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Hypertension management in patients with renal cell cancer treated with anti-angiogenic agents

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ABSTRACT

Inhibitors of the vascular endothelial growth factor (VEGF-IS) signalling pathway have fundamentally changed the treatment of metastatic renal cell carcinoma (MRCC). Hypertension is one of the most common side effects of VEGF-IS and has been reported with almost every VEGF-I used for treatment to date. The exact mechanism of VEGF-I–induced hypertension appears complex and multifactorial, and it remains to be fully explained. No randomized clinical trials are available to guide the management of hypertension during VEGF-I treatment in MRCC patients. The guiding principles suggested here summarize the consensus of opinions on the diagnosis and management of VEGF-I–induced hypertension during treatment of MRCC obtained from an expert working group composed of 4 Canadian medical oncologists and 5 Canadian hypertension specialists. The Canadian Hypertension Education Program guidelines, available literature, and expert opinion were used to develop the guiding principles.

KEY WORDS

Vascular endothelial growth factor inhibitors, hypertension, metastatic renal cell carcinoma

1. INTRODUCTION

Inhibitors of the vascular endothelial growth factor (VEGF-IS) signalling pathway are increasingly used in the treatment of a variety of cancers. These VEGF-IS have fundamentally changed the treatment of metastatic renal cell carcinoma (MRCC). Bevacizumab (Avastin: Genentech, San Francisco, CA, U.S.A.), a monoclonal antibody against VEGF was the first anti-angiogenic agent to demonstrate clinical antitumour activity in RCC. Subsequently, multi-targeted receptor tyrosine kinase inhibitors (TKIS) such as sunitinib (Sutent: Pfizer Canada, Kirkland, QC), sorafenib (Nexavar: Bayer HealthCare AG, Leverkusen, Germany) and more recently pazopanib (Votrient: GlaxoSmithKline, Philadelphia, PA, U.S.A.) have been approved for the treatment of metastatic RCC. The TKIS inhibit multiple tyrosine kinases, including the vascular endothelial growth factor receptors (VEGFRS) 1, 2, and 3; platelet-derived growth factor receptor; and c-Kit, among others.

Today, according to the Memorial Sloan–Kettering Cancer Center classification, sunitinib is considered the reference standard for the first-line treatment of good- and intermediate-prognosis MRCC patients, and sorafenib can be considered for patients with failure of first-line cytokine therapy[1].

These very effective agents have a novel side-effect profile. Hypertension is one of the most common side effects of angiogenesis inhibition by TKIS and bevacizumab. It has been reported with almost every VEGF-I used for treatment to date[2–5].

The maximum benefit from these drugs is obtained in patients who can stay on therapy continuously over a prolonged period of time. Continuous therapy is possible only if the associated adverse events are effectively managed.

The guiding principles suggested in the present manuscript summarize the consensus on the diagnosis and management of VEGF-I–induced hypertension during treatment of MRCC obtained from an expert working group composed of 4 Canadian medical oncologists and 5 Canadian hypertension specialists. The Canadian Hypertension Education Program (CHEP) guidelines, available literature, and expert opinion were the basis for the recommendations presented here. Furthermore, the recently published recommendations from the U.S. National Cancer Institute Cardiovascular Toxicities Panel to optimize assessment, surveillance, and management of blood pressure (BP) in patients receiving VEGF-IS were also taken into account[6]. The present article focuses on the diagnosis and management of VEGF-I–induced hypertension during treatment of MRCC.

2. VEGF-I–ASSOCIATED HYPERTENSION

Several studies have documented the incidence of hypertension in patients on VEGF-IS. Maitland reported a mean increase in systolic BP (SBP) of 10.8 mmHg (95% confidence interval: 5.2 mmHg to 28.7 mmHg) and diastolic BP (DBP) of 8.0 mmHg (95% confidence interval: 6.3 mmHg to 9.7 mmHg) at 6–10 days after initiation of treatment with sorafenib in 54 normotensive patients with advanced cancer[3]. The onset of the BP increase was reported after the first day and appeared to plateau after the first 6 days. Azizi *et al.,* using home monitoring, reported that BP started to increase as early as the first week of therapy with sunitinib in normotensive patients, resulting in a SBP/DBP increase up to 22/17 mmHg at 4 weeks of therapy[7]. The increase in SBP/DBP in hypertensive patients was 16/12 mmHg and appeared to be less than in normotensive patients; however, additional antihypertensive medications were prescribed.

