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The use of 24-h ambulatory blood pressure monitoring (ABPM) during the first cycle of sunitinib improves the diagnostic accuracy and management of hypertension in patients with advanced renal cancer

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ABSTRACT

Aim: Hypertension (HT) complicates treatment with antiangiogenic agents, including the tyrosine kinase inhibitor (TKI) sunitinib. To prospectively evaluate the prevalence and management of HT in patients with advanced renal cell carcinoma (RCC) receiving sunitinib we used 24-h ABPM and we treated HT according to guidelines of the Joint National Committee on Prevention, Detection and Evaluation and the Treatment of High Blood Pressure (JNC7).
Patients and methods: Normal 24-h ABPM at the baseline and at 2, 4 and 6 weeks of the first cycle was ensured with the successive use of hydrochlorothiazide + irbesartan, nebivolol and amlodipine. Office BP measurements were used in subsequent cycles to monitor HT. Sunitinib dose was modified only if BP was not controlled with four anti-hypertensive agents.
Results: Forty patients were included in this analysis. Twenty-one patients (53%) had baseline HT, while 12 of 14 (84%) normotensive patients required anti-HT treatment during the 1st cycle of sunitinib. HT was infrequent in subsequent cycles and increase of anti-HT medication was required in only 2 cases. Two patients permanently discontinued sunitinib due to HT. The remaining 34 (94%) required no dose modifications for HT. One cardiac event (2.8%) was observed. There was no correlation of HT with sunitinib efficacy.
Conclusion: Sunitinib-associated HT is more frequent than previously reported. The use of 24-h ABPM for diagnosis and tailoring of HT according to JNC7 guidelines may achieve uninterrupted, full dose therapy in most patients. The substitution of such protocols for currently used Toxicity Criteria may be warranted.

1. Introduction

Sunitinib is an oral multi-TKI, approved as first-line treatment of metastatic RCC. It blocks the split-kinase-domain family of receptor tyrosine kinases including vascular endothelial growth factor receptor (VEGFR 1–3).[1] This targeted mechanism of action has resulted in impressive antitumour efficacy[2] with less but still existing and rather different toxicities compared to traditional chemotherapy.

HT is a common adverse event of antiangiogenic therapy.[3] The underlying mechanisms have not been fully elucidated but VEGF inhibition has been shown to cause microvascular

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rarefaction[4] leading to increased vascular resistance and HT.[5] Treatment with sunitinib has been associated with a 15–47% incidence of HT.[1–3,6,7] Nevertheless, recent data suggest that it is more frequent.[8,9] This has important implications, since undiagnosed HT may lead to serious complications,[10,11] such as coronary artery disease (CAD) and heart failure, both described in association with sunitinib.[12]

Management of HT caused by antiangiogenic therapy is based on grading according to National Cancer Institute (NCI) Common Toxicity Criteria (CTC).[13] This system has important deviations from the guidelines set by Hypertension Societies, which can lead to inadequate BP control: (a) BP levels, which trigger the initiation of anti-HT treatment in CTC are substantially more relaxed. Therefore, patients aggressively treated according to the cardiological guidelines may be left untreated by oncologists; (b) previous history of HT and anti-HT therapies are not adequately taken into consideration; (c) in most studies Grade 3/4 HT is managed with dose modifications, similar to other toxicities for which no effective treatment exists, although satisfactory control of BP can be usually achieved with proper management.

The recent version 4 (v.4) of NCI CTC[14] bridges some of the above differences. It incorporates the JNC7 guidelines[15] but also Grades 3 and 4 of v.3. Although more correct, the application of this version will be associated with difficulties in comparing the incidence of HT between previous and future studies. In addition, its true advantage over the previous version regarding the clinically important Grades 3 and 4 could be doubtful.

