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REVIEW ARTICLE

Michał Wilk[1, 2], Sebastian Szmit[1]

[1]Department of Pulmonary Circulation, Thromboembolic Diseases and Cardiology, Centre of Postgraduate Medical Education, European Health Centre, Otwock
[2]Oncology Department, European Health Centre, Otwock

Cardiovascular complications of antiangiogenic therapy in ovarian cancer patients

Address for correspondence:
Dr hab. n. med. Sebastian Szmit
Department of Pulmonary Circulation, Thromboembolic Diseases and Cardiology, Centre of Postgraduate Medical Education, European Health Centre Otwock, Poland
e-mail: s.szmit@gmail.com

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ABSTRACT

Therapy with angiogenesis inhibitors carries the risk for health and life-threatening cardio-vascular complications. The most common include the development of arterial hypertension, thromboembolic events (venous and arterial) and bleeding. This study provides a detailed analysis of their incidence, pathomechanisms as well as methods of prophylaxis and treatment among ovarian cancer patients receiving bevacizumab.

Key words: anti-angiogenic drugs, bevacizumab, cardiotoxicity, ovarian cancer

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Introduction

In Poland, ovarian cancer accounts for about 5% of all malignancies and is the fourth leading cause of cancer death among women [1]. In the treatment, we use surgical methods, standard chemotherapy based on platinum derivatives and taxoids or including other cytotoxic agents, and targeted therapies (e.g. anti-angiogenic drugs). The process of blood vessel formation is characteristic for many types of malignant tumours and involves a number of stimulants, the most important and best known of which is vascular endothelial growth factor (VEGF) [2]. The most commonly used VEGF inhibitor in ovarian cancer is bevacizumab. It is a humanised monoclonal antibody that inhibits the formation of new blood vessels and reduces the existing vasculature within the tumour [3]. As a result, the process of local progression and development of distant spread is inhibited [4].

Unfortunately, in addition to favourable anti-tumour effects, antiangiogenic drugs can cause a number of side effects and their toxicity profile is different from that of standard chemotherapy. The most important cardiovascular complications associated with bevacizumab therapy include hypertension and thromboembolic events (venous and arterial), as well as haemorrhagic complications [5]. These complications have specific conditions for ovarian cancer — this type of cancer is an important risk factor for thromboembolic complications, and patients are often over 50 years of age, which is another important risk factor for cardiovascular system [6]. On the other hand, when diagnosing hypertension, it is important to take into account the iatrogenic white coat effect and other causes of arterial hypertension [7].

Arterial hypertension

Hypertension is one of the most common complications of bevacizumab treatment. The pathophysiology of hypertension associated with bevacizumab is not fully known. Hypertension development during bevacizumab treatment is a consequence of inhibition of isoform A of

VEGF (VEGF-A), which results in a reduction of nitric oxide production, being a strong vasodilator. A drop in nitric oxide causes vasoconstriction, which in turn leads to development of hypertension [8]. In addition to inhibiting the nitric oxide pathway, vascular depletion, oxidative stress, and glomerular injury due to lack of VEGF may be other responsible mechanisms [9].

The results of a meta-analysis of 12,625 patients from 20 clinical trials revealed that the overall incidence of bevacizumab-induced hypertension was 23% [10]. Hypertension grade 3/4 according CTCAE (Common Terminology Criteria of Adverse Events) classification concerned up to 7.8% of patients. The authors of the analysis indicate that development of hypertension depends on many factors; for example, the influence of type of tumour and dose of the drug is confirmed. It is important, however, that this meta-analysis did not include patients diagnosed with ovarian cancer.

Currently available data on the incidence of hypertension during bevacizumab treatment of ovarian cancer patients are from several studies published after 2010. In a placebo-controlled phase III study (GOG--218) 1873 previously untreated women with stage III and IV ovarian cancer were included (74% and 26%, respectively). In the study, patients were divided into three groups, each receiving a regimen of carboplatin (AUC 6) and paclitaxel (175 mg/m^2). In the first arm, patients were additionally receiving placebo, and the second arm bevacizumab was given from cycle 2 to 6 followed by placebo until cycle 22. In the third arm, after the second cycle of chemotherapy, bevacizumab was added and maintenance therapy was continued until the end of follow-up. Grade ≥ 2 hypertension — according to CTCAE — occurred in the respective study arms in 7.2%, 16.5%, and 22.9% of patients [11].

