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REVIEW ARTICLE

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Bevacizumab — cardiovascular side effects in daily practice

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ABSTRACT

The formation of new blood vessels is essential for tumour growth and metastasis. Bevacizumab, monoclonal antibody binding VEGF, is applicable in the therapy of several metastatic cancer diseases. This direct interference in the mechanisms of angiogenesis results in certain cardiovascular complications such as arterial hypertension, venous and arterial thromboembolic events, and heart failure. Knowledge of risk factors, early diagnosis, and treatment seem to be crucial for the prognosis of patients. This article presents the problem of cardiovascular side effects related to bevacizumab with some selected recommendations of international experts and the Position Paper of the European Society of Cardiology.

Key words: bevacizumab, angiogenesis, arterial hypertension, venous and arterial thromboembolic events

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Introduction

In the 1970s Folkman formulated a hypothesis that the formation of new blood vessels is an essential factor of cancer growth and progression to metastatic disease [1]. In later decades the impact of neo-angiogenesis was repeatedly confirmed and its mechanism was also recognised. Hypoxia and hypoxia-inducible factors (HIFs) are the strongest pro-angiogenic stimuli, which, among others, influence the processes dependent on vascular endothelial growth factor (VEGF) family and their receptors. Particularly important is the role of VEGF-A as well as VEGFR1 and VEGFR2 receptors [2, 3]. VEGF stimulates angiogenesis, and additionally it is essential factor for the survival of endothelial cells in newly formed tumour vessels, whereas in normal tissue it plays no major role in the functioning of pre-existing vasculature [4, 5].

Bevacizumab is a humanised monoclonal antibody, which binds to VEGF through antigen-binding fragment Fab. Although it does not induce conformational changes of VEGF protein, bevacizumab interferes in spatial interaction with VEGFR1 and VEGFR2 [3]. No bevacizumab-related *in vitro* activity was shown, because the mechanism of anticancer action is mainly indirect and unspecific to the cancer type [6, 7]. According to this, there were many attempts to use bevacizumab in different indications. Currently bevacizumab is registered by the European Medicines Agency (EMA) in combination with chemotherapy for the treatment of a few advanced cancers (carcinoma of the colon or rectum, non-squamous non-small cell lung cancer, ovarian, fallopian tube, or primary peritoneal cancer, carcinoma of the cervix, breast cancer) and in combination with interferon for treatment of patients with advanced renal cell cancer [8].

Pathophysiology of antiangiogenic therapy-induced adverse events

Vascular endothelial growth factor plays a crucial role during embryonic development, but in adults it is less important. Studies in adult animal models have demonstrated several changes in vasculature in some organs upon VEGF action. Significant atrophy of capillaries was mainly observed in pancreatic islets, thyroid gland, adrenal cortex, pituitary gland, gut intestinal villi, choroid plexi, adipose tissue, and trachea. These consequences were not seen in skeletal muscles and myocardium, lungs, brain, and retina. General VEGF impact depends on inhibitor dose and could lead