Since April 2008 we have been using the current JNC7 guidelines for the diagnosis and management of HT in patients with advanced RCC treated with sunitinib.[9] We aim to achieve normal BP prior to the initiation of treatment and correct any abnormalities during the first cycle of sunitinib, since we and others[7–9] have observed that BP usually increases during this period. Preliminary results showed that our approach ensured uninterrupted, full dose therapy in 8 of 10 patients.[9] We are now reporting the validation of this approach in a cohort of 40 patients.

2. Patients and methods

2.1. Patients and BP monitoring

Since April 2008 patients with metastatic RCC treated at our institution have been prospectively assessed and managed during the first cycle of sunitinib according to the protocol described in Table 1. Since the aim was the best BP control during the first cycle, we used the most sensitive 24-h ABPM to diagnose HT and monitor the effect of anti-HT treatment. BP office measurements were also performed during the visits for BP holter placement. All patients started sunitinib with normal baseline 24-h ABPM. During subsequent cycles office BP measurements were performed prior to each sunitinib cycle. Anti-HT treatment was increased if systolic BP >140 mm Hg or diastolic BP >90 mm Hg according to JNC7 guidelines. All patients gave their IRB approved written informed consent for the administration of sunitinib and the analysis of their clinical data.

We defined a cardiac event as the occurrence of acute coronary syndrome or new symptomatic or asymptomatic left ventricular dysfunction, according to Chu et al.[7] Patients with a history of CAD, asymptomatic heart failure, or symptoms suggestive of such conditions underwent echocardiogram prior to sunitinib initiation and monitored every three cycles if abnormal. Otherwise echocardiography was performed only if clinically indicated.

2.2. Anti-cancer therapy

No prior anti-VEGF or anti-VEGFR treatment had been administered although prior interferon was allowed. Sunitinib was administered po at a starting dose of 50 mg daily for 4 weeks followed by a 2-week interval. HT was graded according both NCI CTC (v.3) and JNC7 guidelines based on office measurements.[15] We also reviewed all medical files in order to grade HT according to CTC v.4 after its publication (October 2009). Tumour response was assessed according to RECIST criteria every 3 cycles or earlier if there was clinical suspicion of progression.

Table 1 – Protocol of diagnosis and management of hypertension and monitoring of blood pressure in patients with advanced RCC receiving Sunitinib.

Prior to initiation of Sunitinib	If daytime BP <135/85 mm Hg and nighttime BP <120/70 mm Hg at 24-h ABPM → start Sunitinib If daytime BP ⩾135/85 mm Hg and/or nighttime BP ⩾120/70 mm Hg → diagnosis of hypertension 1. Initiation of anti-hypertensive therapy or increase of existing anti-hypertensive therapy 2. Repeat of 24-h BPM after 1–2 weeks. If still hypertensive, addition of anti-hypertensive agents to achieve normal 24-h BPM 3. Initiation and additional anti-hypertensive management according to the following succession: hydrochlorothiazide + irbesartan, nebivolol, amlodipine
During 1st cycle of Sunitinib	If 24-h BPM abnormal → initiation of anti-hypertensive therapy or addition of anti-hypertensive agents (if already on treatment) without sunitinib interruption Initiation and additional anti-hypertensive management as above
Sunitinib dose modifications	1 Sunitinib treatment interrupted only if BP not controlled with four anti-hypertensive agents. In this case, Sunitinib was restarted at 37.5 mg daily after BP was controlled. A second dose reduction to 25 mg was permitted. If BP was still not controlled, treatment was permanently discontinued 2 Permanent discontinuation of Sunitinib in case of hypertensive crisis

2.3. Statistical analyses

The SPSS software (version 15.0, SPSS Inc.) was used. Correlations between BP measurements and categorical variables (smoking, obesity, history of HT, history of CAD, diabetes, hyperlipidaemia, response rates) were tested using the x^2 test. ABPM differences between time-points were tested with the Wilcoxon paired *t*-test. Median OS and PFS were estimated using Kaplan–Meier curves. The log rank test and the Cox proportional hazards model were used to assess the relationship of OS and PFS with categorical and continuous variables, respectively.

