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REVIEW ARTICLE

Use of Antihypertensive Drugs in Neoplastic Patients

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Abstract The introduction of Vascular Endothelial Growth Factor (VEGF) signaling pathway inhibitor treatment has highlighted the role of the baseline activity of the VEFG system for blood pressure regulation. VEGF signaling pathway is associated with hypertension and proteinuria. Activation of the endothelin system, endothelial dysfunction and capillary rarefaction are among the underlying mechanisms possibly explaining the rise in blood pressure and, to some extent, also the renal injury. The hypertension induced by VEGF signaling pathway inhibition is, usually, responsive to treatment. Recommendations about the management of cardiovascular toxicity in patients receiving VEGF signaling pathway inhibitors include a formal cardiovascular risk assessment before initiation of VEGF signaling pathway inhibitor treatment, active monitoring of blood pressure and cardiac toxicity throughout treatment, with more frequent monitoring during the first cycles of therapy, given that marked and unpredictable blood pressure rises can occur early after treatment with a VEGF signaling pathway inhibitor, and aggressive management of blood pressure elevations and early symptoms and signs of cardiac toxicity to prevent clinically limiting complications. In patients with preexisting hypertension, the blood pressure target for initiating VEGF signaling pathway inhibitor treatment should be $<140/90$ mmHg. Blockers of the renin-angiotensin system and calcium channel antagonists are among the drugs to be preferably used in these clinical conditions.

Keywords Hypertension · Blood pressure · Microvasculature · Angiogenesis · Antiangiogenic treatment

1 Introduction

The population of cancer survivors has gradually increased in recent decades. A study of the relative prevalence of cancer survival in the United States shows that in 2014, nearly 14.5 million Americans with a history of cancer were alive [1]. The number of cancer survivors is projected to increase by 31% to almost 19 million in the next 10 years [1]. The increasing number of cancer survivors is a reflection of an enhanced survival of cancer, as a result of improvements in cancer detection, treatment advances, more adjuvant treatments, and also of an increasing number of new cancer diagnoses due to a growing and aging population as cancer incidence increases with age [1]. However, the cancer survivors are at risk for conditions related to the disease and its treatment, which are of increasing importance as survival rates improve. These conditions include complications of the treatment received, in particular drug treatment. Cardiovascular complications, including hypertension, are common side effects of anticancer drugs [1].

Several factors possibly contribute to chemotherapy-associated vascular toxicity [2]. Multiple stimuli, such as cardiovascular risk factors, cancer itself, and anticancer drugs, influence vascular function and arterial structure leading to increased reactivity, altered vascular tone, impaired endothelial function, and platelet activation [2].

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These processes, in turn, contribute to cardiovascular disease, such as hypertension, cardiac ischemia and thrombosis, which might be facilitated and aggravated by chemotherapy in cancer patients [2]. In particular, both alkylating agents and vascular endothelial growth factor (VGEF) signalling pathway inhibitors may cause or aggravate hypertension [2]. Bevacizumab, for example, may significantly increase the risk of high-grade hypertension in cancer patients [3], and this increase may have also a consequence in terms of fatal events [4]. Substantially VEGF inhibitor increases the risk of myocardial infarction, hypertension, arterial thromboembolism and proteinuria [5, 6].

On the other hand, anti-angiogenic targeted therapies are now major tools in the management of solid tumors [7]. Briefly, one can distinguish between monoclonal antibodies such as bevacizumab directed against VEGF and small molecules such as those targeted against receptors with tyrosine-kinase activity [7].

As mentioned, hypertension and proteinuria are the most frequent and specific side effects of anti-angiogenic targeted therapies. The prevalence of hypertension appears rather different according to the type of targeted therapy and also to the type of studies. Elevated blood pressure was initially observed with bevacizumab in 20–30% of patients also receiving chemotherapy [7]. The mechanisms possibly involved in hypertension induced by inhibitors of angiogenesis are summarized in Fig. 1 [8], although the role of endothelial dysfunction is not unanimously accepted [9]. Pre-existing hypertension, age, and body mass index identify patients at risk for significant anti-VEGF therapy-induced blood pressure elevation [10]. Hypertension appears to be a clinical biomarker of efficacy of anti-VEGF therapies in a broad range of malignancies [10].

2 Capillary Rarefaction in the Onset of Hypertension Induced by Anti-VEGF Therapies

A reduction of capillary density is a frequent finding in essential hypertension [11], and it is due to a structural and functional disappearance of microvessels.