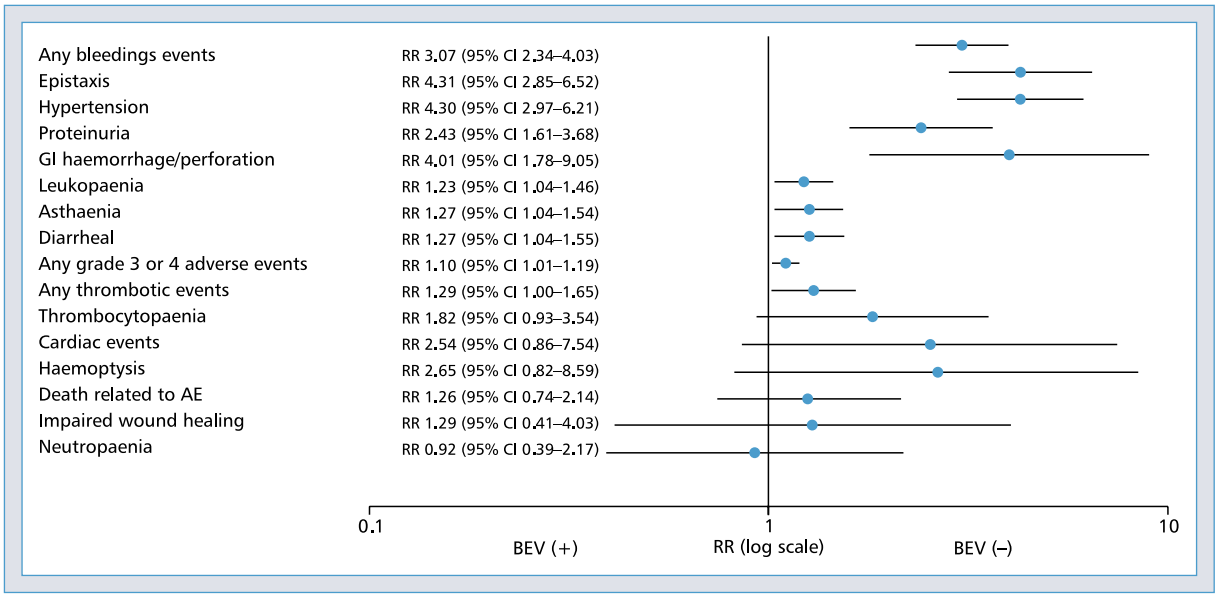

Figure 1. Adverse events of bevacizumab — meta-analysis according Geiger-Gritsch et al. 2010 [11]

(e.g. in thyroid gland) to atrophy of more than two-thirds of capillaries. The second important sequence of VEGF inhibitors' action was decreasing of endothelial fenestration, mainly in thyroid gland, pancreatic islets, and renal glomeruli [4, 9]. Despite the fact that those changes were reversible, it does not exclude their clinical input (especially in organs with abundant vasculature as well as with secretory functions) [10].

Safety and toxicity of bevacizumab

There are many data available regarding the safety of bevacizumab use, from clinical trials and daily clinical practice. The results of two meta-analyses were published in 2010 and 2013, respectively [11, 12].

The first meta-analysis included the observations of approximately 6500 patients with colon, breast, non-small cell lung cancer (NSCLC), and renal-cell cancer (RCC), treated in 13 randomised clinical trials (RCTs). The risk of serious adverse events was significantly higher in patients treated with chemotherapy combined with bevacizumab than in the chemotherapy alone group — the risk ratio (RR) was 1.10 with 95% confidence interval (CI) 1.01–1.19. Grade 3 or 4 toxicities were noted in 1 of 14 treated patients, which corresponds to a number needed to harm (NNH) of 14. Bevacizumab use was associated with increased hypertension and haemorrhage risk, including epistaxis and GI bleedings or perforation. Also noted was significantly more frequent occurrence of proteinuria, leukopaenia, diarrhoea, and asthaenia. The prevalence of other adverse events (including venous and arterial thromboembolism, cardiac episodes, haemoptysis, thrombocytopaenia, neutropaenia, and wound healing problems) did not differ between the groups. Furthermore, there was no increased risk of treatment-related deaths in a group receiving chemotherapy with bevacizumab [11]. For summary see also Figure 1.

The second meta-analysis included nearly 11,500 patients from 24 trials with the cancers mentioned above as well as gastric, pancreatic, prostate cancer, and melanoma. Patients treated with bevacizumab indicated higher risk of grade 3 and 4 complications as compared to chemotherapy alone. The death risk was also higher, particularly in lung cancer patients. Among all complications the biggest differences associated with bevacizumab use were related to hypertension and proteinuria, and, to a lesser extent, haemorrhage and GI perforation. In the general population there were no differences regarding thromboembolic episodes; however, in breast and RCC patients it was significantly higher in patients treated with bevacizumab [12]. Table 1 summarises the results.