3. Results

3.1. Patients and treatment

Fouty patients had baseline evaluation. Their characteristics are shown in Table 2.Eleven patients did not complete the 6-week evaluation: 4 had only baseline evaluation (because of

Table 2 – Demographics of 40 patients with advanced RCC receiving sunitinib.

Characteristics	No (%)
Age	
Median (Range)	67 (30–84)
Sex	
Male	29 (72)
Female	11 (28)
ECOG PS	
0	23 (58)
1	13 (32)
2	4 (10)
Nephrectomy	
Yes	36 (90)
No	4 (10)
Histology	
Clear cell	32 (80)
Papillary	4 (10)
Chromophobe	1 (2.5)
Mixed	2 (5)
Unclassified	1 (2.5)
Time from diagnosis to initiation of Sunitinib	
⩽12	24 (60)
>12	16 (40)
Serum calcium (corrected)	
Median (Range)	9.6 (8.2–12.2)
Hb	
Median (Range)	13.3 (8.6–16.2)
Serum LDH	
Normal	38 (95)
Elevated	2 (5)
MSKCC stratification	
Low	10 (25)
Intermediate	23 (58)
High	7 (17)
Hypertension prior to initiation of sunitinib	21 (53)
History	15 (38)
Newly diagnosed	6 (15)
Uncontrolled hypertension	8 (20)
Controlled hypertension	32 (80)
Disease-and lifestyle-associated cardiovascular risk factors[a]	
Smoking	14 (35)
Obesity	11 (27)
NIDDM	3 (7)
Hypercholesterolaemia	11 (27)
Coronary artery disease	3 (7)

[a] Categories are not mutually exclusive.

early progression [n = 1, did not receive sunitinib [n = 2 or premature discontinuation [n = 1), while the remaining 7 did not attend all their appointments. These patients were included in the analysis at the respective time points.

3.2. Baseline BP evaluation

The flow of the study regarding the diagnosis and management of HT based on the 24-h ABPM measurements during the first 6 weeks of sunitinib therapy are shown in Fig. 1. Eight patients (20%) had uncontrolled HT at the baseline. Three of them (37%) had normal BP office measurements. Overall 21 (53%) required anti-HT medication starting sunitinib therapy. Inadequate BP control at the baseline was associated with obesity: 5 of 11 (45%) obese patients had uncontrolled BP as opposed to 3 of 29 (10%) non-obese patients ($p = 0.025$).

3.3. BP evaluation during first cycle of sunitinib

Up to now 180 cycles of sunitinib (median: 3.5, range: 1–21) have been administered and 15 patients are still on treatment. The variation of 24-h ABPM and the respective median values are shown in Fig. 2. There was a rise from baseline at 2 weeks, which declined at 4 weeks. At the start of 2nd cycle (6 weeks) values were similar to those at the baseline.

The percentage of abnormal 24-h ABPM was gradually reduced from 83% at 2 weeks to 13% at 6 weeks (Fig. 3). Patients with normal monitoring at 2 weeks did not show abnormalities at subsequent measurements apart from one case. Similarly, normal 4-week monitoring remained normal at 6 weeks.

Table 3 shows HT grading according to CTC v.3 and 4, and JNC7 (based on office measurements) and the respective 24 h ABPM results during the first 2-week period. As expected, CTC v.4 grouping was identical to that of JNC7 in Grades 0 and 1. On the contrary, no correlation was observed at Grades 2 and 3, suggesting that most of these patients required a combination rather than single anti-HT agent. Eight patients (23%) with abnormal 24 h ABPM would not require treatment according to the 3 grading systems and, therefore, would wrongly remain untreated.

The requirement for initiation or intensification of anti-HT therapy was studied in 33 of the 40 patients. Four patients with only baseline evaluation and 3 without all 24-h ABPMs on sunitinib and no requirement for intensification were not included in this analysis. During the first 6 weeks of treatment with sunitinib, 26 patients (79%) required initiation or intensification of anti-HT medication. Cardiovascular risk factors or history of HT were not associated with requirement for modification of anti-HT treatment.