Both total capillary density (all capillaries, including those recruited during venous congestion) and basal capillary density (capillaries perfused in basal conditions) may be reduced in essential hypertension. Capillary density in various regions of the skin (nailfold, dorsum of the fingers, forearm) may be evaluated non-invasively by videomicroscopy/capillaroscopy [11]. Microvascular rarefaction may cause impaired tissue perfusion and, consequently, target organ damage and clinical events in hypertension [12].

Anti-angiogenic drugs may cause microvascular rarefaction as part of their mechanisms of action (inhibition of

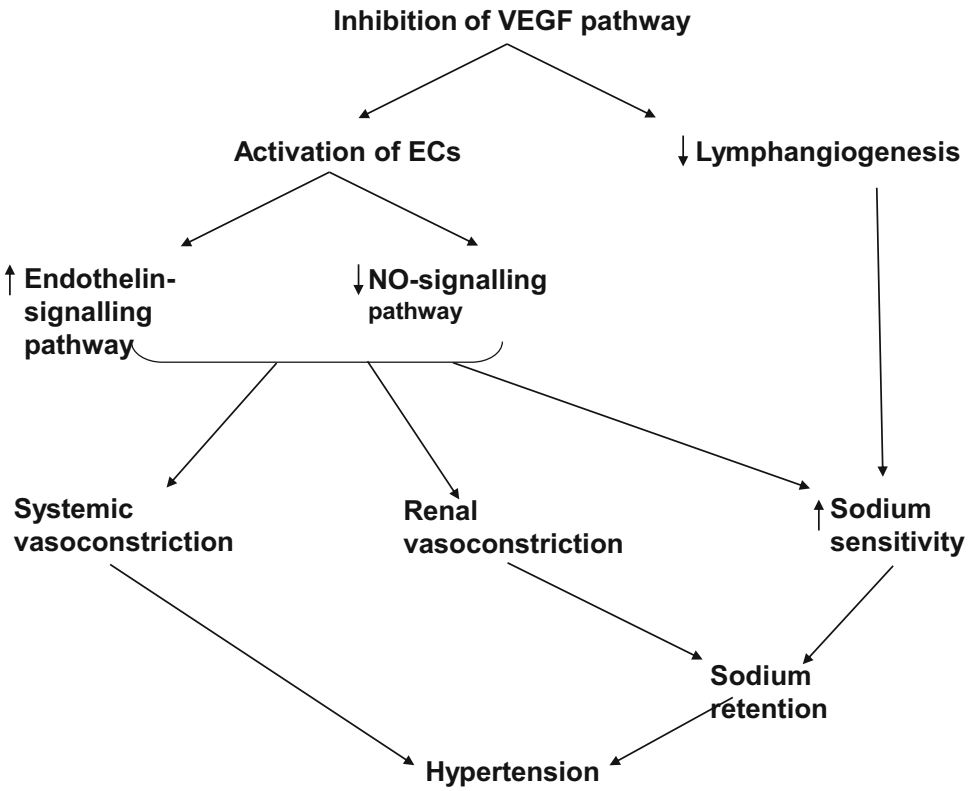

Fig. 1 Possible mechanisms involved in hypertension induced by vascular endothelial growth factor inhibition. *EC* endothelial cell, *NO* nitric oxide, *RTKIs* receptor tyrosine kinase inhibitor, *VEGF* vascular endothelial growth factor From Reference [8]

vascular growth factors) [13], and, actually, a reduction of capillary density after treatment with anti-angiogenic drugs was observed [11] and considered related with increased blood pressure values [14]. As previously mentioned, because blood pressure elevation with VEGF inhibition appears to be a mechanism-dependent toxicity, the notion that elevations in blood pressure may predict superior tumor outcomes is gaining considerable interest in the oncological community as a means to optimize dosing and outcomes [13].

3 Management of Anti-Angiogenic Therapy-Induced Hypertension

In the last years several authors and institutional authorities have provided suggestions and recommendations concerning the management of cardiovascular side effects of anti-angiogenic drugs.

In 2011, des Guetz et al. suggested that active management of hypertension should be performed before initiation of such therapies. Blood pressure should be measured at least once a week during the first 6 weeks of therapy [7]. As inhibitors of VEGF signaling pathway frequently induce proteinuria in association with hypertension, it seems logical to systematically perform a screening test for proteinuria before initiation of therapy and to recommend angiotensin-converting enzyme (ACE) inhibitors for the management of hypertension [7]. Verapamil and diltiazem, which are non-dihydropyridine calcium channel blockers inhibiting CYP 3A4, should be avoided in patients taking sunitinib or sorafenib, which are potent inhibitors of CYP3A4 [7]. Dihydropyridine calcium channel blockers and ACE inhibitors might be recommended as first-line anti-hypertensive therapy in this population [7]. If, during the first week after initiation of anti-angiogenic therapy, systolic blood pressure rises over 165 mmHg or diastolic blood pressure over 100 mmHg, anti-angiogenic therapy should be held until effective titration of anti-hypertensive therapy [7].

