1). In particular, there were 23 out of 25 patients on LEN, all the six patients on VAN, and two out of the five cases on SELP.

The ACTH stimulation test was performed in 26 patients, and an impaired response <15 µg/dL was recorded in 5/26 patients (19%): 3/18 (17%) on LEN, 2/6 (33%) on VAN and 0/2 (0%) on SELP (Table 2, Fig. 1, Supplementary Table 1, see section on supplementary materials given at the end of this article). Moreover, a significant negative linear correlation was found between ACTH during the stimulation test and cortisol at 30 and 60 min ($P = 0.001$ and $P < 0.001$, respectively). At baseline, ACTH and cortisol levels had a linear inverse correlation with a tendency towards significance ($P = 0.2$). Of note, above ACTH > 100 ng/L, basal cortisol levels were progressively lower (Supplementary Fig. 1).

An ACTH increase above the normal range (normal value 8–50 ng/L), with normal cortisol levels, was found in 21 patients on LEN, in six patients on VAN and in four patients on SELP (Table 2, Fig. 2A), with a mean increase of 391% (range: 0–2021%, not shown). The mean ACTH level during treatment was 154.4 ng/L (range: 10.8–326 ng/L) (Fig. 2B).

The ACTH increase was observed after a mean time of 7 months (range: 1–47) from the start of the systemic treatment. Interestingly, patients treated with MKIs (LEN + VAN) showed an earlier onset of ACTH increase compared to SELP patients (50% vs 20% of patients, at 3 months) (Fig. 3A). The rate of patients with increased ACTH levels progressively rose to 55% and 60% at 6 months and 75% and 60% at 12 months, for MKIs and SELP, respectively. The mean increase in ACTH at 12 months with respect to basal levels was higher in patients treated with MKIs than in those on SELP, namely from 53 to 116 ng/L and from 39 to 45 ng/L, respectively (Fig. 3B).

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Table 2 Results of adrenal function evaluation in 36 patients receiving TKIs treatment for advanced thyroid cancer.

	All patients (*n* = 36)	Lenvatinib (*n* = 25)	Vandetanib (*n* = 6)	Selpercatinib (*n* = 5)
Patients who developed fatigue	31/36, 86%	23/25, 92%	6/6, 100%	2/5, 40%
Patients analysed for cortical adrenal function	27/36, 75%	18/25, 72%	5/6, 83%	4/5, 80%
Patients analysed for medullary adrenal function	17/36, 47%	10/25, 40%	5/6, 83%	2/5, 40%
Patients with ACTH elevation during TKI treatment	31/36, 86%	21/25, 84%	6/6, 100%	4/5, 80%
Patients with cortisol levels <15 µg/dL after ACTH stimulation test/ ACTH test performed	5/26, 19%	3/18, 17%	2/6, 33%	0/2, 0%
Patients in CA treatment for proven adrenal insufficiency	10/10, 100%	7/7, 100%	3/3, 100%	0/0, 0%
Patients in CA treatment for fatigue and ACTH elevation	7/21, 33%	7/14, 50%	0/3, 0%	0/4, 0%
Patients with reduced fatigue after CA treatment	14/17, 82%	11/14, 79%	3/3, 100%	0/0, 0%

ACTH, adrenocorticotropic hormone; CA, cortisone acetate; TKI, tyrosine kinase inhibitor.

The mean basal cortisol values during systemic treatment were all within the normal range, with values below the median of the normal range in 60% of patients on LEN and SELP and in 33% of patients on VAN. Only 1/36 patients showed basal cortisol values below the 5th percentile (Table 3).

In the subgroup of LEN patients, neither the main clinical–pathological features nor the drug dosage significantly correlated with the presence/absence or degree of adreno-cortical impairment (data not shown). On the other hand, grade >3 AEs were significantly more frequent in patients with increased ACTH levels, associated or not with impaired response to the ACTH test, compared to the cases with preserved adrenal function ($P = 0.01$, data not shown).

Serum sodium and potassium levels were mostly within the normal range: median sodium values were 142 mmol/L (range: 130–148, NV: 136–145 mmol/L) and median potassium values were 4.35 mmol/L (range: 3–5.2, NV: 3.5–5.5 mmol/L). Adrenal autoantibodies were negative in all patients, and no morphological adrenal abnormalities were detected at the CT scans.

Sexual hormones during LEN, VAN and SELP treatment

Levels of androgens, oestradiol and 17-OH progesterone in males and females during treatment are reported in Table 3.