Hypertension may be an efficacy biomarker in patients treated with VEGF-IS. A phase I open-label study evaluating the cardiovascular safety of sorafenib in patients with advanced cancer showed that the patient with a confirmed partial response had the highest mean increase from baseline in both SBP and DBP after cycle 1 and after 4 cycles of sorafenib (a cycle consists of 28 days of continuous therapy)[8]. Two separate retrospective analyses of studies involving patients with MRCC treated with sunitinib[9] and patients with solid tumours treated with axitinib[10] showed that drug-induced hypertension was associated with improved clinical outcome. In particular, patients taking axitinib with a DBP of 90 mmHg or more on treatment had a significantly lower relative risk of progression and death than did those with a DBP lower than 90 mmHg throughout therapy[10].

Table I summarizes the reported incidence of grade 3 hypertension in patients with MRCC treated with VEGF-I. The severity of hypertension was defined, in most cases, using the definition set out by the *Common Terminology Criteria for Adverse Effects,* version 3 (therapy requiring more than 1 drug or more intensive treatment than previously)[21]. This classification of hypertension is different from the classifications used by hypertension societies, and it may overestimate the percentage of patients with a significant increase in BP.

The exact mechanism of VEGF-I–induced hypertension appears complex and multifactorial, and it remains to be fully explained. Vascular endothelial growth factor has a significant impact on BP by increasing NO synthesis and release through upregulation of endothelial NO synthase. The result is vasodilatation and increased endothelial permeability, which lowers BP. Conversely, the decreased NO synthesis mediated by VEGF inhibition leads to vasoconstriction, decreased endothelial permeability, increased systemic vascular resistance, and a higher BP[22]. Other factors mediated through VEGF inhibition that appear to contribute to hypertension include reduced vessel density (vascular rarefaction); thyroid dysfunction; and upregulation of baroreceptor function, leading to increased vascular stiffness and renal toxicity—in particular, proteinuria and microangiopathy[22].

A recent review by Kappers *et al.*[23] described significant cardiac, renal, and thromboembolic complications associated with the use of the VGFR-IS. Apart from hypertension, such complications affect only a small number of patients. However, arterial hypertension is, by itself, associated with end-organ damage, including left ventricular hypertrophy, congestive heart failure, coronary artery disease, and myocardial infarction. Hypertension is also associated with atherosclerotic vascular disease, aortic aneurysms, and cerebrovascular diseases such as strokes, transient ischemic attacks, and cerebral hemorrhages. Hypertension is also one of the prime causes of proteinuria and end-stage renal disease. Thus, as the long-term survival of cancer patients on anti-angiogenic therapy increases, the foregoing complications may become an important issue in their management.

3. GENERAL CONSIDERATIONS

The severity of vascular damage from hypertension is modulated by the level of BP increase, the duration of hypertension, and the presence of other risk factors such as diabetes and hyperlipidemia. However, the primary determinant of the vascular risk—whether it is cardiac, cerebral, vascular, or renal—is the BP level. It is important to note that hypertension is a chronic disease. Over the long term, it will cause significant vascular damage; however, if very severe, it is associated with conditions such as cerebral hemorrhage and malignant hypertension. Effective treatment (available as either single-agent or combination therapy) can normalize BP in most cases. Prospective randomized controlled trials have confirmed that such therapy can significantly reduce the risks associated with long-term hypertension.

Patients with MRCC who receive VEGF-I therapy have a very different clinical course and prognosis than otherwise healthy hypertensive patients with or without other cardiovascular risk factors. The decision to treat or simply to observe hypertension depends on the BP level, the rapidity of the BP increase, and the individual's cardiovascular history, renal function, and extent and prognosis of RCC. The fact that antihypertensive medications may potentially lead to additional adverse events should also be taken into account. Hypertension and its treatment should generally not be limiting factors for VEGF-I dose and schedule selection or for treatment duration.

TABLE I Incidence of grade 3 hypertension in metastatic renal cell carcinoma patients treated with inhibitors of the vascular endothelial growth factor signalling pathway

Agent	*Reference (study name)*	*Study type*	*Hypertension ≥ grade 3 (%)*[a]
Monoclonal antibody			
Bevacizumab with interferon alfa	Escudier *et al.,* 2007[11]	Phase III first-line randomized trial	3
	Rini *et al.,* 2008[12]	Phase III first-line randomized trial (CALGB 90206)	11
Small-molecule tyrosine kinase inhibitor			
Sunitinib	Motzer *et al.,* 2006[13]	Phase II second-line single-arm trial	6
	Motzer *et al.,* 2009[14]	Phase III first-line randomized trial	12
Axitinib	Rixe *et al.,* 2007[15]	Phase II second-line cytokine-refractory	8
	Rini *et al.,* 2009[16]	Phase II second-line sorafenib-refractory	16
Sorafenib	Escudier *et al.,* 2007[17]	Phase III second-line randomized controlled trial	4
	Escudier *et al.,* 2009[18]	Phase II first-line randomized trial	2
Abt-869	Tannir *et al.,* 2009[19]	Phase II second-line after sunitinib failure	24
Pazopanib	Sternberg *et al.,* 2010[20]	Phase III first-line randomized controlled trial	4

[a] All-cause adverse event grading based on the *Common Terminology Criteria for Adverse Events,* version 3.0.

