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# Anti-cancer agents and endothelium

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### ABSTRACT

Recent advances in oncology have improved the treatment outcomes and life expectancy of cancer patients; therefore, late effects of oncological treatment are of high clinical importance. Recent studies have shown that cardiovascular events are among the leading causes of premature morbidity in cancer survivors. Cardiotoxicity of some chemotherapeutic agents have been already confirmed; however, this issue seems to be more complex. Endothelium dysfunction is one of the first recognisable signs of atherosclerosis, which occurs long before the development of overt cardiovascular disease. Thus, it could be considered as an initial step, leading to increased risk of cardiovascular events. This process is not easy to recognise; however, there are some laboratory tests and imaging techniques that provide an insight into the progression of endothelial dysfunction. In this review we discuss the influence of oncological treatment on endothelium, according to the hypothesis that it increases cardiovascular morbidity and mortality in cancer survivors. Additionally, we present diagnostic and therapeutic measures that could reduce cardiovascular risk in cancer patients.

**Key words:** endothelium, cancer, chemotherapeutic agents, radiotherapy

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## Introduction

There has been tremendous progress in early detection, treatment, and supportive care in cancer patients, which contributes to longer life expectancy. The side effects of chemotherapy and radiotherapy have already been well defined, but it seems that late consequences of cancer treatment are of high clinical importance. Cancer survivors have significantly increased risk of cardiovascular (CV) events as compared to cancer-free individuals [1]. Radiation therapy is associated with a three-fold increased risk of myocardial infarction (MI) and congestive heart failure [2]. Even more pronounced vascular abnormalities are observed in the survivors of childhood cancers [3–5].

Chemotherapeutic agents with known cardiotoxic effects include: anthracyclines, taxoids, 5-fluorouracil, cisplatin, cyclophosphamide, some monoclonal antibodies, and multi-kinase inhibitors [6–9]. Most of these cytotoxic drugs, as well as radiotherapy, can cause elusive, progressive endothelial damage leading finally to CV events.

Nonspecific endothelial damage disrupts the homeostatic balance and leads to a sequence of pathological changes including: constriction of blood vessels, leukocyte adherence, platelet activation, thrombosis, impaired coagulation, inflammation, and atherosclerosis. In general, this is not an easily recognisable process, mainly due to late clinical presentation; however, endothelial dysfunction can be considered as an initial step increasing CV risk. It is also difficult to distinguish whether presented symptoms result from comorbidities or the oncological treatment itself [10].

This review discusses the influence of cytotoxic agents on endothelium, which could be considered as a cause of increased morbidity and mortality in cancer survivors. This theory can be integrated into a comprehensive conceptual model explaining accelerated development of atherosclerosis in cancer-survivors. Additionally, strategies of endothelium function monitoring in clinical practice will be presented along with methods of possible intervention that may modify outcomes in high-risk patients.

## Endothelium and vascular homeostasis

The endothelium plays a key role in maintaining vascular homeostasis. It acts not only as a barrier between tissues and circulating blood but also as a signal transducer that regulates vasomotion [11].

Vascular homeostasis is based on the balance between vasoconstrictors and vasodilators. Nitric oxide (NO) is an endothelium-derived relaxing factor that plays a crucial role in maintaining vascular tone. Endothelial NO synthase (eNOS) — the enzyme catalysing the production of NO from L-arginine — is activated by a shear stress or signalling molecules [12]. Prostacyclin, which acts independently from NO and is derived from the cyclooxygenase system, also contributes to vasodilatation. Conversion of angiotensin I to angiotensin II on the endothelial surface, generation of endothelin, and vasoconstrictor prostanoids are the factors responsible for the increasing of a vascular tone [13].

Established cardiovascular risk factors such as: smoking, dyslipidaemia, obesity, diabetes, hypertension, and chronic inflammation [14] shift the balance between vasoconstrictors and vasodilators in favour of vasoconstrictors and activate endothelium. This condition is also considered as “NO-deficiency” due to a leading role of this substance in maintaining a proper vessels lumen. Subsequently, endothelium starts to produce procoagulant and proinflammatory molecules, triggering a sequence of events that finally lead to development of atherosclerosis [15].