De Jesus-Gonzalez et al., in 2012, provided in a schematic flow chart (Fig. 2) some suggestions about the management of anti-angiogenic therapy-induced hypertension [13], whose main principles are substantially in agreement with the previously mentioned ones [7].

In 2013, Bair et al. [15], suggested that, prior to anti-angiogenic treatment, an aggressive management of blood pressure consistent with JNC7 guidelines and a urine analysis for proteinuria should be done; after initiation of treatment the suggestions are the following:

1. Frequent (weekly) monitoring of blood pressure in the first 6 weeks.
2. Use of automated or home blood pressure monitoring for high-risk patients.
3. Urine analysis for detection of proteinuria.
4. Aggressive blood pressure management with the use of angiotensin-converting enzyme inhibitors and dihydropyridine calcium channel blockers (1st and 2nd line therapy).
5. Titration of blood pressure medications during chemotherapy ‘‘holiday’’ (if necessary).

More recently, Cameron et al. [2] also provided a very brief flow chart summarizing the suggested clinical approaches to the problem, in general confirming the suggested blood pressure target of 140/90 mmHg and the suggestion to use, as preferred drugs, angiotensin-converting enzyme inhibitors (ACE) or calcium channel antagonists. The Authors provided also detailed information about specific drugs to be used in the management of chemotherapy-associated hypertension, also considering indications/benefits and cautions/contraindications (Fig. 3) [2].

Finally, Van den Meiracker and Danser [16] provided further indications, including evaluations of newer drugs. The two Authors observed that the calcium channel blocker amlodipine and the dual endothelin-receptor antagonist macitentan could effectively prevent the rise in blood pressure [16] in these situations. In contrast, the ACE inhibitor captopril and the phosphodiesterase inhibitor sildenafil reduced proteinuria, but these agents had no effect on blood pressure [16]. Interestingly enough, macitentan also reduced proteinuria. These experimental findings agree well with previous clinical and experimental studies that the hypertension induced by VEGF signaling pathway inhibition is a low-renin, high-endothelin-1, salt-sensitive form of hypertension [16]. Based on these data, they propose to use a dihydropyridine calcium channel blocker as a first line treatment of hypertension in these patients [16]. In case of proteinuria, an ACE inhibitor or angiotensin II receptor blocker should be added [16]. An endothelin-receptor antagonist may be a valuable alternative, but such agents are not approved for the indication of hypertension or renal injury [16]. The use of endothelin-receptor antagonists may also be hampered by potential pharmacokinetic interaction (metabolized by cytochrome CYP3A4) [16]. Furthermore, currently available endothelin-receptor antagonists are expensive [16].

4 Further Considerations and Conclusions

The introduction of VEGF signaling pathway inhibitor treatment has highlighted the role of the baseline activity of the VEFG system for blood pressure regulation and