In another phase III study (ICON7), which analysed the effect of bevacizumab added to carboplatin/paclitaxel-based first-line standard chemotherapy, 1528 patients were divided into two groups. The first group (n = 753) received standard chemotherapy (carboplatin — AUC 5–6, paclitaxel — 175 mg/m^2). In the second group (n = 745), bevacizumab was also used. The incidence of grade 2 hypertension in the first group was 2% (14 patients), and in the second group it was greater and reached 12% (90 patients). Grade ≥ 3 hypertension occurred in < 1% (two patients) in the chemotherapy group as compared to 6% (46 patients) in the group receiving additionally bevacizumab [12].

The phase III placebo-controlled OCEANS study included patients with recurrent and platinum-sensitive ovarian cancer. All patients (n = 484) were treated with gemcitabine and carboplatin in combination with placebo (n = 233) or bevacizumab (n = 247). In the first group grade ≥ 3 hypertension occurred in one patient (0.4%), and in the bevacizumab group it was shown in 43 patients (17.4%) [13].

Another study that provided information on the incidence of hypertension in women with recurrent ovarian cancer treated with bevacizumab was the GOG 0213 study (n = 673). In the group receiving standard chemotherapy (carboplatin — AUC 5, and paclitaxel — 175 mg/m^2), hypertension occurred at a rate of 0.6% compared to 11% with patients who additionally received bevacizumab [14].

The above studies are summarised in a meta-analysis by Wu et al., published in 2016, in which the relative risk of hypertension on bevacizumab was significantly increased; the odds ratio was 21.27 with a 95% confidence interval of 9.42–48.02 [15].

Relations between arterial hypertension and prognosis

The correlation between prognosis of patients and development of iatrogenic hypertension has not definitively been explained. Many reports indicate that the development of the discussed form of hypertension is closely related to the prognosis of patients with various cancers (e.g. colorectal cancer [16], breast cancer [17], recurrent glioblastoma [18]). However, there are data that do not confirm this correlation [10, 19].

In their retrospective analysis Nick et al. evaluated patients with recurrent ovarian cancer, who received bevacizumab alone or in combination with chemotherapy. It was found that in the case of development of hypertension during the treatment with bevacizumab the response was 2.5-fold more likely than in women without that complication [95% confidence interval (CI) 1.24–5.66; p = 0.006] [20]. In order to finally confirm the prognostic significance of bevacizumab-induced hypertension in ovarian cancer patients, large prospective observational studies with a good hypertension diagnostic algorithm are warranted.

Treatment

According to the latest ESC (European Society of Cardiology) Position Paper [21, 22], the primary goal of management of bevacizumab-related hypertension should be to correctly identify iatrogenic hypertension (≥ 140/90 mm Hg) and maintain adequate control (< 140/90 mm Hg or less for overt proteinuria). Before initiating treatment with bevacizumab or another VEGF inhibitor the following should be done:

— all potential cardiovascular risk factors should be identified;
— hypertension in medical history should be excluded or, in the case of positive history, current values as well as efficacy of previous antihypertensive treatment should be evaluated;
— pain and stress should be effectively managed;

— the impact of other drugs on increased blood pressure should be analysed [e.g. corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), erythropoietin];
— differential diagnosis should consider "white coat effect" (in which case, home-based measurements should be considered and the patient should be encouraged to change their lifestyle).