Seven patients did not complete the 28-day cycle due to other toxicities (missed days 2–14). There was no correlation between the requirement for anti-HT treatment modification and the occurrence of any other type of toxicity. Only 2 patients discontinued sunitinib due to HT. They both had history of HT. One developed hypertensive crisis (pulmonary oedema) during the 2nd cycle in spite of the use of 4 anti-HT agents. Another patient had insufficient BP control and deterioration of renal function during the first cycle of sunitinib in spite of the use of 4 anti-HT agents and dose reduction to 25 mg. No other cardiac events were observed and no treatment delays or dose modifications for HT were necessary in the remaining 34 patients (94%). Nine patients had a baseline echocardiogram. They all showed normal left ventricular function. No repeat echocardiogram was necessary during the study.

3.4. BP evaluation during subsequent cycles of sunitinib

Thirty patients received at least 2 cycles of sunitinib. HT (based on office measurements) in subsequent cycles was

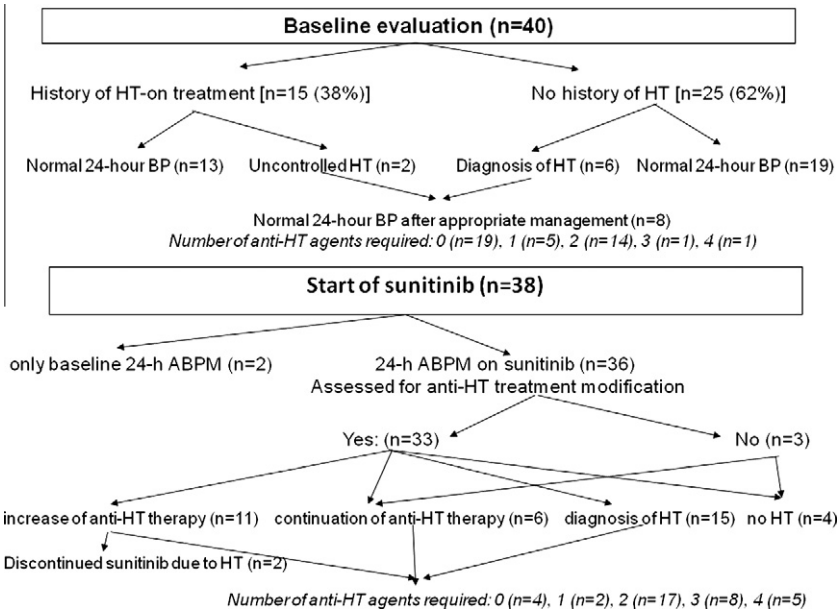
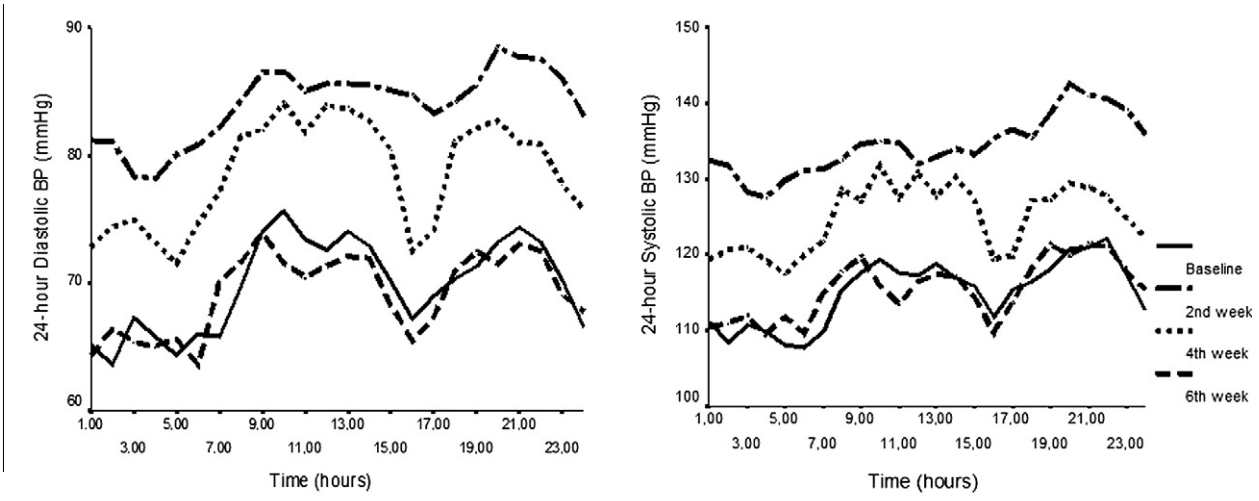