No currently available randomized controlled trials in cancer patients taking relatively short-term therapy can be associated with intermittent hypertension. Hence, the risk associated with the (usually mild) short-term hypertension seen in this group of patients is unknown. The suggestions that follow are based on the CHEP guidelines and the clinical experience of the participating medical experts[24–26]. The CHEP guidelines have been published annually since 1999. The methodology used in the preparation of those guidelines has been previously described elsewhere[27,28].

4. MEASUREMENT OF BP

Protocols for recording BP should be followed in mRCC patients regardless of whether the patient is normotensive or hypertensive before initiation of treatment. At their Web site (http://www.hypertension.ca), the CHEP makes recommendations for accurate measurement of BP. Health care professionals should be trained to measure BP correctly, and BP should be recorded at each visit in patients receiving drugs that can cause hypertension.

Blood pressure can be recorded in 4 different settings:

- Office recordings made with a sphygmomanometer (aneroid, mercury, or electronic) by a nurse or physician
- Office recordings made with an automated office blood pressure recorder such as the BpTRU (BpTRU Medical Devices, Coquitlam, BC) or a similar device, with the patient alone in an examining room
- Home measurements made with an automatic electronic device by the patient or by a third person such as a visiting nurse
- Recordings made over 24 hours with an ambulatory BP measurement (ABPM) device

Home BP measurement can be used for the diagnosis and follow-up of patients with hypertension and to establish baseline BP and to observe patients for the development of hypertension after initiation of VEGF-I therapy. For example, the hypertension associated with sunitinib taken on a schedule of 4 weeks on and 2 weeks off may not be diagnosed if BP is taken at only at baseline and during the 2 weeks off VEGF-I therapy when BP may have normalized again. Bamias *et al.* demonstrated that the use of 24-hour ABPM during the first cycle of sunitinib treatment improved the diagnostic accuracy and management of hypertension in patients with advanced RCC[29]. Therefore, in such patients, the BP measurement schedule should be adjusted to the administration schedule of the particular agent, taking into account its specific pharmacokinetic properties to determine the mean BP for the entire period between treatments.

In accordance with CHEP guidelines, ABPM is useful for classifying the BP status of patients with suspected isolated office hypertension ("white coat" effect)[30]. Compared with routine manual BP measurement in the office, ABPM is a significantly better predictor of cardiac complications in relation to a patient's BP status. Other advantages of ABPM include detecting nocturnal hypertension, symptomatic hypotension related to inappropriate antihypertensive drug therapy, and fluctuating BP with transient

hypertension. More recently, ABPM has been used to confirm a diagnosis of "white coat" effect when readings from an automated office blood pressure recorder are in the borderline range[31].

5. DEFINITION OF HYPERTENSION

Hypertension is defined as a SBP by manual office recording of 140 mmHg or more, or a DBP of 90 mmHg or more, or both, on repeated measures across 5 visits, or an SBP of 160 mmHg or more, or a DBP of 100 mmHg of more, or both, across 3 visits[24]. The diagnosis of hypertension can also be made in patients with a SBP 140 mmHg or more, or a DBP of 90 mmHg or more, or both, on a 2nd visit in the presence of end-organ damage, chronic kidney disease (creatinine clearance < 60 mL/min), or diabetes mellitus[24].

Using an ABPM instrument, the diagnosis of hypertension can be made on the basis of an average BP recording over 24 hours of 130/80 mmHg, or a daytime recording (06h00 to 22h00) of 135/85 mmHg[24].

If ABPM is not available, automated office BP and home BP recordings can be used to diagnose hypertension if BP is 135/85 mmHg or more, or to follow the BP status of patients[24].

6. TREATMENT OF HYPERTENSION

These general guidelines for the treatment of hypertension are based on a combined approach of lifestyle changes and pharmacologic therapy[25].

6.1 Lifestyle Management

The recommended lifestyle changes are based on physical exercise, weight reduction, dietary change, and sodium restriction, among others[25]. Those lifestyle changes are generally very difficult to apply in MRCC patients and are thus unlikely to be used, but they may be considered in selected patients. Weight loss is a common problem in metastatic RCC patients, and adequate caloric intake is a priority. Exercise may not be possible for many reasons. Sodium restriction has a significant impact on BP and may be particularly relevant in selected patients. The contribution of pain to poor BP control should be considered, and pain should be treated appropriately.