DHEA-S levels were below the lower reference limit (LRL) in 53% of patients on LEN and in 20% of patients on VAN or SELP. If we consider the median levels, lower levels were detected in 82% of patients on LEN and in 60% of cases on VAN or SELP. Levels below the 5th percentile were found in 59%, 20% and 20% of patients on LEN, VAN and SELP, respectively (Fig. 4A).

Androstenedione levels were in the normal range in 87%, 100% and 80% of the patients on LEN, VAN and SELP, respectively. Nevertheless, levels were below the median levels of the reference range in 87% of LEN patients (44% below the 5th percentile) and in 60% of patients on VAN and SELP (Table 3 and Fig. 4B).

Similarly, 17-OH progesterone levels were in the normal range in the majority of cases but below the median levels in all patients on LEN (43% below the 5th percentile), VAN (66% below the 5th percentile) and in

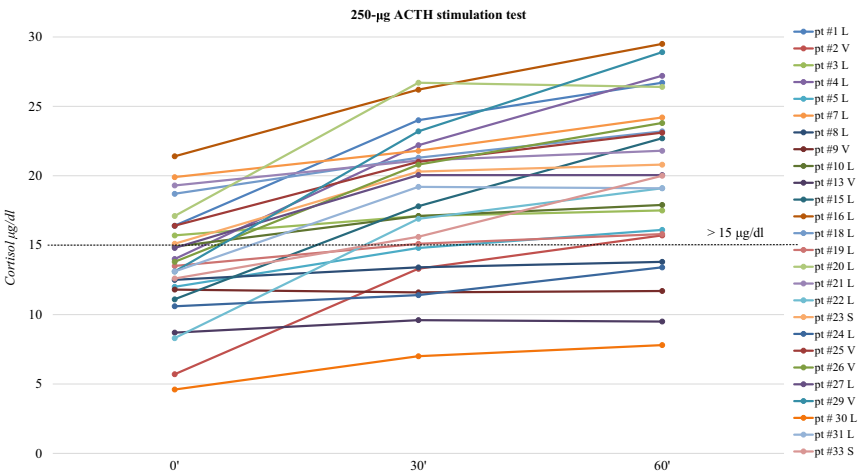

Figure 1

Cortisol levels at baseline and at 30 and 60 min after stimulation test performed through infusion of 250 µg ACTH in 26/36 patients (18 LENV, 6 VAND and 2 SELP). Peak cortisol levels <15 µg/dL (dotted line) at 30 or 60 min indicate primary adrenal insufficiency, according to new cut-off proposed for new cortisol assays (23, 24, 25). Cortisol response to the ACTH 250 µg stimulation test was reduced in 5/26 patients (19%): 3/18 (17%) on lvatinib and 2/6 (33%) on vandetanib. No patients in SELP treatment had a reduced response after ACTH stimulation. ACTH, adrenocorticotropic hormone; p #, patient ID; L, lenvatinib; V, vandetanib; S, selpercatinib.

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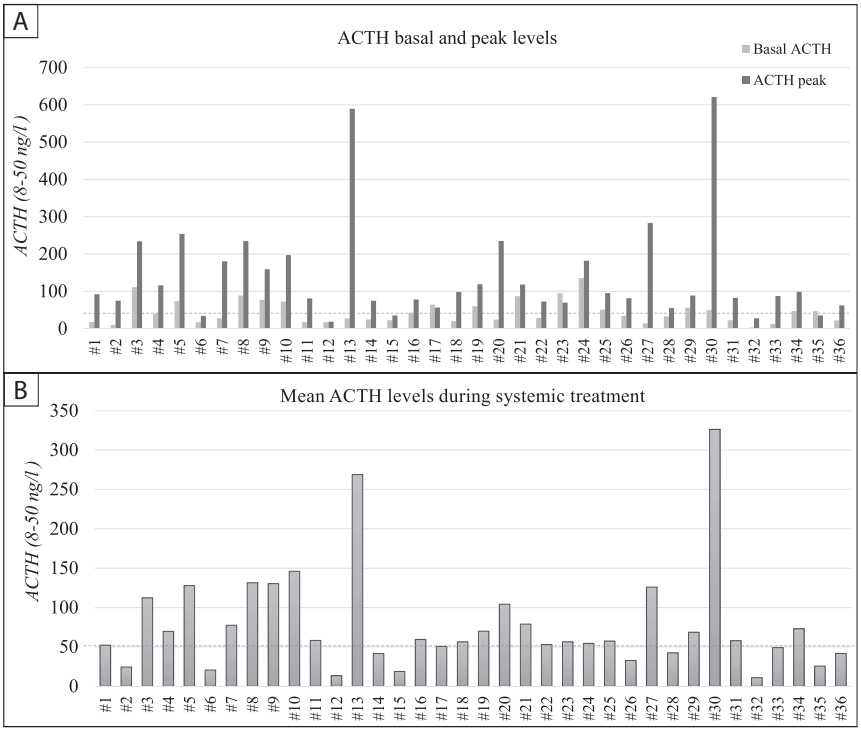