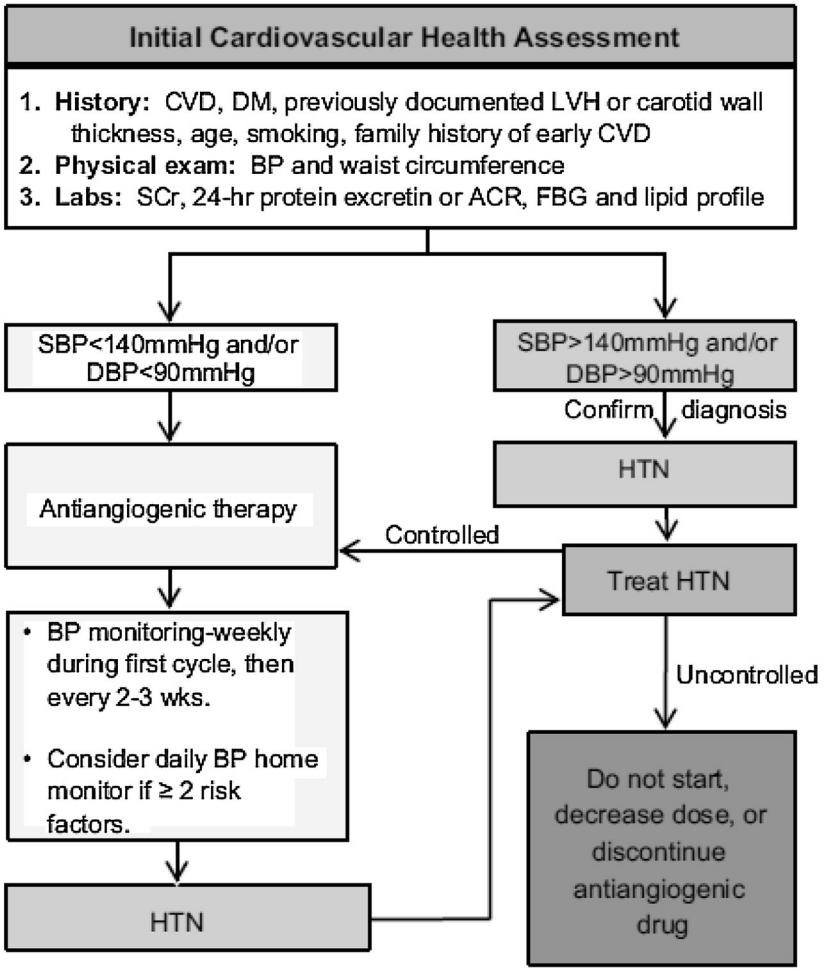

Fig. 2 Management of antiangiogenic therapy-induced hypertension. Initial cardiovascular evaluation and monitoring of blood pressure in candidates for antiangiogenic therapy. *CVD* cardiovascular disease, *DM* diabetes mellitus, *LVH* left ventricular hypertrophy, *BP* blood pressure, *SCr* serum creatinine, *ACR* albumin:creatinine ratio, *FBG* fasting blood glucose, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HTN* hypertension From Reference [13]

maintenance of renal function [16]. The hypertension and renal injury induced by VEGF signaling pathway inhibition as many feature in common with those of preeclampsia and share similar pathophysiological mechanisms [16]. As mentioned, evidence indicates that activation of the endothelin system, most likely as a reflection of an activated state of endothelial cells because of VEGF blockade, is a possible mediator of the rise in blood pressure and, to some extent, also of renal injury [16]. The hypertension induced by VEGF signaling pathway inhibition is, usually, responsive to treatment [16].

In 2012, the Cardiovascular Toxicities Panel of the National Cancer Institute has provided launched recommendations about the management of cardiovascular toxicity in patients receiving VEGF signaling pathway inhibitors [16, 17]. The panel recommended a formal cardiovascular risk assessment before initiation of VEGF signaling pathway inhibitor treatment, active monitoring of blood pressure and cardiovascular toxicity [16, 17] throughout treatment, with more frequent monitoring during the first cycles of therapy, given that marked and unpredictable blood pressure rises can occur early after treatment with a VEGF signaling pathway inhibitor, together with an aggressive management of blood pressure elevations and early symptoms and signs of organ damage. In patients with preexisting hypertension, the blood pressure target for initiating VEGF signaling pathway inhibitor treatment should be less than 140/90 mmHg, if possible [16].

Because clinical trials about the most optimal treatment of hypertension or renal injury induced by VEGF signaling pathway inhibitors are presently not available and difficult to perform, advice about treatment in these clinical conditions should be based mainly on insight into pathophysiological mechanisms, as well as on the relatively limited data obtained in preclinical and clinical studies [16].

The prevention of cardiovascular damage associated with other chemotherapic agents was specifically addressed in 2016 Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the European Society of Cardiology [18]. Strategies for prevention and attenuation of cardiovascular complications of cancer therapy include selection of an alternative non-cardiotoxic chemotherapy, anthracycline preparations with