Fig. 1 – Flow of the study. Results of diagnosis and management of hypertension during the first 6-weeks of sunitinib, based on 24-h ambulatory blood pressure measurements.



ABPM parameters	Baseline	2 weeks	4 weeks	6 weeks
24-hour SBP (mmHg)	117 (9) †¥	136 (16) * ¥ ‡	130 (18)* †‡	117 (12) †¥
24-hour DBP (mmHg)	70 (7) †¥	84 (9) * ¥ ‡	81 (10)* †‡	70 (7) †¥
24-hour HR (b/min)	78 (9) ¥	74 (10)	73 (9)* ‡	77 (12) ¥
Daytime SBP (mmHg)	119 (9) †¥	138 (18) * ¥ ‡	131 (18)* †‡	119 (11) †¥
Daytime DBP (mmHg)	72 (7) †¥	86 (10)* ¥ ‡	82 (10)* †‡	72 (7) †¥
Daytime HR (b/min)	81 (10) †¥ ‡	77 (10)*	76 (10)*	79 (13)*
Night-time SBP (mmHg)	111 (12) †¥	132 (17)* ‡	127 (20)* ‡	113 (15) †¥
Night-time DBP (mmHg)	65 (8) †¥	80 (10)* ¥ ‡	77 (12)* †‡	66 (8) †¥
Night-time HR (b/min)	71 (9) ¥	68 (10)	66 (8)* ‡	71 (10) ¥

* p<0.05 versus baseline
† p<0.05 versus 2 weeks
¥ p<0.05 versus 4 weeks
‡ p<0.05 versus 6 weeks

Fig. 2 – Variation of 24-h ABPM at the four different time points and the respective median values. Twenty-nine patients with all four measurements are included in this analysis.

recorded in 9 cases (31%) according to CTC v.4 and in 7 (23%) according to v.3 (Fig. 4). Increase of anti-HT medication in subsequent cycles was required in only 3 cases (10%).

3.5. *Correlation of HT with response and outcome*

Twenty-five patients were evaluable for response [1 CR (4%), 9 PRs (36%), 5 SD (20%), 10 PD (40%). There was no association of the requirement of intensification of anti-HT with anti-tumour responses ($p = 0.667$).

Median OS and PFS were 19.3 months (95% CI: 4.6–34) and 8.4 months (95% CI: 0–16.7), respectively. There was no correlation of the development or worsening of HT with OS ($p = 0.178$) or PFS ($p = 0.156$). No correlation was also found with dBP (studied both as continuous or categorical variable with a cut-off at 90 mm Hg).