Figure 2

(A) Peak ACTH levels reached during systemic therapy compared to basal ACTH level in the 36 patients analysed. (B) Mean values of serum ACTH during systemic treatment in the 36 patients analysed. ACTH, adrenocorticotropic hormone.

all the patients on SELP (50% below the 5th percentile) (Fig. 4C).

In females, testosterone levels were below the median of the normal range in 66%, 100% and 0% of patients on LEN, VAN and SELP treatment, respectively. In males, oestradiol levels were always in the normal range but below the median levels in 57%, 100% and 50% of patients on LEN, VAN and SELP, respectively (Table 3).

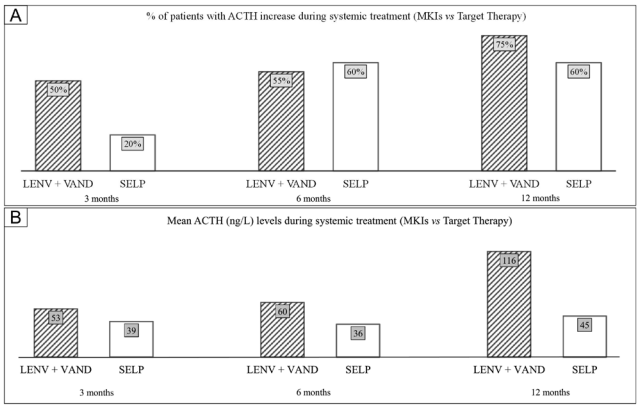

Figure 3

(A) Percentage of patients with ACTH increase at 3, 6 and 12 months of treatment, comparing patients treated with MKIs (LEN, VAN) with patients treated with target therapy (SELP). (B) Mean ACTH levels (normal values 8–50 ng/L) at 3, 6 and 12 months of follow-up, comparing patients treated with MKIs (LEN, VAN) with patients treated with target therapy (SELP); ACTH, adrenocorticotropic hormone; MKIs, multi-kinase inhibitors; LEN, lenvatinib; VAN, vandetanib; SELP, selpercatinib.

A significant inverse correlation was found between DHEA-S and androstenedione levels and age ($P = 0.030$ and $P = 0.0014$, respectively). However, 17-OH progesterone and testosterone levels did not correlate with age (P = NS) (data not shown).

Aldosterone and catecholamine during LEN, VAN and SELP treatment

Following appropriate discontinuation of interfering antihypertensive drugs, 15/24 patients (10/16 LEN, 2/4 VAN and 3/4 SELP) showed aldosterone levels below the median of the reference range (below the 5th percentile in seven patients) (Table 3). Renin levels were always in the normal range.

Urinary metanephrines levels were within the normal range in 17/17 patients (median: 127 µg/24 h, URL: <329 µg/24 h), whilst 24-h urinary normetanephrines were normal in 12/17 patients and higher than the URL in five cases, for whom the presence of pheochromocytoma/paraganglioma was excluded (Table 3).

Cortisone acetate replacement therapy

In 17 patients, including 10 patients with confirmed PAI and seven patients with grade 2 fatigue and increased ACTH values, CA replacement therapy was started and titrated according to patients' clinical status, with an average dosage of 25.3 mg daily (range: 12.5–50) (Table 2). In one patient (#13), we associated fludrocortisone acetate therapy. The four SELP patients with ACTH elevation were not treated with CA since they had

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Table 3 Evaluation of adrenal hormones during LEN, VAN and SELP treatment.