Aspect of therapy	Drug class	Examples	Indications/benefits	Cautions/contraindications
First- and second-line therapy	ACE inhibitors	Captopril Enalapril Lisinopril Perindopril Ramipril	• VEGFI associated hypertension • Younger patients • Proteinuria • Diabetic nephropathy • Left ventricular dysfunction • Quick onset of action	• Renovascular disease • Peripheral vascular disease • Renal impairment • Chemotherapy with renal clearance • Hyperkalaemia
	Angiotensin II receptor antagonists	Candesartan Irbesartan Losartan Valsartan	• VEGFI-associated hypertension • Cough related to ACE inhibitor • Younger patients • Proteinuria • Diabetic nephropathy • Left ventricular dysfunction • Quick onset of action	• Renovascular disease • Peripheral vascular disease • Renal impairment • Chemotherapy with renal clearance • Hyperkalemia
	Dihydropyridine calcium channel antagonists	Amlodipine Lercanidipine	• Cisplatin-associated hypertension • Elderly patients • Isolated systolic hypertension	• Ankle swelling • Slow onset of action
Third-and fourth-line therapy	Thiazide diuretics	Bendroflumethiazide Chlorthalidone Hydrochlorothiazide Indapamide	• Elderly patients • Isolated systolic hypertension	• Gout • Hypercalcaemia • Hypokalaemia • QTc prolonging drugs
	Mineralocorticoid receptor antagonists	Eplerenone Spironolactone	• Resistant hypertension	• Hyperkalemia • Gynecomastia (spironolactone)
	β-blockers	Bisoprolol Carvedilol Metoprolol	• Ischemic heart disease	• Bradycardia • Heart block • Asthma or COPD
Agents to avoid	Non-dihydropyridine calcium channel antagonists	Verapamil Diltiazem	N/A	
BP management during chemotherapy "off periods" or after stopping or completing chemotherapy	• Monitor for rebound hypotension with or without downtitration or stop antihypertensive therapy • Regular monitoring of blood pressure after stopping or completing chemotherapy			

Fig. 3 Summary of the approaches to management of chemotherapy-associated hypertension. *ACE* angiotensin-converting enzyme, *BP* blood pressure, *COPD* chronic obstructive pulmonary disease, *N/A* not applicable, *VEGFI* vascular endothelial growth factor inhibitor From Reference [2]

lower cardiotoxicity (e.g. liposomal doxorubicin), reduced-dose schedules and/or additional cardioprotective drugs (e.g. ACE inhibitors, beta-blockers, aldosterone antagonists or dexrazoxane) [18]. Strategies for attenuation of complications related to use of specific agents are also reported [18].

Finally, hypertension associated with anti-reject immunotherapy in solid organ transplantation may have some similarities to what observed with anti-cancer drugs. Arterial hypertension is a common complication after kidney transplantation and a major risk factor for adverse outcome and graft rejection due to blood pressure elevation by immunosuppressive medications [19]. Calcineurin inhibitors induce hypertension by a mechanism related to the imbalance of vasoactive substances endothelin and nitric oxide, and probably by causing overactivity of thiazide-sensitive sodium-chloride-cotransporter. Corticosteroids are well known for their hypertensive effects. The interactions of calcineurin inhibitors and mammalian target of rapamycin inhibitor sirolimus also promote hypertension [19]. Management of arterial hypertension is a complex problem in the care of kidney transplant recipients. Target blood pressure values of <130/80 mmHg are suggested by the National Kidney Foundation/Kidney Disease Outcomes Quality Initiative [19]. Calcium channel blockers may be useful in antagonizing the vasoconstrictive effects of calcineurin inhibitors. The renin-angiotensin system inhibitors seem a good option, especially in patients with proteinuria, however their effects on long-term graft and patient survival are controversial [19]. β-Blockers could be beneficial in patients with coronary heart disease, but caution is required due to metabolic adverse effects. Until more evidence is provided, the choice of optimal antihypertensive therapy in kidney transplant recipients should be based on previous individual antihypertensive tolerability and efficacy, comorbidities, concomitant medications and post-transplant kidney function [19].

4.1 Conclusions

According to the available evidence, our suggestions about how to manage hypertension during anti-angiogenic treatment may be summarized as follows:

- Control effectively blood pressure before starting treatment.
- Check blood pressure values before and during/after treatment.
- Check proteinuria.
- Use home blood pressure measurements.
- Preform titration of drugs during holidays of anti-angiogenic treatment.

Additional recommendations may be the following:

- Check, control and correct other cardiovascular risk factors.
- Use antiplatelet therapy in high risk patients.
- Start drug treatment with calcium channel blockers and/or renin-angiotensin system inhibitors.
- Detect complications early.
- Consider that, in general, healthy lifestyle increases survival.
- Most importantly: consider that multidisciplinary decisions are mandatory in this area.

The 2013 Guidelines of the European Society of Hypertension and the European Society of Cardiology for the management of arterial hypertension in the section "treatment strategies in special conditions" did not address specifically the problem of the management of anti-angiogenic therapy-induced hypertension [20]. It is possible, however, that in the new version that is expected to be available in the near future, this important aspect will be covered.

Compliance with Ethical Standards

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Conflict of interest Damiano Rizzoni, Carolina De Ciuceis, Enzo Porteri, Claudia Agabiti-Rosei, Enrico Agabiti-Rosei declare that they have no conflict of interest in relation to the present manuscript.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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