The next analyses, published in 2011 and 2014, respectively, included approximately 10,000 and 25,000 patients. Both aimed to assess the safety of bevacizumab treatment, and the results were similar. There was increased death risk RR 1.33; 95% CI: 1.02–1.73 and RR 1.29; 95% CI: 1.05–1.57, respectively; however, the relationship between bevacizumab dose/treatment duration and complication occurrence was not unambiguously established. The general percentage of treatment-related deaths was 1.48% and there were no between-study differences. The highest percentage was noted in pancreatic cancer patients, and the lowest in breast cancer patients (6.06% and 0.69%, respectively). A higher risk of fatal complications was indicated in lung, pancreatic, prostate,

Table 1. Bevacizumab adverse events — meta-analysis (based on [12])

	RR	95% CI	p
Adverse events > G2	1.2	(1.15–1.24)	< 0.00001
Proteinuria	7.08	(4.54–11.04)	< 0.00001
Hypertension	4.96	(3.82–6.44)	< 0.00001
Haemorrhage	1.34	(1.02–1.76)	0.28
Venous thromboembolic events	1.07	(0.9–1.27)	0.1
Arterial ischaemic events	1.32	(0.98–1.78)	0.13
GI perforation	2.3	(1.34–3.95)	0.66
Fatal events	1.48	(1.11–1.98)	0.02
Fatal pulmonary haemorrhage (lung cancer studies)	**5.65**	**(1.26–25.26)**	**0.02**

and ovarian cancer patients and during treatment with cisplatin-based and taxoid-based chemotherapy (when lower risk — breast cancer) [13, 14].

Also available are the data from patients (mainly with colorectal cancer) treated with bevacizumab out of RCTs. All of these mentioned trials — BEAT (Bevacizumab Expanded Access Trial), BRiTE ((Bevacizumab Regimens: Investigation of Treatment Effects and Safety), and ARIES (Avastin Registry — Investigation of Effectiveness and Safety) — included approximately 2000 patients receiving bevacizumab with chemotherapy, most frequently in first-line setting. The mentioned studies allow us to assess the safety in populations close to daily clinical practice. In the BEAT study bevacizumab-related serious adverse events occurred in 11% of patients. The most frequent adverse events included hypertension (5.3%), haemorrhage (3%), GI perforation (2%) and thromboembolic complications, proteinuria, and wound healing problems (each 1%). In patients with no primary tumour resection perforations occurred in 4% of treated patients. Bevacizumab-related fatal complications were noted in 2% of patients [most frequently during venous thromboembolic disease (VTE), GI perforation, and haemorrhage]. The risk of serious adverse events was independent of the chemotherapy scheme with which bevacizumab was used [15]. In the BRiTE study the majority of complications was observed up to 6 months after treatment initiation. Thromboembolic episodes were more frequent in patients at the age of 75 years and older and in worse performance status (PS) [≥ 1 in Eastern Cooperative Oncology Group (ECOG) scale]. Age below 65 years, presence of primary tumour, and previous radiotherapy were associated with higher risk of GI adverse events. No favouring haemorrhage-related factors were identified. The risk of hypertension was higher in patients with previously diagnosed abnormal blood pressure (BP) values and arterial diseases as well as in patients untreated with anticoagulant drugs. Similarly to other observations, it was the most common adverse event. Hypertension was diagnosed in 22% of patients, previously with no abnormal BP values. In another 22% of patients already treated due to hypertension, its signs and symptoms intensified. Standard antihypertensive monotherapy was sufficient in the majority of cases [16]. In the ARIES study the percentage of complications in bevacizumab-treated patients was slightly higher when treated together with chemotherapy in the first-line than in the second-line setting (23.5% and 16.4%, respectively), although it seems with no relation to chemotherapy protocol [17]. Toxicity profile and adverse event prevalence in patients at the age of 65 years and older was similar to that in younger patients. Hypertension could be an exceptional case. In the Czech population registry the occurrence and exacerbation of hypertensive signs and symptoms were noted in 7.8%, 3.6%, and 3.3% of bevacizumab-treated patients at the age of over 75 years and 65–75 years, and below 65 years, respectively [18].