## Assessment of endothelial function

Endothelial dysfunction constitutes a preclinical stage of atherosclerosis. It can be detected before atherosclerosis plaque formation, when this process is still reversible. Hence, it is important to detect endothelial dysfunction at an early stage in order to prevent its progression and to reduce cardiovascular risk. Currently there are many evaluation methods available that provide an insight into the condition of endothelium.

Exposition to the cardiovascular risk factors leads to detachment of endothelial cells and the release of several autocrine and paracrine substances. Endothelial cells, which might be detected in the bloodstream, known as circulating endothelial cells (CECs), are very uncommonly present in healthy individuals. They are characteristic for diseases associated with widespread vascular damage, including: MI, congestive heart failure, stroke, diabetes, systemic vasculitis, systemic lupus erythematosus, infectious diseases, and cancers. Moreover, CECs could be locally released after coronary angioplasty [16].

Endothelial damage leads to higher expression of adhesions molecules such as: E-selectin, endothelin-1, and vascular cell adhesion molecule-1 (VCAM-1), and increased levels of proinflammatory cytokines: interleukin-6 (IL) and C-reactive protein (CRP). Activated endothelial cells also release endothelium-derived glycoproteins: von Willebrand factor (vWF) as well as other molecules, such as soluble thrombomodulin (sTM) and tissue plasminogen factor (t-PA), which could be the markers of procoagulant activity [9, 13, 17, 18].

Asymmetric dimethylarginine (ADMA) is a novel, promising biomarker, which is endogenously synthesised through arginine methylation and antagonises the effect on endothelium-dependent vasodilatation. This is achieved by eNOS inhibition and superoxide generation. An increased ADMA plasma concentration was found in hypertriglyceridaemia, hypertension, diabetes, insulin resistance, and chronic heart failure [19, 20].

Finally, endothelial-dependent vasomotion, which actually means an ability of endothelium to release NO, can be determined using a brachial artery flow-mediated dilatation (FMD), a noninvasive ultrasound-based test developed by Celermayer [21, 22]. This technique assesses endothelium response to reactive hyperaemia (shear stress), subsequent nitric oxide release, and vasodilatation. The severity of atherosclerosis might be assessed by common carotid artery (CCA) intima-media thickness (IMT) and aortic stiffness during routine transthoracic echocardiography (TTE) [17]. Evaluation of the carotid artery enables detection of subclinical alterations in the wall structure that precede CV events in seemingly healthy individuals. The aforementioned tests are non-invasive and relatively easy to perform, which makes them clinically useful [14].

## The influence of anti-cancer agents on endothelial homeostasis

Endothelial dysfunction is very common in the course of malignancies [23]. *In vitro* and *in vivo* studies suggest that some tumour cells may induce apoptosis and therefore hamper endothelial integrity. Moreover, in order to metastasise, tumour cells need to interact with endothelial cells, which promotes their extravasation into surrounding tissues spaces [24]. This effect is even more pronounced in patients treated with cytotoxic agents which cause endothelial damage. Anti-endothelial effect is the first step of vascular toxicity [25].

Cytotoxic agents affecting endothelium can be classified according to their mechanism of action as: anti-tumour antibiotic (bleomycin and anthracyclines), plant alkaloids (taxanes, vinca alkaloids), alkylating agents (cisplatin, cyclophosphamide), antimetabolites (5-fluorouracil), and biological therapies (bevacizumab,

sunitinib, sorafenib). Additionally, the role of radiation therapy will be further presented.

**Anti-tumour antibiotics** such as bleomycin and anthracyclines [doxorubicin (Adriamycin) and daunorubicin] are used for patients with different solid tumours and haematological malignancies, i.e. sarcomas, breast cancer, Hodgkin's lymphoma, and myeloma. In general, they act by the intercalation into DNA and the inhibition of topoisomerase, which prevents cells from further division. Subsequently, it decreases protein synthesis and causes ROS generation, directly leading to DNA damage [26]. Anthracyclines are characterised by well-known cumulative, dose-dependent, irreversible cardiotoxicity that limits their clinical usefulness. However, there are only a few studies on their effect on endothelium.