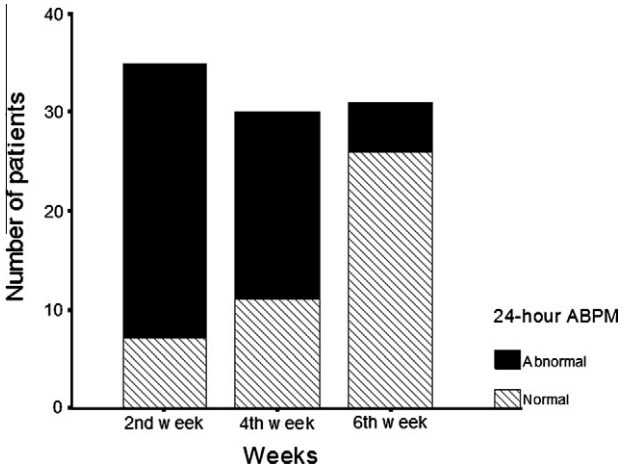


Fig. 3 – Number of normal and abnormal 24-h ABPM at 2, 4, and 6 weeks after initiation of sunitinib.

4. Discussion

To our knowledge, this is the first prospective study specifically assessing the incidence and management of sunitinib-induced HT. Our single institution experience has the advantages of homogeneity in underlying malignancy and treatment, criteria of HT diagnosis, monitoring and management according to the guidelines of the JNC7. We showed that HT is caused by sunitinib much more frequently than previously reported.[16–19] The most likely reason is the prospective evaluation and the use of 24-h ABPM. Several studies have confirmed the superiority of this method over office measurements.[20] We also confirmed

Table 3 – Grading of hypertension and correlation with 24 h BP monitoring after 2 weeks of treatment with sunitinib.

JNC7				NCI-v.4				NCI-v.3			
Definition	N(%)	24 h[a]		Definition	N(%)	24h[b]		Definition	N(%)	24 h[c]	
		N	HT			N	HT			N	HT
Normal SBP <120 and DBP <80	1 (3)	1	0	0	1 (3)	1	0	0	11 (31)	3	8
Pre-hypertension SBP 120–139 and/or DBP 80–89	10 (28)	2	8	Grade 1	10 (28)	2	8				
HT stage 1 SBP 140–159 and/or DBP 90–99 Treatment indicated	15 (43)	2	13	Grade 2 HT stage 1 or Grade1 v.3 but limit to 140/90 Treatment indicated	2 (6)	2	0	Grade 1 Transient (<24 h), asymptomatic increase by > 20 mm Hg (DBP) or to 150/90 if previously WNL Treatment not indicated	0 (0)	0	0
								Grade 2 Recurrent or persistent (⩾24 h) or symptomatic increase by > 20 mm Hg (DBP) or to 150/90 if previously WNL Treatment indicated	3 (9)	1	2
HT stage 2 SBP ⩾ 160 and/or DBP ⩾ 100 Treatment indicated	9 (26)	1	8	Grade 3 HT stage 2 or Grade 3 v.3 Treatment indicated (Dose reduction?) Grade 4 Grade 4 v.3 Usually discontinuation	22 (63)	1	21	Grade 3 Requiring more than one drug or more intensive therapy than previously Treatment indicated (Dose reduction?) Grade 4 Life-threatening Usually discontinuation	21 (60)	0	21

p Values denote differences between the results of the respective method and those of 24-h ABPM.
[a] $p = .139$.
[b] $p = .085$.
[c] $p = .008$.

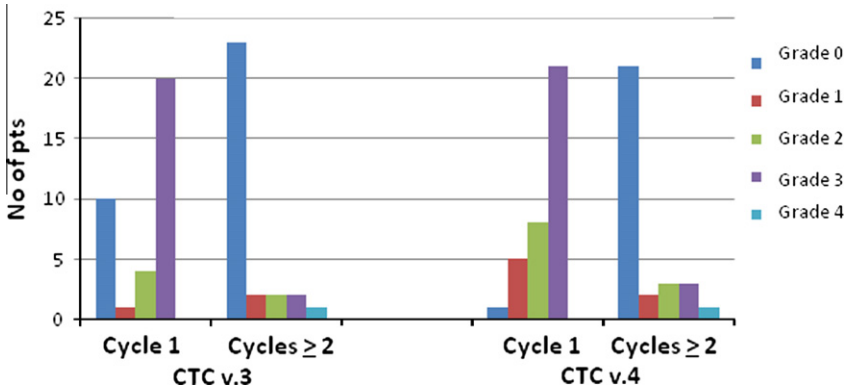


Fig. 4 – Cases of hypertension during the 1st and subsequent cycles of sunitinib according to NCI CTC versions 3 and 4.

its superiority in this setting, since 24-h ABPM measurements were abnormal in a significant number of patients with normal or pre-HT office measurements as well as Grade 0 or 1 according to CTC v.3 or v.4.