6.2 Pharmacologic Management

No prospective studies have compared classes of antihypertensive agents in MRCC patients on VEGF-I therapy. Retrospective analyses of studies involving MRCC patients treated with sunitinib have shown that treatment with an antihypertensive agent does not affect the antitumour activity of sunitinib[9]. Thus, there is no evidence that MRCC patients should be treated differently than other hypertensive patients; however, the potential for interactions between antihypertensives (which inhibit the cytochrome P450 system) and VEGF-IS should be taken into consideration. The VEGF-IS such as sunitinib are metabolized in the liver by cytochrome P450 3A4, and inhibitors of that isoenzyme such as diltiazem or verapamil should be avoided[32].

In view of the randomized controlled trials available for long-term cardiovascular protection, the CHEP guidelines[25] suggest the use of 5 classes of agents: thiazide or thiazide-like diuretics, beta adrenergic blockers with or without alpha-blocking properties, angiotensin converting-enzyme inhibitors (ACEIS), angiotensin II receptor blockers (ARBS), and dihydropyridine (DHP) and non-DHP calcium channel blockers. More experience and scientific evidence support those classes of agents as initial therapy than support the centrally acting agents and peripheral alpha adrenergic blockers, which can be used as additional therapies if BP is not sufficiently controlled. In the absence of long-term studies, the role of renin inhibitors such as aliskiren is still under evaluation.

Choice of antihypertensive therapy will depend on associated risk factors and the presence or absence of end-organ damage. Medications should be chosen according to the CHEP guidelines and preferably include calcium channel blockers, thiazide diuretics, and ACEI or ARB used alone or in combination with other agents, but not the combination of ACEI and ARB[25].

In patients with a single kidney secondary to nephrectomy, and in the absence of information on the arterial system in such patients, an ACEI, ARB, or aliskiren should be added only with caution. Electrolytes and creatinine should be checked within 72 hours and after 1 week on therapy.

In patients with tachycardia, addition of a beta-blocker can be useful to normalize heart rate and lower BP (especially in those under the age of 60 years, in whom beta-blockers remain a first-line treatment).

In patients with diabetes and proteinuria, the use of an ACEI or ARB as the first therapy for high BP may be appropriate in an effort to protect renal function[25]. Electrolytes and creatinine should be checked within 72 hours and after 1 week on therapy.

6.3 Whom to Treat and When to Treat

Patients should be treated to avoid acute hypertensive complications (encephalopathy, heart failure). For patients without a previous history of hypertension, potential elevations in BP should be monitored either at home or in the clinical setting. Patients should be advised to monitor for symptoms of acute hypertensive elevation (dyspnea, retrosternal chest pain), although target organ damage secondary to the type of BP rise expected in this case is unlikely. During the first 2 weeks and the first cycle of treatment, BP should be measured daily. If patients are normotensive, BP should then be measured during clinic visits. If patients have a manual office BP greater than 140/90 mmHg, daily recording should be obtained.

Patients on antihypertensive medication with a BP less than 140/90 mmHg during VEGF-I therapy should have recordings of BP made weekly or at clinic visits.

Antihypertensive therapy should be considered for patients with a manual office BP above 140/90 mmHg and signs of end-organ damage (cardiac, cerebral, or renal), although there is a debate among hypertension experts about the BP level at which therapy should be initiated, given that the primary goal of therapy is to avoid acute hypertension-related complications (encephalopathy, heart failure, kidney failure). Therapy should also be initiated or very strongly considered if BP is greater than 160/100 mmHg, even without signs of end-organ damage. However, therapy for elevations in BP less than 160/100 mmHg in patients with no signs of end-organ damage should generally be avoided, because the BP increase attributable to VEGF-I therapy is of limited duration and tends to normalize on withdrawal of therapy.

For patients who receive continuous VEGF-I treatments, antihypertensive treatment should be initiated when manual office BP is above 160/100 mmHg, and considered or initiated when BP reaches 140/90 mmHg in the presence of symptoms or end-organ damage, including renal dysfunction.

Patients with a previous history of hypertension should be treated to maintain an average blood pressure of 140/90 mmHg or less through each cycle of therapy—reflecting both the acute increases in BP during VEGF-I therapy and the decline during a treatment break. (Table II). If baseline BP is higher than 140/90 mmHg, treatment should be considered to prevent further increases in BP after a VEGF-I is started. Antihypertensive treatment should be initiated if BP is higher than 160/100 mmHg at baseline.