When bevacizumab or another VEGF inhibitor is initiated, early detection of pressure increases and appropriate treatment are needed to avoid clinically relevant complications. It is suggested that the first-choice drugs should include angiotensin-converting-enzyme inhibitors (ACEI) or angiotensin receptors blockers (ARB) and dihydropyridine (DHP) calcium channel blockers (amlodipine, felodipine) [23]. During selection of an antihypertensive drug, it should be remembered that:
— ACEI and beta-blockers are the preferred antihypertensives in patients with previously diagnosed cardiac dysfunction or high risk of developing cardiac dysfunction;
— drugs increasing nitric oxide release (e.g. nebivolol) may be valuable as angiogenesis inhibitors also inhibiting nitric oxide pathway [24];
— other beta-blockers with vasodilatory effect are also very effective (e.g. carvedilol);
— diuretics pose a risk of electrolyte loss and should not be considered in the first line of treatment (especially in patients experiencing vomiting and diarrhoea);
— there is no clear evidence to suggest a predominant class of antihypertensive drugs in patients treated with VEGF inhibitors [25];
— bevacizumab is not affected by unfavourable interactions with cytochrome P-450.

It should be emphasised that withdrawal of the antiangiogenic agent due to hypertension should be related to the occurrence of grade 4 toxicities according to CTCAE score (version 4.0 and earlier), which means that hypertension complications have direct life-threatening risk (e.g. malignant hypertension, transient or persistent neurological deficits, hypertensive crisis). The occurrence of these complications is unlikely when daily monitoring of blood pressure is performed at the beginning of treatment with a VEGF inhibitor and early antihypertensive drugs are used or modifications to pre-existing antihypertensive therapy.

The second condition for withdrawal of an antiangiogenic drug may be long-term stage 3 adverse effects. However, this recommendation seems to refer to toxicity other than hypertension itself. According to CTCAE version 4, grade 3 hypertension means systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg. These values may occur with bevacizumab or another VEGF inhibitor. In such cases medical intervention is recommended with use of more than one antihypertensive drug or intensification of pre-existing antihypertensive treatment (increase of dose/doses of medication). The use of two or more antihypertensive drugs with different mechanisms of action should result in optimal level of blood pressure. Thus, with an optimised pressure control strategy, this intensity of long-term toxicity also seems unlikely.

In patients treated with bevacizumab hypertension is often diagnosed at grade 2, which means recurrent or persistent (≥ 24 hours) symptomatic rises > 20 mm Hg (diastolic) or > 140/90 mm Hg (if previously normal). Intervention limited to monotherapy or a maximum of two drugs (or one combined drug) could be sufficient. Treatment may only be needed periodically (i.e. on days of occurrence of abnormal blood pressure). When normalisation of blood pressure is observed in home measurements, antihypertensive medication can be stopped in order not to expose patients to the consequences of symptomatic iatrogenic hypotension. A similar recommendation applies to a two-week pause in algorithm of therapy with sunitinib.

Venous thromboembolism (VTE)

Venous thromboembolism (VTE) is the second leading cause of death among patients with malignant neoplasms, and its prevalence in this population is about five times higher than in people without cancer [26, 27]. There are many defined risk factors for venous thrombosis (among others — the use of anticancer drugs, including antiangiogenic).

The effect of bevacizumab treatment on increase of VTE incidents is controversial. In 2007, a meta-analysis of 1745 patients with colorectal cancer (69%), breast cancer (25%), and non-small cell lung cancer (6%) was published. There was no increased risk of VTE during treatment with bevacizumab [hazard ratio (HR) 0.89; 95% CI: 0.66–1.20; p = 0.44] [28].

In 2008, the results of another meta-analysis were published that evaluated the risk of VTE among patients receiving bevacizumab for different malignancies (renal cancer, breast cancer, colorectal cancer, non-small cell lung cancer). In total, 7956 patients enrolled in 15 randomised clinical trials were analysed. The results of this analysis showed that the incidence of thromboembolic events in the bevacizumab group was 11.9% (range 6.8–19.9%) and in the control group 6.3% (range 4.8–8.3%). Among patients treated with bevacizumab, the relative risk of VTE was 1.33 (range 1.13–1.56; p < 0.001) [29].

In 2011 Hurwitz et al. published the results of another meta-analysis evaluating the incidence of VTE during bevacizumab treatment. The study included 6055 patients in 10 randomised phase II and III clinical trials (advanced colorectal cancer, pancreatic cancer, breast

cancer, and non-small cell lung cancer). There was no statistically significant increased risk of VTE among patients receiving bevacizumab (10.9% *vs*. 9.5%, p = 0.13) [30].