	LEN patients	VAN patients	SELP patients
Basal cortisol			
Within normal levels	25/25, 100%	6/6, 100%	5/5, 100%
Below LRL	0/25, 0%	0/6, 0%	0/5, 0%
Below median	15/25, 60%	2/6, 33%	3/5, 60%
Below 5th percentile	1/25, 4%	0/6, 0%	0/5, 0%
DHEA-S			
Within normal levels	8/17, 47%	4/5, 80%	4/5, 80%
Below LRL	9/17, 53%	1/5, 20%	1/5, 20%
Below median	14/17, 82%	3/5, 60%	3/5, 60%
Below 5th percentile	10/17, 59%	1/5, 20%	1/5, 20%
Δ4 androstenedione			
Within normal levels	14/16, 87%	5/5, 100%	4/5, 80%
Below LRL	2/16, 13%	0/5, 0%	0/5, 0%
Below median	14/16, 87%	3/5, 60%	3/5, 60%
Below 5th percentile	7/16, 44%	1/5, 20%	2/5, 40%
17-OHP			
Within normal levels	12/14, 86%	2/3, 66%	3/4, 75%
Below LRL	2/14, 14%	1/3, 33%	1/4, 25%
Below median	14/14, 100%	3/3, 100%	4/4, 100%
Below 5th percentile	6/14, 43%	2/3, 66%	2/4, 50%
Testosterone			
Within normal levels	3/9, 33%	0/1, 0%	2/2, 100%
Below LRL	6/9, 66%	1/1, 100%	0/2, 0%
Below median	6/9, 66%	1/1, 100%	0/2, 0%
Below 5th percentile	5/9, 55%	1/1, 100%	0/2, 0%
Oestradiol			
Within normal levels	7/7, 100%	1/1, 100%	2/2, 100%
Below LRL	0/7, 0%	0/1, 0%	0/2, 0%
Below median	4/7, 57%	1/1, 100%	1/2, 50%
Below 5th percentile	0/7, 0%	1/1, 100%	0/2, 0%
Aldosterone			
Within normal levels	15/16, 93%	4/4, 100%	4/4, 100%
Below LRL	0/16, 0%	0/4, 0%	0/4, 0%
Below median	10/16, 63%	2/4, 50%	3/4, 75%
Below 5th percentile	5/16, 31%	0/4, 0%	2/4, 50%
Metanephrines-U			
Within normal range	10/10, 100%	5/5, 100%	2/2, 100%
Normetanephrines-U			
Within normal range	7/10, 70%	3/5, 60%	2/2, 100%
Above normal range	3/10, 30%	2/5, 40%	0/2, 0%
Renin			
Within normal levels	15/16, 94%	3/4, 75%	4/4, 100%
Below LRL	1/16, 6%	0/4, 0%	0/4, 0%
Below median	13/16, 81%	2/4, 50%	4/4, 100%
Below 5th percentile	6/16, 37%	0/4, 0%	2/4, 50%

DHEA-S, dehydroepiandrosterone sulphate; 17-OHP, 17-hydroxyprogesterone; LEN, lenvatinib; LRL, lower reference limit; SELP, selpercatinib; U, urinary; VAN, Vandetanib .

a normal ACTH test or reported a grade 1 fatigue. As expected for PAI, ACTH levels remained higher than the normal range during replacement therapy (Supplementary Fig. 2A). Importantly, upon CA start, 14/17 (82%, 11 LEN, 3 VAN) patients showed an improvement in the degree of fatigue (Supplementary Fig. 2B). Patients 7, 11 and 17 did not show an improvement in fatigue.

Discussion

In the present real-life study, including patients treated with multikinases/antiangiogenic drugs and a RET-targeted compound, we show for the first time that the related toxicity does not affect only the cortisol-producing adrenal zona fasciculata but can also involve