Anthracycline-induced endothelial toxicity seems to be a complex process. The most common theory assumes that this is a free radical-mediated process highly integrated with eNOS. Adriamycin binds to eNOS leading to the diversion of an electron from the enzyme's oxygenase domain. It decreases NO concentration and leads to the production of superoxide. Diminished NO concentration switches endothelium to pro-coagulant status and significantly impairs vasodilatation. Moreover, oxidative stress causes direct damage of endothelial cells [6, 8, 27–30]. The organ culture method revealed that doxorubicin interferes with DNA of endothelium causing dose-dependent excoriation of endothelium and subsequent apoptosis [31, 32]. This process is enhanced by accumulation of anthracyclines in the endothelial cells nuclei [33]. Another possible mechanism of doxorubicin-induced vascular toxicity is based on impairment of lipid metabolism, which is known to be caused by chemotherapy in general [6, 34].

Jenei et al. [4] presented in their study that after adriamycin administration FMD rapidly decreased to 4%, which was accompanied by reduction in nitric oxide plasma concentration. Interestingly, anthracyclines cause not only acute cardiovascular adverse events but also chronic ones, as was observed in long-term survivors of childhood cancer [3, 4, 35].

**Taxanes (docetaxel, paclitaxel)** — derivatives of plants of the genus *Taxus* are used in the treatment of lung, colon, ovarian, breast, and prostate cancers [36, 37]. Taxanes are the cell-cycle targeting anticancer agents that inhibit mitosis by interfering with the mitotic spindle. It promotes formation of abnormal microtubules, which results in apoptosis of mitotically-arrested cells [38]. These changes affect cells in G2 and M cell cycle, which inhibits completion of division and leads to the accumulation of cells in G2 phase [39]. Because tubulin cytoskeleton is crucial for maintenance of endothelial-barrier function, administration of taxanes leads to increased permeability of vessels not only within the tumour but also in the whole body [37, 40]. Moreo-

ver, taxanes potentiate the effect of anthracyclines by increasing their plasma concentration [41]. Chemotherapy regimens which contain both taxanes and doxorubicin have a synergistic effect on endothelial damage [42]. Taxanes cause impairment of endothelial cell migration and proliferation, which was evaluated by Hotchkiss et al. [37] in three *in vitro* pharmacokinetic assays. They reported that inhibition of endothelial cell migration was caused by an inhibition of centrosome reorientation at lower concentrations than those affecting microtubule morphology and causing cell apoptosis. In the study by Belotti et al. [43] the authors observed that paclitaxel influences endothelial cell proliferation, chemotaxis, migration, and cord formation on the Matrigel model of angiogenesis. They also detected antiangiogenic potential of paclitaxel *in vivo*.

**Cisplatin** is an alkylating agent that is used in the curative setting of testicular [5], ovarian [44, 45], urological [46], lung, and head and neck cancers [47]. Because it is accumulated in plasma, administration of cisplatin-based regimens results in prolonged damage of endothelial cells. Cisplatin might be detected in plasma even years [20] after the treatment of testicular cancer [48]. The most common side effects associated with this agent include: nausea, emesis, myelosuppression, and nephrotoxicity. Typical vascular toxicities include Reynaud phenomenon, as presented in recent reports, myocardial infarct, stroke, and hypertension [5, 44, 45, 49].

Damage of endothelial cells with subsequent hypercoagulation may explain the cisplatin-related vascular toxicity. Cisplatin may inhibit proliferation of endothelial cells *in vitro* and cause apoptosis, which was assessed on the human dermal microvascular epithelial cell line [50]. Cisplatin also inhibits endothelial cell motility *in vitro* on the Matrigel model of angiogenesis, but it occurs only in doses that inhibit cell proliferation [43]. Platinum derivatives induce the endothelial release of IL-1 and IL-6 as a result of inflammatory reaction (e.g. production of hydrogen peroxide) [47]. Treatment with cisplatin-based chemotherapy resulted in increased vWF serum level immediately after chemotherapy of germ cell tumour patients and in patients with testicular cancer, which normalised in several months after the treatment [51, 52]. Because vWF is released from endothelial cells after injury, these findings confirm cisplatin-induced endothelial toxicity. Additionally, cisplatin increases platelet aggregation via the arachidonic acid pathway on human platelet-rich plasma, which explains the pathogenesis of thrombotic complications after cisplatin administration [53]. However, there is an interesting concept, which is that cisplatin-related vascular events might be provoked not only by endothelial damage but also by vasospasm caused by cisplatin-induced hypomagnesaemia. Cisplatin causes a tubular injury and decreases reabsorption of magnesium ions in renal tubules, which subsequently

increases calcium ions flux into the cellular matrix, which in turn triggers muscular contractions [44, 45].