24-h ABPM detected undiagnosed or uncontrolled HT at the baseline in 20% of our patients, in contrast to the 3% reported by Schmidinger, who relied on office measurements and self reporting.[19] The more accurate diagnosis at the baseline as well as the more vigorous monitoring during the first cycle of therapy, resulting in intensification or initiation of anti-HT medication in most patients (79%), may have prevented acute complications associated with HT. In contrast

a

Grade	Definition	Management
0	No HT 24-h BPM: daytime BP<135/85 mmHg and nightime BP<120/70 mm Hg (1st cycle) Office measurement: < 140/90 mmHg (subsequent cycles)	No intervention
1	HT 24-hour BPM: daytime BP≥135/85 mmHg and/or nightime BP≥120/70 mm Hg (1st cycle) Office measurement: ≥ 140/90 mmHg (subsequent cycles)	Initiation or intensification (if already on treatment) of anti-HT therapy without sunitinib interruption according to algorithm in Fig.3b. Sunitinib treatment interrupted only if BP not controlled with four anti-HT agents and restarted at 37.5 mg daily after BP control. A second dose reduction to 25 mg can be applied if necessary
2	Hypertensive crisis No control with 4 anti-HT agents (maximum doses) in spite of appropriate dose modification of anti-VEGF therapy	Discontinuation

b

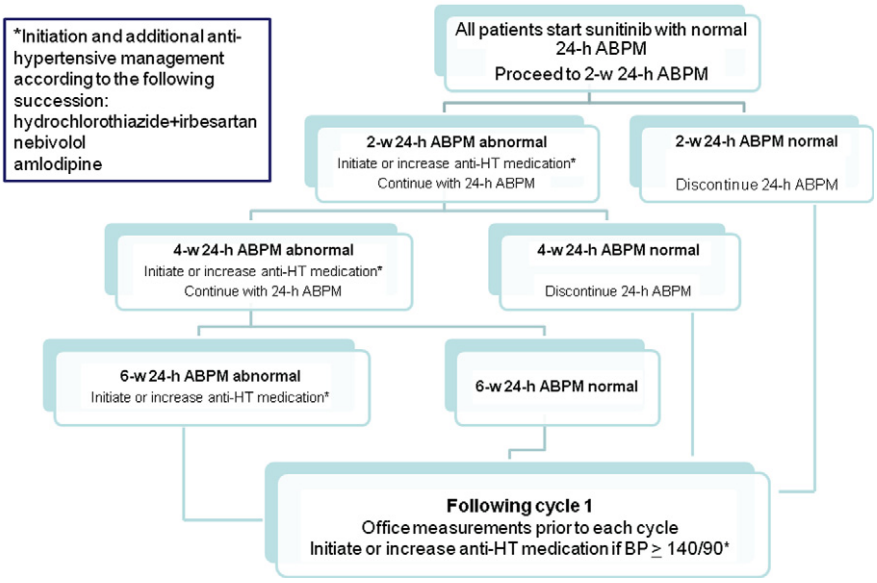


Fig. 5 – Proposed algorithm for grading (a) and diagnosis and management (b) of sunitinib-induced hypertension.

to previous data suggesting an incidence of 11–34%,[7,18,19] we observed only 1 cardiac event (2.8%). Although differences in definitions and the fact that we did not routinely perform echocardiograms to detect asymptomatic heart failure should be taken into account, still our results appear more promising than the recently reported 11%[7] and 18%[19] of symptomatic events.