The clinical impact of the most common complications of therapy with bevacizumab

Taking into consideration known risk factors of complications (e.g. at least a 4-week period after surgical operation), treatment with bevacizumab is associated with the prevalence of grade 3 and 4 adverse events in approximately 10% of patients in total [15, 16]. Table 2 presents the most frequent adverse events together with their grading, and Table 3 summaries the management suggested by experts.

Hypertension

Hypertension requiring introduction or modification of previous antihypertensive treatment can occur at every stage of bevacizumab use. This is the most frequent adverse event, which affects up to 40% of patients. Administration of antihypertensive drugs could be desired even in one-fifth of bevacizumab-treated patients [15, 16]. In approximately 1% of patients hypertension

Table 2. The most common adverse events of bevacizumab (based on [21])

Grade	Hypertension	Proteinuria	Bleeding	Venous thromboembolism
1	Asymptomatic, transient (< 24 hrs) increase by > 20 mm Hg (diastolic) or to > 150/100 if previously BP normal	1+ or 0.15–1.0 g/24 hrs	Mild; intervention not indicated	–
2	Recurrent/persistent or symptomatic increase by > 20 mm Hg (diastolic) or to > 150/100 mm Hg if previously BP normal	2+ to 3+ or 1.0–3.5 g/24 hrs	Symptomatic and medical intervention indicated	Deep vein thrombosis or cardiac thrombosis; intervention not indicated
3	Requiring more than one hypertensive agent or more intensive therapy than previously	4+ or > 3.5 g/24 hrs	Transfusion of erythrocyte concentrate, interventional radiology, endoscopic or operative intervention indicated	Deep vein thrombosis or cardiac thrombosis; intervention (anticoagulation, lysis, filter, invasive procedure) indicated
4	Life-threatening consequence, such, hypertensive crisis	Nephrotic syndrome	Life-threatening consequences; major urgent non-elective intervention indicated	Embolic event including pulmonary embolism or life-threatening thrombosis

was a reason for anticancer therapy discontinuation [19]. Potentially favouring factors include age below 75 years, arterial disease, and previous abnormal BP values [16, 18]. Antihypertensive treatment started before bevacizumab use did not increase the risk of severe complications during treatment. Grade 4 hypertension was observed to be very uncommon and there are no reports about fatal complications [19–21].

Proteinuria

Proteinuria is quite common (up to 27–38% of patients), but it is a very rare cause of bevacizumab-based anticancer therapy discontinuation. It could indicate a clinical significance in app. 1% of bevacizumab-related patients; however, nephrotic syndrome was described only in single cases. No relationship was shown between the occurrence and grade of proteinuria and hypertension and renal functions impairment [19, 21].

Thromboembolic events

The prevalence of thromboembolic complications, including deep venous thrombosis (DVT) and pulmonary embolism (PE), is similar in patients receiving chemotherapy alone and in those treated with bevacizumab (3.2–15.2% and 2.8–17.3%, respectively) [21, 22]. However, there was an increased number of arterial thromboembolic events, which were observed in 3.8% of patients receiving combination therapy as compared to 1.7% of patients with no anti-angiogenic therapy. Notably, it was not associated with higher death risk. Risk factors could include age over 65 years and positive history of ischaemic heart disease (IHD) or atherosclerosis [23].

Haemorrhage

Haemorrhage during bevacizumab treatment can occur in 20–40% of patients, usually having low intensity (e.g. epistaxis not requiring intervention). More severe haemorrhage can be observed in less than 5% of patients, which is similar to the frequency during chemotherapy [15, 16]. NSCLC patients receiving a combination of chemotherapy with bevacizumab are an exception: approximately 9% of those patients experienced serious pulmonary bleeding. The most important risk factors include central tumour localisation and squamous histology [24, 25]. The prevalence of bleedings in patients with metastases in the central nervous system (CNS) is unknown, because such patients are excluded from clinical trials. In patients treated with bevacizumab due to primary cancers in CNS, grade 3 and 4 bleedings were observed in from 0 to 4% of patients [26]. Small procedures (e.g. vascular port implantation) seem not to significantly increase the risk and do not require specific modification of bevacizumab treatment [19].