Another alkylating agent, **cyclophosphamide** has been found to be clinically useful in the treatment of haematological malignancies (lymphoma, leukaemia, multiple myeloma), breast cancer, and in an immunosuppressive setting for the treatment of autoimmune diseases [54]. It is thought that cyclophosphamide directly injures endothelial cells, leading to subsequent leakage of plasma to the extravascular environment [55]. Colleoni et al. [56] observed a significant decrease in vascular endothelial growth factor level in breast cancer patients after oral administration of cyclophosphamide in low doses, which is associated with its anti-angiogenic effect. This finding was also confirmed by Folkman et al. [57], who found that systematic administration of cyclophosphamide, anthracyclines, or paclitaxel (but not others drugs) inhibits neovascularisation in the mouse cornea. Acrolein, which is the principal metabolite of cyclophosphamide, has been found to be involved in direct injury of pulmonary artery endothelial cells evaluated on an *in vitro* model (51Cr-labelled bovine artery pulmonary endothelial cell line) [58]. Bocci et al. [59] reported that the first active metabolite of cyclophosphamide (4-hydroxycyclophosphamide) inhibited human umbilical vein endothelial cell line (HUVEC) proliferation in concentrations that did not cause cells apoptosis.

**5-fluorouracil** (5-FU) and its orally administered pro-drug (capecitabine) are the antimetabolites used in treatment of gastrointestinal adenocarcinoma, breast, gynaecological, as well as head and neck tumours. The effect on endothelium was studied in rabbits using transmission electron microscopic evaluation of endothelium in small arteries after exposure to 5-FU. It has been discovered that 5-FU has a direct cytotoxic effect on endothelial cells, leading to its damage and subsequent thrombus formation [60, 61]. The study on human and bovine endothelial cells in a cell culture model showed an increased release of prostacyclin by bovine endothelial cells after 48-h incubation with 5-FU, which indicates leakage secondary to endothelial cell injury [62]. Focaceti et al. [63] discovered that in the xenograft model of colon cancer, 5-FU induces ultrastructural changes in the endothelium of various organs. Endothelial damage is enhanced by elevation of ROS concentration and an autophagic process in cells [63]. After administration of 5-FU in 10 patients receiving 5-FU as a constant intravenous infusion over a four-day or five-day period the level of fibrinopeptide A (peptide cleaved from fibrinogen by thrombin) in blood samples was elevated. Most of the patients had a marked increase in the level of fibrinopeptide A 24 hours after infusion, compared with their pre-infusion levels, with normalisation by the end of the infusion. This result shows the effect of 5-FU on activation of intravascular coagulation [64].

Several reports described patients who developed myocardial ischaemia after infusion of 5-FU [64, 65]. The possible explanation is that 5-FU causes protein kinase C-mediated vascular smooth muscle constriction [66]. In the study of Südhoff et al. [67] 50% of patients after 5-FU infusion presented contraction of the brachial artery associated with an increased endothelin plasma level.