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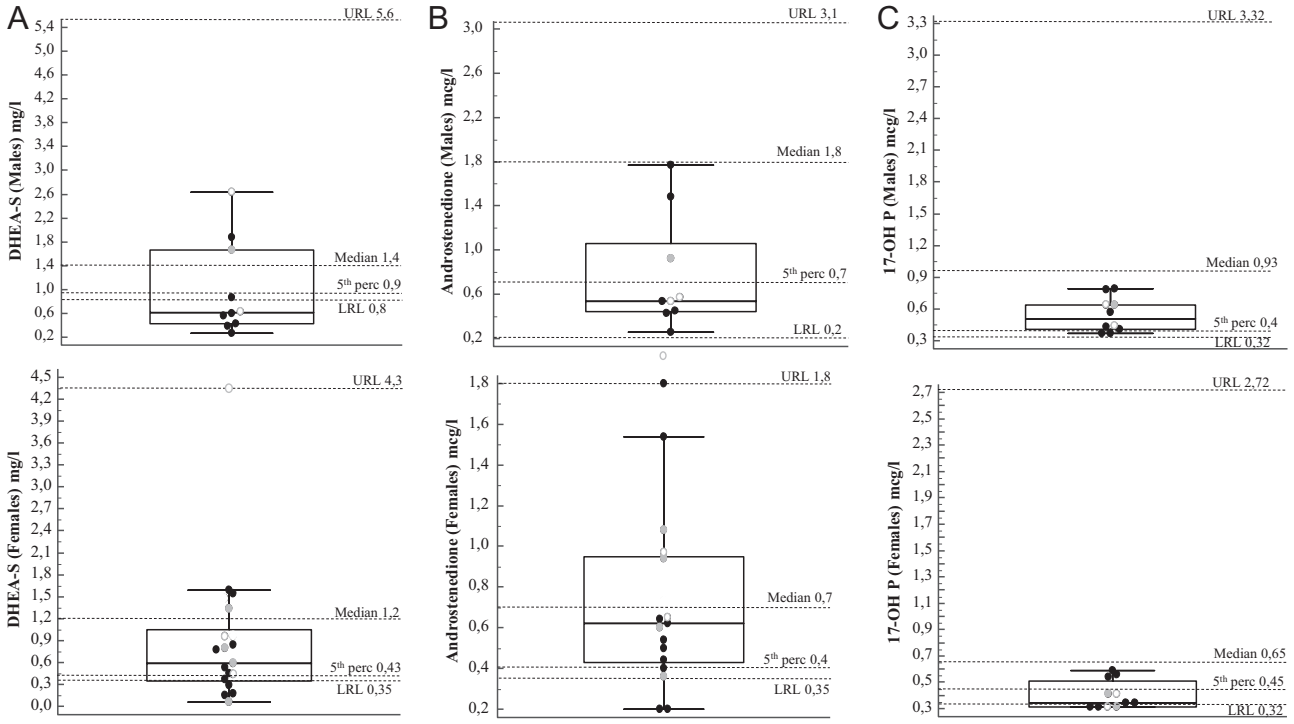

Figure 4

(A) Box and Whisker plots representing the distribution of dehydroepiandrosterone sulphate (DHEA-S) levels in 27/36 patients. Black dots represent patients treated with LEN (lenvatinib), grey dots patients treated with VAN (vandetanib) and white dots represent patients treated with SELP (selpercatinib). Seven out of ten (70%) males and 13/17 (76%) females showed DHEA-S values below the median level of reference. (B) Box and Whisker plots representing the distribution of Δ4 androstenedione levels in 26/36 patients evaluated during systemic therapy. Black dots represent patients treated with LEN, grey dots represent patients treated with VAN and white dots represent patients treated with SELP. Nine male patients (100%) and 11/17 (65%) female patients showed Δ4 androstenedione values below the median of the reference range (of which 10 patients below the 5th percentile). (C) Box and Whisker plots representing the distribution of 17-OH P levels in 21/36 patients. Black dots represent patients treated with LEN, grey dots represent patients treated with VAN, and white dots represent patients treated with SELP. We observed in 21/21 (100%) patients (10 males and 11 females) values below the median of the reference range and in 10 patients below the 5th percentile.

the whole adrenal cortex, leading to combined hormone deficiencies.

Even though not demonstrated in humans, the most probable mechanism underlying these alterations in adrenal hormonal secretion is the impairment of the capillary microvasculature and cortical cell necrosis. The hypothesis of a drug-induced injury of the whole adrenal gland is consistent with data coming from monkeys and rats treated with the multikinase inhibitor sunitinib, in which adrenal cortical congestion and haemorrhagic necrosis with consequent reduction in cortisol/corticosterone and aldosterone levels were observed after 13 weeks of treatment (29).

The increase in ACTH, still in the presence of normal cortisol levels, was the first hallmark of the impaired adrenal secretion and was found in almost all patients reporting fatigue (30). Interestingly, here we show in 13/36 patients, for whom basal ACTH and cortisol levels before starting treatment were available, an increase in ACTH levels during treatment. This finding argues against a possible ACTH increase due to the stressful situation related to the progressive cancer and suggests a TKI-mediated effect.

This mild alteration progressed in LEN and VAN patients (17% and 33% of cases, respectively) towards a more severe impairment leading to the reduced cortisol response to the 250 µg ACTH stimulation test, allowing for the diagnosis of PAI (22). To note, the trend of ACTH increase and the negative correlation between ACTH and basal/stimulated cortisol levels observed are consistent with a progressive reduction of adrenal function due to the systemic treatment rather than to stressful conditions or chronic diseases. Acute stress usually leads to a significant temporary peak, whilst chronic stress can lead to an adjustment of glucocorticoid stress response with a consequent reduction of ACTH levels (31).