GI perforation

Perforations of gastrointestinal tract are very rare (up to 2% of patients) but potentially threatening complications of bevacizumab treatment. The possible risk factors include diseases with inflammation within the abdominal cavity: previous radiotherapy, diverticulitis, and peptic

Table 3. Summary of recommended clinical management of selected adverse events of bevacizumab (based on [19, 21])

Adverse event	Monitoring/precautions	Management/therapy
Hypertension	Monitor blood pressure every 2–3 weeks during treatment	Grade 1: continue bevacizumab Grade 2: continue bevacizumab Grade 3: start or modify antihypertensive treatment, hold bevacizumab and resume when hypertension is controlled Grade 4: discontinue bevacizumab
Proteinuria	Monitor by dipstick urinalysis before start of bevacizumab and before each cycle If proteinuria increases to > 2+ on dipstick urinalysis, check 24-hour urinary protein	Grade 1: continue bevacizumab Grade 2: proteinuria < 2 g (24-hrs urine): continue bevacizumab and monitor 24-hour urine protein; proteinuria > 2 g (24-hour urine): hold bevacizumab and resume if proteinuria decreases to < 2 g/24 hrs Grade 3: discontinue bevacizumab Grade 4: discontinue bevacizumab
Venous thromboembolic event	Check clinically for development of DVT	Grade 1: continue bevacizumab Grade 2: continue bevacizumab Grade 3: start anticoagulant therapy, hold bevacizumab for 2 weeks until full anticoagulation established, then resume bevacizumab* Grade 4: discontinue bevacizumab
Arterial thromboembolic event	Exercise caution in patients with a previous history of arterial thromboembolism or > 65 years of age	Discontinue bevacizumab for any grade arterial thromboembolic event
Bleeding	Exercise caution in patients on full-dose anticoagulant therapy, with history of coagulopathy, and metastases to central nervous system	Grade 1: continue bevacizumab Grade 2: continue bevacizumab Grade 3: discontinue bevacizumab Grade 4: discontinue bevacizumab
GI perforation	Physical examination and history for symptoms/signs of perforation (fever, pain, peritonitis) Wxercise caution if active intra-abdominal inflammatory process present, e.g. diverticulitis, and recent radiotherapy/bowel biopsy)	Discontinue bevacizumab for any grade event According clinical situation, severity and patients general state Conservative measures (fluids, antibiotics) Surgical intervention
Wound-healing complication	Delay start of bevacizumab for at least 28 days following surgery or until wound is fully healed	Grade 1: consider hold bevacizumab until fully resolved For elective surgery during bevacizumab therapy, wait for at least 8 weeks after stopping bevacizumab Grade 2: consider hold bevacizumab until fully resolved Grade 3: discontinue bevacizumab Grade 4: discontinue bevacizumab

*Not applied to the patients with severe bleeding episodes before bevacizumab treatment and/or cancer infiltration of large blood vessels

ulcer disease, and peritonitis carcinomatosa. It should be noted that almost one-third of GI perforation cases did not identify any of the above risk factors [15, 16, 27].

Other events

Other complications, e.g. nasal septum perforation or reversible posterior leukoencephalopathy syndrome (RPLS), are very rare and their associations with bevacizumab treatment, pathophysiology, and risk factors are not entirely clear. RPLS occurred in less than 0.1% of patients, but according to serious clinical signs and symptoms (convulsions, confusion, severe headache, visual disturbances, and cortical blindness) and possible causative relations with hypertension, close monitoring is recommended [28, 29].

Statement of the European Society of Cardiology

The Position Paper on Cancer Treatments and Cardiovascular Toxicity developed under the auspices of the Committee for Practice Guidelines of the European Society of Cardiology (ESC) was published and communicated in August 2016 [30]. This report also mentioned cardiovascular toxicity during bevacizumab treatment.