Endothelial damage is also an adverse event of novel **targeted therapies**, especially inhibiting vascular endothelial growth factor (VEGF) [36, 38, 54, 68]. This group of drugs includes monoclonal antibodies: bevacizumab — a humanised monoclonal antibody targeting VEGF, which is used in the treatment of breast, lung, colorectal, and renal cancers, as well as multiple kinase inhibitors: sunitinib, sorafenib — a multi-targeted inhibitor approved for treatment of metastatic renal cell carcinoma and gastrointestinal stromal tumours (GIST) [36, 54]. VEGF inhibitors are usually associated with hypertension, which is the most common side effect, with an overall incidence of 32% (in patients treated with bevacizumab) [69–71]. The risk of thromboembolic events seems to be moderately increased [68, 72]. The mechanism leading to VEGF inhibitor-induced hypertension is still poorly understood. Veronese et al. [73] did not observe any changes in the level of VEGF receptor expression after three weeks of treatment with sorafenib, despite detected hypertension. Based on this, it could be concluded that hypertension is independent of VEGF receptor levels. Moreover, the authors stated that hypertension is not related to sodium retention, increased level of catecholamine, renin, aldosterone, and any of the renovascular pathologies. The other theory proposed by Mir et al. [74] states that VEGF-inhibitors increase the risk of cholesterol embolism syndrome, and thus lead to acute CV complications. In another study [75] the authors did not observe any changes in a vascular tone after intravenous administration of bevacizumab. Microvascular dysfunction was also observed in the dermal capillary densities in the dorsal surface of fingers using intravital video capillaroscopy [76].

The antiangiogenic multiple kinase inhibitors (sunitinib and sorafenib) target a range of different receptor tyrosine kinases and other intracellular kinases, and thus their effect on endothelial damage is much more complex [38]. Thijs et al. [77] proved that in an animal model exposure to high concentrations of sunitinib diminishes FMD by reducing endothelial release of nitric oxide. However, they did not observe any reduction in FMD before hypertension developed in patients treated with sunitinib. Therefore, according to their hypothesis, sunitinib-induced hypertension does not depend on endothelium, and is probably due to decreased arteriole diameters. Recent data suggest that inhibition of platelet-derived growth factor receptor (PDGFR)

causes coronary microvascular dysfunction due to loss of pericytes, supporting the mechanical stability of the capillary wall in some tissues [78, 79]. Both sunitinib and sorafenib are also known to inhibit the stem cell growth factor receptor (c-Kit or CD117), which is expressed on the surface of precursors of endothelial progenitor cells, and therefore debilitates mobilisation of these cells to the sites of injury [80].

It should be highlighted that not only chemotherapeutic agents contribute to endothelial damage in cancer patients. **Radiation therapy (RTH)** is the other factor potentiating the harmful effect on endothelial cells. It has been confirmed that RTH directly causes arteriosclerosis in various mechanisms. Irradiation increases concentration of ROS with subsequent lipoprotein oxidation and vascular inflammation [81], causes intimal fibrous thickening [82] and damages endothelium and vasa vasorum, which finally leads to arterial wall necrosis [83]. In the animal model (rabbit ear artery) endothelial response to acetylcholine was decreased after irradiation, and some morphological changes were observed in endothelial cells (cellular shrinking, widened cellular junctions, detachment of endothelial cells) due to reduction in eNOS expression [84]. In the literature there are many case reports and research studies describing arterial occlusive disease in regions previously exposed to radiation [82, 83, 85–87]. Beckman et al. [88] revealed that external-beam radiation therapy impairs endothelium-dependent vasodilatation, measured as a decline in FMD of the axillary artery in patients treated for breast cancer. In young individuals without CV risk factors, IMT significantly increased (0.46 mm vs. 0.41 mm) after neck irradiation. In addition, arteriosclerotic plaque was detected in 18% of treated patients [89]. Therefore, it is possible to assume that RTH impairs endothelial function mostly by reduction of bioavailability of endothelium-derived NO, which is followed by acceleration of atherosclerosis development, increased CV risk, and arterial occlusions.

## Endothelial protection

### Lifestyle modification

Endothelial protection might be achieved by a range of non-pharmacological strategies known to reduce CV risk such as: physical exercise, weight control, smoking cessation, and Mediterranean diet [90]. In a recent pilot study, Jones et al. [91] investigated the effects of aerobic exercise training on brachial artery FMD in women with newly diagnosed breast cancer. They reported an improvement in FMD in the exercise training group. However, the difference in FMD between the two groups did not achieve statistical significance due to the small sample size.