In patients with documented PAI, but also in patients with persistently increased ACTH levels and fatigue grade 2 or higher, CA replacement treatment was shown to be effective. It is worth noting that the titration of CA must rely on the fatigue grade since this replacement treatment does not lead to ACTH levels normalisation.

The reduction of adrenal function was not limited to cortisol secretion but involved all adrenal steroids. In particular, the most relevant impairment concerned

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DHEA-S and Δ4 androstenedione, which are mainly produced by the adrenal gland. The impairment of the whole cortical adrenal function was confirmed by the finding of low levels of 17-OHP (below the median of normal values in all patients on LEN, VAN and SELP cases), which is a crucial precursor of adrenal hormone biosynthesis, and whose levels reflect the adrenal secretory reserve (32, 33). Our data could be biased by the fact that androgens decrease with age, and several of our patients are elderly. Consistently, the decreased levels of some androgens (DHEA-S and androstenedione) significantly correlated with an older age, thus confirming literature data (34). Differently, other androgens (17-OH progesterone and testosterone) were found not to correlate with age, suggesting that their low levels could be related to the systemic treatments.

Note, that hormones produced by the mineralocorticoid region were found to be reduced as well. Indeed, aldosterone levels were below the median of the reference range in the majority of cases, with normal renin levels. Low levels of aldosterone can be found in healthy and well-hydrated subjects, too, but the original finding of the present report is that up to 30% of these patients had aldosterone levels below the 5th percentile. Nevertheless, in the absence of renin increase and electrolyte disorders, the presence of hypoaldosteronism could not be definitely diagnosed.

Additional treatment with fludrocortisone acetate could be considered, at least in patients with severely impaired mineralocorticoid function.

Metanephrines and normetanephrines levels were in the normal/high range in all patients analysed. These data could be explained by two potential mechanisms. On one hand, metanephrines and normetanephrines production can also occur in the sympathetic system, thus reducing the impact of adrenal impairment. On the other hand, the adrenal medulla could be preserved from drug-induced microvascular damage due to its peculiar vascularisation characterised by a dual arterial supply (35, 36, 37, 38).

Interestingly, compared to patients treated with LEN and VAN, patients treated with SELP showed a later and lower increase in ACTH values, with normal ACTH test, and the decrease in the other adrenal hormones was lower. This finding is likely consistent with the milder activity on vascular endothelial growth factor receptor (VEGFR) (half-maximal inhibitory concentration, IC_{50} = 100) of SELP with respect to the antiangiogenic LEN and VAN (IC_{50} = 4 and 40, respectively) (39).

The data reported may be of interest for patient management, but it is crucial to highlight some limitations of the present study. First, since this was a retrospective study, we could not provide the basal evaluation of sexual steroids before systemic treatment. Thus, we cannot exclude that the reduced levels could be due, at least partially, to age or to intercurrent illnesses. Nevertheless, in order to reduce the interferences due to gonadal secretion, we measured only the levels of steroid hormones primarily produced by the adrenal cortex, such as DHEA-S and 17-OH-P in females and males, and testosterone in postmenopausal women. Future studies, including the androgen and mineralocorticoids evaluation both at baseline and during the follow-up, will give more insights into the degree of impairment of adrenal function during systemic treatment for thyroid cancer.

Conclusion

In conclusion, our data obtained from patients with advanced thyroid cancer and receiving systemic treatments show that fatigue is potentially related to PAI development. For the first time, we demonstrated that this adverse event could involve the whole adrenal cortex, leading to a combined hormonal deficiency, probably through an anti-VEGF-mediated effect.

Accordingly, targeted treatment with SELP seems to induce weaker damage to the adrenal gland, possibly due to its lower antiangiogenic effect. Replacement therapy with CA and, at least in some cases, fludrocortisone acetate, may improve the fatigue, with a positive impact on quality of life and compliance to treatment.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/ETJ-23-0246.

Declaration of interest

LF is a consultant for Eisai, Ipsen and Lilly. The other authors have no disclosures to make.

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Author Contribution Statement

CC, DC and MS: conceptualisation, data collection, formal analysis, writing and editing; SDL, MT, NG and CM: data collection, formal analysis and editing; LF and LP: supervision; CC and LF: conceptualisation, supervision and writing. All the authors were responsible for the final approval of the manuscript.

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