Firstly, based on literature data it was estimated in the report that during bevacizumab treatment the risk of heart failure is 1.6–4% [31]. The results of a large clinical trial in breast cancer patients, prospectively assessing heart function, shows that treatment with bevacizumab after chemotherapy is responsible for left ventricle (LV) dysfunction in 2% of patients, and symptomatic heart failure class III or IV according to NYHA (New York Heart Association) classification in 1% of patients [32]. In European experts' opinion the main risk factors include: 1) previous heart failure, important coronary artery disease or left heart valve disorders (e.g. mitral insufficiency), chronic ischaemic cardiomyopathy, and 2) previous treatment with anthracyclines. The ESC report does not present a detailed strategy of heart function monitoring during treatment with VEGF inhibitors, which needs to be determined. It is known that in some patients heart dysfunction develops shortly after treatment initiation, whilst in others after a few months' delay. Echocardiographic control evaluation at occurrence of the signs and symptoms suggesting cardiotoxicity (e.g. newly diagnosed dyspnoea or peripheral oedema, gradually increasing fatigue, making daily life activities difficult) seems reasonable. Heart dysfunction associated with anticancer therapy leads to decreasing of left ventricular ejection fraction (LVEF) by more than 10 percentage points to values below the lower limit of normal range. This is also an indication for pharmacotherapy use for secondary prevention of cardiovascular complications — angiotensin-converting enzyme (ACE) or angiotensin receptor blocker (ARB) in combination with beta-blocker drug is recommended to prevent heart failure progression. Echocardiography should be repeated during subsequent follow-up in order to confirm resolution or irreversible heart dysfunction.

Secondly, the ESC report highlights that the prevalence of arterial thrombosis varies according to cancer stage and is below 1% during adjuvant chemotherapy in breast cancer patients and even 3.8% during metastatic disease [23, 32]. The most important aspect of stratification is identification of patients diagnosed with coronary artery disease before starting of anti-angiogenic treatment. In the case of acute coronary syndrome or new symptoms of coronary artery disease the management should be highly individualised. The possibility of conservative and invasive treatment, and thereby administrations of antiplatelet and antithrombotic drugs, depend on individual risk of haemorrhage. Each patient with diagnosis of coronary artery disease during the treatment with VEGF inhibitors due to cancer should continue antiplatelet therapy because the potential benefits outweigh the risk of bleeding complications. On the other hand, the use of antiplatelet drugs as part of primary prevention in patients treated with VEGF inhibitors without coronary artery disease is not recommended.

Thirdly, the ESC report underlines the very important problem associated with high prevalence of venous thrombosis in cancer patients. It is very frequently diagnosed in an outpatient setting during chemotherapy of common cancers (e.g. colon, cystic, ovarian, lung, gastric, and pancreatic cancer). The role of primary prophylaxis during anticancer treatment is not yet defined. It was noticed that a combination of chemotherapy with VEGF inhibitor may increase the risk of venous thromboembolic complications [33]. Despite higher pro-thrombotic risk, this group of patients should not be routinely given primary antithrombotic prophylaxis, in view of high bleeding risk and a lack of explicit results showing clinical benefits. Diagnosis of thrombotic episodes in patients during anticancer treatment (including anti-VEGF) is based on recognition of the clinical signs and symptoms of thrombosis of lower extremity veins or pulmonary embolism. No benefits from any strategy of systematic screening were demonstrated. Management of a confirmed episode of acute venous thrombosis or pulmonary embolism is based on administration of low-molecular-weight heparins (LMWH) for at least 3–6 months. After this period of time the choice between cessation of anticoagulant therapy and continuous treatment with LMWHs or vitamin K antagonists should be considered on an individual basis, taking into account the efficacy of previous anticancer therapy, risk of recurrence of VTE or bleedings, as well as the patient's preferences [34]. The new oral anticoagulants, being non-vitamin K antagonists (e.g. dabigatran, rivaroxaban, apixaban), are not currently recommended in cancer patients because there are no data regarding their efficacy and safety in this group of patients. Moreover, those drugs could significantly vary between each other for the sake of drug-drug interactions (including interactions with anticancer drugs and oncological supportive therapies) and correlations between pharmacodynamics and renal and hepatic functions [35].