### Antioxidant therapy

Most of the chemotherapeutics and RTH impair endothelial function via ROS. According to this, free radical scavengers have been used in clinical trials in order to diminish side effects, but the results were not satisfactory [6]. However, dexrazoxane — an iron chelating molecule — has been approved for anthracycline-induced cardiotoxicity. It hampers ROS formation in cardiomyocytes, but its effect on endothelium needs further evaluation [92]. Some studies indicated a beneficial effect of vitamin D supplementation on endothelium by an increase in FMD of the brachial artery [93]. Vitamin D may be particularly useful in an oncological setting due to its demonstrated *in vivo* and *in vitro* antiangiogenic properties [94]. According to meta-analysis [93] vitamin D supplementation significantly decreases mortality due to cancer and CV events. The effect of vitamin D on endothelium still needs further evaluation, especially to establish a proper supplemented dosage. Heitzer et al. [95] showed that vitamin E improves endothelial function in patients with multiple CV risk factors. Some animal studies revealed that deficiency of dietary vitamin C is associated with increased atherogenesis [96]. Although vitamin E and C supplementation has recently attracted a lot of attention, clinical trials have not shown any benefits, especially in patients already diagnosed with coronary artery diseases [97]. Because chemotherapeutic agents cause endothelial injury via various mechanisms, antioxidants may be just one part of the strategy of endothelial protection; however, they may be insufficient in this setting.

### Lipid-lowering therapy

There is strong evidence that lipid-lowering therapy restores endothelial function. This aim may be achieved by diet modification or by HMG CoA reductase inhibitors (statins). Despite the fact that they prevent atherosclerotic plaque formation and stabilise the already existing plaques, statins have been shown to decrease the incidence of adverse CV events. Furthermore, statins and angiotensin converting enzyme inhibitors (ACEi) cause vasodilatation by increasing plasma NO availability [38, 98]. This pleiotropic effect on endothelial NO synthase is also relevant.

### Other medications

Several commonly used cardiac drugs have a protective effect on the endothelium. The third generation of beta-blockers (carvedilol, nebivolol) have shown a strong anti-oxidant activity and additional properties such as  $\beta_3$  receptor stimulation. This receptor is known to activate eNOS and increase NO release [90, 99, 100]. Ticlopidine reduces thromboxane and increases

prostacyclin production, thus preventing atherosclerotic plaque formation [23]. ACEi reduce the production of angiotensin II, decrease NADPH synthesis (NADPH synthesis is stimulated by angiotensin II), and therefore hinder production of ROS. Additionally, ACEi promote stabilisation of bradykinin, which induces the release of NO and prostacyclin [90, 101].

In patients with a decrease in LVEF from 60% to 40% after administration of cardiotoxic chemotherapeutics (anthracyclines, trastuzumab, and tyrosine kinase inhibitors) ACEi, beta-blockers, and statins significantly restore myocardial function and increase LVEF up to 53% [102]. ACEi have been confirmed to be useful in prevention of anthracycline-related cardiac dysfunction [103]. Chemotherapeutic agents in combination with ACEi/ARB can improve the survival outcome in patients with different types of cancer [104].

Vasospasm caused by cisplatin has been successfully treated with calcium channel blockers [105]. Discontinuation of 5-FU infusion together with administration of a calcium channel blocker and nitrate usually gives a good outcome in the case of signs of myocardial ischaemia [65].

#### Newer interventions

Räsänen et al. [106] analysed the effect of vascular endothelial growth factor-B (VEGF-B) gene therapy in doxorubicin-treated mice. The results are very promising in terms of cardio and endothelial protection. VEGF-B pretreatment inhibited doxorubicin-induced endothelial dysfunction in a test of aortic relaxation to acetylcholine after phenylephrine-induced contraction. Despite the good preliminary results of such methods in animals, their use in humans is still a long way off.

## Conclusions

The integrity of endothelium plays a crucial role in maintaining vascular homeostasis. Hampering its function leads to development of atherosclerosis and subsequently increases CV risk with all possible consequences (e.g. stroke, myocardial ischaemia, heart failure). Cancer patients are at high risk of CV events due to endothelial dysfunction caused by chemotherapeutic agents (most of them generate free radicals). The endothelial function might be assessed using a wide range of laboratory tests and imaging techniques; however, their implementation in routine clinical practice is not easy and requires the establishment of reference ranges. Patients may benefit from early interventions preventing endothelial damage and restoring endothelial function. These strategies not only reduce CV risk but also diminish adverse effects of oncological treatment, thus enabling its continuation.

*Conflict of interest: The authors declare no conflict of interest*

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