It should be noted that the studies mentioned above did not include ovarian cancer patients. The data on the incidence and risk of VTE in ovarian cancer were derived from GOG0218, ICON7, OCEANS, and GOG0213 studies previously described. According to the meta-analysis of the aforementioned studies by Wu et al., the incidence of VTE among patients treated with bevacizumab for ovarian cancer was higher than in ones not receiving this drug — relative risk (RR) 1.43, 95% CI: 1.04–1.96, I^2 = 39% [15].

Correlation between venous thromboembolism and prognosis

In 2007, Khorana et al. published a large analysis of 1 824 316 patients (1 015 598 with cancer), which showed increased mortality among cancer patients with venous thromboembolism as compared to patients without this complication (16.3% *vs*. 6.3%; p < 0.0001) [31].

In another study, Kuderer et al. suggested that VTE incident during chemotherapy for malignancy influences early mortality. The study included 4458 patients with diagnosis of cancer or lymphoma, who were observed for 75 days. Statistical analysis showed that VTE was a significant predictor of early death (HR 4.5; 95% CI: 1.61–12.53; p < 0.004) [32]. Poorer prognosis in patients with cancer and concomitant VTE is also reported in studies of the population of pancreatic cancer patients [33], lung cancer [34], breast cancer [35], and colorectal cancer [36]. In a population of women diagnosed with ovarian cancer a similar correlation was also observed. In a study of 2743 patients undergoing chemotherapy (carboplatin + paclitaxel) after primary surgical treatment, overall survival (OS) was reduced in women after venous thromboembolism (29.8 months *vs.* 36.2 months in the population without this complication; p = 0.03) [37].

Based on the available literature it can be assumed that an episode of VTE has negative prognostic role in patients treated for selected malignant neoplasms.

Treatment and prevention

Diagnosis of VTE during anticancer therapy (chemotherapy, antiangiogenic treatment) is based on clinical symptoms. Pulmonary embolism during administration of an angiogenesis inhibitor should always lead to treatment discontinuation.

Treatment of a confirmed episode of acute thrombosis or pulmonary embolism in haemodynamically stable patients (i.e. without significant decrease in blood pressure) should include low-molecular weight heparin (LMWH) administered for 3–6 months [38]. American Society of Clinical Oncology (ASCO) recommendations prefer at least six months [39]. The advantage of LMWH over oral vitamin K antagonists (VKA) has been demonstrated with respect to the lower incidence of subsequent venous thromboembolism but with no difference in mortality and incidence of bleeding [40]. There is ongoing research into the role of new oral anticoagulants, but until the final results are available, these drugs are not recommended for oncologic patients [41]. Continuation of anticoagulation treatment with LMWH beyond the recommended 3–6 months or change to VKA should be considered individually, taking into account the efficacy of previous anticancer treatment, risk of recurrent thromboembolism and bleeding, and patient's preference. Consequently, chronic anticoagulation should be considered until cancer is cured. In the case of metastatic disease, which is a usual indication to antiangiogenic treatment, anticoagulant therapy due to newly diagnosed VTE should be considered as lifelong.

The use of primary antithrombotic prophylaxis in patients with cancer receiving chemotherapy due to advanced/metastatic disease is very controversial [42]. Prophylaxis can be used in patients with high risk of venous thrombotic events but without excessive bleeding risk [43]. According to the criteria proposed by Khorana [44], theoretically these indications can be accurately estimated in ovarian cancer patients if there are additional risk factors with references to morphology and body mass index, but the risk of bleeding appears to be particularly high in patients receiving angiogenesis inhibitors. However, the exact risk-benefit ratio is not known in candidate for therapy with angiogenesis inhibitor (similarly to other groups of patients receiving anticoagulation prevention — for example — because of the recognition of atrial fibrillation).