Patients who are already on antihypertensive therapy should be maintained on their treatments unless there is a potential for interaction, such as that with the non-DHP calcium channel blockers (diltiazem and verapamil). Before initiation of VEGF-I treatment, BP should be normalized. Patients should have BP measurements made in clinic and should also be advised to measure BP at home as previously described. They should report to their heath care professional if their BP exceeds 140/90 mmHg for several days. When VEGF-I is withdrawn for a treatment break, patients on antihypertensive medication should make BP measurements on a regular basis, preferably daily or every other day. If their BP declines to less than 140/90 mmHg during a treatment break, patients should be advised to contact their health care professional to reevaluate their antihypertensive medications, which could then be reduced by 50%. Those medications could be temporarily withdrawn if BP is less than 120/80 mmHg. Ideally, home BP recorders with a memory should be used so that BP readings can be verified at the next clinic visit, thus eliminating reporting bias.

7. SUMMARY

Hypertension is a common adverse effect of VEGF-I treatment. The incidence of this adverse event needs clarification, although it appears that almost all patients have some increase in BP, and a significant percentage develop hypertension according to standard hypertension guidelines. Although a short-term increase in BP will generally not be associated with cardiovascular damage, the need for antihypertensive therapy depends on the degree of the increase in BP, the underlying cardiovascular status of the patient, and other associated risk factors. In general, VEGF-I dose reductions, VEGF-I schedule changes, and treatment discontinuations are rarely necessary in the management of hypertension. Nearly all patients developing hypertension are well controlled with 1 or 2 antihypertensive medications.

8. DISCLAIMER

The recommendations in this manuscript reflect the consensus from an expert working group composed of 4 medical oncologists and 5 hypertension specialists. The CHEP guidelines, available literature, and expert opinion were used to develop the recommendations. Nevertheless, clinical judgment based on the medical history and clinical status of the individual patient should dictate the appropriate management and actions to take, if any, in response to hypertension as a side effect of VEGF-I.

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10. CONFLICT OF INTEREST DISCLOSURES

PL has received research grants and consulting honoraria from Pfizer, Boehringer Ingelheim, Novartis, Merck, and AstraZeneca. CK has received consulting honoraria from Pfizer, Novartis, GlaxoSmithKline, and Roche. RDF has received research grants and consulting honoraria from Pfizer, Bayer, Boehringer Ingelheim, Merck, Nektar, Novartis, Servier, and AstraZeneca. ELS has received research grants and consulting honoraria from Novartis, Daiichi–Sankyo, Janssen, Merck, Novartis, and Servier. FP has received consulting honoraria from Pfizer. MM has received consulting honoraria from Servier. GB has received research grants and consulting honoraria from Pfizer, Novartis, and GlaxoSmithKline. LP and DR have no financial conflicts of interest to declare.

TABLE II Recommendations for blood pressure (BP) management before and during treatment with inhibitors of the vascular endothelial growth factor (VEGF-I) signalling pathway

Manual office blood pressure recording (mmHg)	*VEGF-I treatment*	*Anti-hypertensive treatment*	*Timing of follow-up blood pressure (BP) recordings*
Before initiation of VEGF-I			
<130/80	Initiate		At each clinic visit and at home daily for 2 weeks
130–139/80–89	Initiate		At weekly clinic visits and at home daily for 2 weeks after initiation
140–159/90–99	Initiate if no signs of end organ damage	Measure BP in clinic or at home daily Initiate if SBP > 160 or DBP > 100	Before VEGF-I: at clinic visits and at home daily After VEGF-I: at home daily and report if hypertension is not controlled
	If signs of end organ damage, initiate when BP < 140/90	Suggest initiation or adjust to maintain BP < 140/90	
>160/100	Initiate when BP<140/90	Suggest initiation Adjust to maintain BP<140/90	At weekly clinic visits or by family physician and at home daily
>180/110	Not until hypertension is controlled	Initiate and refer to specialist for investigation and treatment	
During VEGF-I treatment (after initial 2 weeks)			
<130/80	Maintain		At home weekly
130–159/80–99	Maintain	If already initiated: maintain dose and follow renal function and electrolytes If not already initiated: consider initiating if patient is symptomatic or if end-organ damage is evident (cardiac, vascular, CVA, renal)	At home weekly and at each clinic visit if receiving anti-hypertensive treatment
>160/100	Maintain	Adjust to BP<160/100	At home daily and at weekly clinic visits
>180/110	Interrupt	Refer for evaluation and treatment	

CVA = cerebrovascular accident.

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