Most problems with HT occurred during the first cycle of sunitinib. Although it could be argued that more cases of HT would have been detected in subsequent cycles, had 24-h ABPM been continued, the difference in the occurrence of HT between the first and subsequent cycles was also evident when only office BP measurements were taken into account (69% versus 23% for CTC v.3) HT was infrequent in subsequent cycles and intensification of anti-HT medication was seldom required. This is in contrast to results from retrospective analyses, suggesting an increasing incidence and continuous need for anti-HT therapy introduction.[7] We suggest that these represent undiagnosed cases, which manifest later with more serious HT.

The optimal evaluation and management of anti-VEGF-induced HT has not been defined. CTC v.4 represents an improvement over the previous version regarding HT definition because it incorporates the JNC7 criteria regarding BP levels. Nevertheless, it seems that most sunitinib-treated RCC patients with JNC7 stage 1 HT (the corresponding stage for Grade 2) require more than one anti-HT agent. They are, therefore, categorised to Grade 3 (which in fact corresponds to a higher BP level, according to JNC7). This stage migration creates confusion and underlines the need for a unifying grading system. Furthermore, Grade 3 HT has not the same implications in management as other non-treatable toxicities. We showed that with proper diagnosis and management, no treatment interruptions or dose modifications for HT were necessary in the majority of cases (94%). Therefore, we suggest that a simpler grading system, based on the requirement for anti-HT medication (Fig. 5a), could be substituted for the existing CTC grading.

HT is a common side-effect of all anti-VEGF therapies and we believe that our results are also applicable to other available

anti-angiogenic agents used in mRCC. A possible limitation of our study is the applicability of 24-h ABPM in a multicenter setting. This method is now widely accepted for the diagnosis of HT and most centres can provide it. We only used it in the first cycle of treatment, which considerably reduces the inconvenience and the cost involved. Although more expensive than office measurements, the improvement in diagnosis and management of HT may save money in the long term, by diminishing the rate of emergency room and office visits as well as hospitalisations related to inadequate control and complications, leading to an acceptable cost-benefit ratio.[21] Furthermore, our findings suggest that it can become simpler. Patients who achieved normal results did not show abnormalities in subsequent measurements apart from one case, suggesting that further 24-h ABPM can be safely omitted. For this reason, our algorithm has been modified (Fig. 5b) and is now being evaluated in a multicenter setting.

We found no correlation of the development of HTwith sunitinib efficacy. Our finding is in contrast to previous data regarding the VEGFR TKIs sunitinib and axitinib.[22–24] An important limitation of these studies is the lack of homogenous reporting and management of HT. Although the incidence of HT after the first cycle was lower than that reported in other studies, we observed a similar response rate in our series. Without disregarding the fact that the number of evaluable for response patients is fairly small and definite conclusions cannot be drawn from our study, we believe that optimal management of HT is necessary and does not preclude benefit from sunitinib. Recently, associations of sunitinib-induced HTwith VEGF single nucleotide polymorphisms[25] and baseline VEGFR-2 levels[26] have been reported. These data suggest that the interaction of anti-VEGF agents with the molecular background of VEGF and the change in VEGFR and VEGF levels may in fact be related with both drug efficacy and induction of HT, thus creating an artificial correlation between two unrelated factors.

In conclusion, HT is extremely common but easily manageable in the vast majority of RCC patients treated with sunitinib. The application of a limited number of 24-h ABPMs during only the first cycle, and the use of JNC7 guidelines ensures uninterrupted, full-dose anti-cancer therapy in more than 90% of cases with low incidence of symptomatic cardiac events. The diagnosis and management of anti-VEGF induced HT could be based on simple grading systems and widely accepted and easily applicable algorithms.

Conflict of interest statement

Aristotle Bamias has received honoraria or consulting fees from PFIZER, BAYER, NOVARTIS, and ROCHE.

No other author declared any conflict of interest.

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