Arterial complications

Arterial thromboembolic events (ATE) associated with bevacizumab treatment include many different diseases (e.g. ischaemic stroke, acute coronary syndrome, or even myocardial infarction). Bevacizumab reduces the anti-inflammatory effect of VEGF and consequently can induce inflammatory processes and atherosclerotic plaque instability with subsequent rupture, platelet activation, and intravascular arterial thrombosis [45]. Other mechanisms include reduction of regenerative properties of endothelium, increased expression of procoagulant factors, reduction of nitric oxide production resulting in vasoconstriction, and increased platelet aggregation and adhesion to vascular endothelium [46]. Additionally, bevacizumab can inhibit formation of small vessels that play an important role in the creation of collateral circulation and prevent the development of acute ischaemia [47].

In the aforementioned 2007 meta-analysis of five randomised clinical trials, patients treated with bevacizumab indicated statistically significantly higher risk of artery embolism (HR 2.0; 95% CI 1.05–3.75; p = 0.031). Based on the analysis, potential risk factors of this complication include positive history of arterial embolism ($p < 0.001$), age > 65 years ($p < 0.01$), and previous exposure to bevacizumab ($p < 0.04$) [28].

Ranpura et al. published in 2008 a meta-analysis of 20 clinical trials involving totally 12,617 patients with different cancers. Patients receiving bevacizumab had statistically significantly increased risk of artery thromboembolic events as compared to control group (HR 1.44; 95% CI 1.08–1.91; p = 0.013), in particular myocardial ischaemia (HR 2.14; 95% CI 1.12–4.08; p = 0.021). The increased risk was mainly reported in patients with renal and colorectal cancer and was bevacizumab dose-independent. In a meta-analysis there was no increased risk of ischaemic stroke during treatment with bevacizumab (HR 1.37; 95% CI 0.67–2.79; p = 0.39) [48].

Another meta-analysis was published in 2011. It covered 13,026 patients receiving bevacizumab due to advanced cancers. Data derived from 16 randomised clinical trials and four presentations of international ASCO (American Society of Clinical Oncology) conferences [49, 50]. There was a statistically significant higher risk of arterial thromboembolic events in the bevacizumab group compared to patients not receiving this drug (HR 1.46; 95% CI: 1.11–1.93; p = 0.007). Meta-analysis results confirmed previous observations regarding the greatest risk of arterial events in patients with metastatic colorectal cancer and renal cell carcinoma. There was no statistically significant difference in the incidence of arterial embolism in breast cancer, pancreatic cancer, and mesothelioma patients. Based on the analysis, there was no correlation between the occurrence of arterial events and the dose of bevacizumab [51].

Data on arterial thromboembolic events in ovarian cancer patients are based on previously described randomised trials GOG0218, OCEANS, ICON7, and GOG0213, and their meta-analysis. It can be stated that the use of bevacizumab in ovarian cancer statistically significantly increases the risk of arterial events (HR 2.39; 95% CI: 1.39–4.10; $I^2 = 14\%$; p = 0.002) [15].

It should be also noted that in studies included in the meta-analysis no information was collected about death and serious complications of artery embolism, or these data were incomplete. Therefore, we do not know the effect of arterial events induced by bevacizumab on the prognosis. However, it should be assumed that many of these complications are life threatening (e.g. myocardial infarct [MI] or ischaemic stroke). These diseases can adversely affect not only the prognosis but also deteriorate patients' quality of life.

Treatment and prevention

The ESC Position Paper emphasises that treatment of arterial thromboembolic events in cancer patients has not been the subject of much research and analysis. A severe arterial incident (acute coronary syndrome or stroke) observed during treatment with angiogenesis inhibitors is an indication for treatment discontinuation.

The method of pharmacological treatment and, above all, qualification for endovascular intervention should be considered individually after multidisciplinary consultation, preferably with a cardio-oncology team. The potential benefits of invasive procedures in cancer patients should always be considered, especially in patients receiving angiogenesis inhibitors, with significantly increased bleeding risk.

It is suggested that primary prevention should be based on control of all potential risk factors (e.g. dyslipidaemia, diabetes, hypertension). Pharmacological treatment in secondary prevention after previous arterial events should be intensified (e.g. with use of antiplatelet agents, ACEI, statins, beta-blockers).

Potential contraindications to dual antiplatelet therapy should be assessed in cancer patients, in regard to risk of bleeding resulting from type and stage of tumour, as well as from previous and further anticancer therapy [52].