Fourthly, based on available meta-analyses, the ESC report indicates that hypertension morbidity during bevacizumab treatment is 7.5-fold higher [36, 37]. Collectively, it was estimated, based on observation of a few thousand patients, that the frequency of bevacizumab-induced hypertension accounts for approximately 23.6%, and grade III or IV hypertension — approximately 7.9% [38]. However, it should be underlined that in many oncological clinical trials

Table 4. Differences in diagnosis of hypertension in oncology patients during last years

	CTCAE v. 3 (2003)	CTCAE v. 4 (2009)
1.	Asymptomatic, transient (< 24 hrs) increase by > 20 mm Hg (diastolic) or to > 150/100 mm Hg if previously within normal limits; intervention not indicated	Prehypertension (systolic blood pressure 120 to 139 mm Hg or diastolic blood pressure 80 to 89 mm Hg)
2.	Recurrent or persistent (≥ 24 hrs) or symptomatic increase by > 20 mm Hg (diastolic) or to > 150/100 mm Hg if previously within normal limits; monotherapy may be indicated	Stage 1 hypertension (systolic blood pressure 140 to 159 mm Hg or diastolic blood pressure 90 to 99 mm Hg) medical intervention indicated; recurrent or persistent (≥ 24 hrs); symptomatic DBP increase by > 20 mm Hg; monotherapy indicated
3.	Requiring more than one drug or more intensive therapy than previously	Stage 2 hypertension (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg) medical intervention indicated; more than one drug or more intensive therapy than previously used indicated
4.	Life-threatening consequences (e.g., hypertensive crisis)	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated

hypertension is diagnosed according to the criteria, which are no longer relevant (Tab. 4). According to ESC experts' opinion, hypertension in cancer patients could be treated conventionally. Early and intensive therapy is encouraged in order to prevent development of complications (e.g. heart failure). VEGF inhibitors could lead to hypertension through a specific mechanism, causing increased peripheral vascular resistance and harmful influence on endothelium and podocytes in renal glomeruli [39]. ACEs, ARBs, and calcium antagonists from dihydropyridine derivatives should be the preferred antihypertensive drugs. Calcium antagonists from the non-dihydropyridine derivatives group (verapamil, diltiazem) should be avoided, taking into account the risk of significant drug-drug interactions; however, this problem mainly affects patients treated with small-molecule tyrosine kinase inhibitors (TKIs) (e.g. sunitinib, sorafenib). As a rule, one should choose antihypertensive drugs, which could not cause fluctuations of anticancer drug serum concentration, in other words they do not change its effectiveness and do not increase toxicity risk. The National Cancer Institute (NCI) recommends weekly monitoring of blood pressure during the first cycle of anticancer treatment with each VEGF inhibitor and thereafter not more rarely than every 2–3 weeks during the remaining therapy [40]. The usefulness of regular daily home-based pressure measurement is currently highlighted. This allows avoidance of the "white coat effect", very often observed in cancer patients, who experience permanent stress. It is recommended that every effort be made in each case of iatrogenic hypertension caused by VEGF inhibitor to best tailor hypertensive treatment, without the desire of dose reduction and treatment discontinuation [41]. Modification of antiangiogenic treatment should be considered in cases of iatrogenic hypertension as well as other toxicity symptoms, which could threaten the patient's life and lead to significant worsening of quality of life.

Summary

Large observational trials (BRiTE and BEAT) indicate that the toxicity profile of bevacizumab used in daily clinical practice is well known and predictable, and differs from toxicities of chemotherapeutic drugs. The risk of complications does not significantly depend on a protocol of chemotherapy combined with bevacizumab, but it could differentiate based on cancer type and localisation and previous anticancer therapy. Consideration of the mentioned factors is of significant importance during qualification of patients and is a prerequisite for safe bevacizumab use. The most frequently reported iatrogenic hypertension rarely requires discontinuation of anticancer therapy and should not adversely affect the prognosis of patients. The optimal use of antihypertensive therapy is needed. During observation of the patients continuing the treatment for 3–5 years or more it no association between prolonged bevacizumab use and increased toxicity was noted [15–19, 21, 42].

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