The role of acetylsalicylic acid in the prevention of arterial events induced by bevacizumab is also discussed. The available analysis [28] demonstrated that the group receiving acetylsalicylic acid in combination with bevacizumab include more patients with previous arterial events, at an advanced age (65 years or older), receiving the drugs due to dyslipidaemia (mainly statins), and with diabetes mellitus or arterial hypertension in their medical history ($p < 0.001$ for each of these risk factors). Additionally, it was noticed that:

— the risk of arterial events induced by bevacizumab:
  - was significantly increased among patients who did not take aspirin — 3.6% *vs.* 1.7% (p= 0.03);
  - was insignificantly increased among patients who took aspirin — 5.1% *vs*. 1.2% (p = 0.16);
— in the subgroup with the two most important risk factors (previous arterial events, age ≥ 65 years), the risk of arterial events induced by bevacizumab was:
  - significantly increased among patients who did not take acetylsalicylic acid — 22.9% *vs.* 3.4% (p = 0.03);
  - insignificantly increased among patients who took acetylsalicylic acid — 12.5% *vs*. 0% (p = 0.29).

Bleeding

Bleedings occur in about 10% of patients with advanced cancers [53]. They can be caused by many different factors (such as infiltration of large blood vessels by tumour masses, decrease in number or impaired platelet functions). Bleeding can also be caused by iatrogenic factors (e.g. chemotherapy, radiotherapy or antithrombotic prophylaxis and treatment). Bleeding can occur in the form of haematemesis, tarry stools or melena, haematuria, epistaxis, haemorrhages from the genitourinary tract, ulcerative skin lesions, and bleeding in the central nervous system (CNS) [54]. It is believed that molecular targeted drugs that inhibit angiogenesis (e.g. bevacizumab) may also cause an increased risk of clinically significant bleeding.

Hapani et al. performed a meta-analysis of 20 randomised clinical trials involving 12,617 cancer patients. Statistical analysis showed that patients treated with bevacizumab had a significantly increased risk of all bleeding (HR 2.48; 95% CI: 1.93–3.18; $I^2 = 53\%$), which was not dose-dependent. The frequency also depends on tumour location (patients with non-small-cell lung cancer have the highest risk) [55].

In 2014 a meta-analysis of studies on the incidence of cerebrovascular events was published, which included 12,917 patients from 17 randomised clinical trials. Bevacizumab treatment was associated with more than a three-fold increase in CNS bleedings (HR 3.09; 95% CI: 1.36–6.99; p = 0.007) [56]. In a meta-analysis of studies testing the efficacy of bevacizumab in ovarian cancer patients a three-fold increase in the incidence of bleeding was also indicated (HR 3.16; 95% CI 1.59–6.30; p = 0.001) [15].

Based on another meta-analysis [28] grade 3 and 4 bleedings were reported in 36 (3.7%) of 963 patients treated with bevacizumab and acetylsalicylic acid in a dose below 325 mg, and in 14 (1.8%) of 782 patients in a comparative group treated with bevacizumab without acetylsalicylic acid. A comparison of 100 patient-years showed a difference of 5.3 versus 3.3 events (p = 0.13). It has been estimated that the use of acetylsalicylic acid is associated with an approximately 1.3-fold increased risk of grade 3 and 4 bleedings in patients treated with bevacizumab. No statistical correlation was found with histological diagnosis of cancer.

Summary

Modern methods of anticancer treatment increase the range of possibilities for prolonging patients' lives. The introduction of bevacizumab to daily clinical practice has allowed the achievement of prolonged overall survival, better disease control, and improved quality of life in some cancers. However, treatment with bevacizumab is associated with a higher prevalence of cardiovascular complications (e.g. arterial hypertension, venous and arterial thromboembolic events, and bleeding episodes). Further observations are needed, especially prospective and well designed, preferably with a methodology that also uses the assessment of sensitive and specific biomarkers [57]. Results of such studies may allow for an optimal stratification of cardiovascular complications risk during bevacizumab treatment and the determination of their prognostic significance.

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