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EDITORIAL COMMENT

When cardiotoxicity demonstrated in Cardio-oncology is investigated in other contexts: Research into the cardiovascular effects of antiangiogenic drugs used in ophthalmology

Quando a cardiotoxicidade demonstrada na cardio-oncologia é pesquisada noutros contextos: a investigação dos efeitos cardiovasculares dos fármacos antiangiogénicos usados em oftalmologia

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The development of new therapies for cancer has led to dramatic improvements in survivorship. Angiogenesis inhibitors represent one such advancement, revolutionizing treatment for a wide range of malignancies. However, these drugs are associated with cardiovascular toxicities which can impact optimal cancer treatment in the short-term and may lead to increased morbidity and mortality in the longer term[1]. Vascular endothelial growth factor inhibitors (VEGFIs) are associated with hypertension, left ventricular systolic dysfunction (LVSD) and heart failure as well as arterial and venous thromboembolism, QTc interval prolongation and arrhythmia.[1]

Bevacizumab, a recombinant vascular endothelial growth factor (VEGF) neutralizing antibody, is commonly used in the treatment of various cancers, including colorectal, cervical, ovarian, glioblastoma, and non-small cell lung cancers.[2] It is the most widely used VEGFi.[2] Bevacizumab has been associated with cardiovascular complications such as hypertension, venous and arterial thromboembolism, left ventricular dysfunction, and less commonly, myocardial infarction and cerebrovascular events. Overall, the incidence of any bevacizumab-associated cardiotoxicity has been reported to be as high as 35%, with the predominant toxicity being hypertension.[2]

A meta-analysis of more than 20 000 patients, analyzing cardiovascular adverse events in patients with cancer treated with bevacizumab showed that treatment with bevacizumab increases the risk of arterial adverse events, particularly cardiac and cerebral ischemia, venous adverse events, bleeding, and arterial hypertension.[3] This risk is additionally increased with high doses of bevacizumab.[3]

Sonaglioni et al. investigated whether two-dimensional speckle tracking echocardiography can non-invasively

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detect early evidence of cardiotoxicity in metastatic colorectal cancer (mCRC) patients treated with bevacizumab.[4] At six-month follow-up, they assessed the occurrence of global longitudinal strain (GLS) impairment (>15% decrease in GLS compared with baseline) as a primary end-point and a new-onset systemic hypertension (secondary end-point). On average, with GLS there was a progressive significant impairment after bevacizumab at six-month follow-up and a more than 15% decrease in GLS (primary end-point) was detected in nine patients (36%).[4] New-onset systemic hypertension (secondary end-point) was diagnosed in five patients (20%).[4]

Antagonists of vascular endothelial growth factor (anti-VEGF) are widely administered by intravitreal injection for the treatment of ocular pathologies such as age-related macular degeneration, diabetic macular edema, proliferative diabetic retinopathy and occlusion of retinal vessels.[5] Whereas the systemic administration of anti-VEGF agents in oncology is burdened by increased risk of arterial hypertension and embolism, agents administered for ophthalmic indications are delivered locally into the eye globe in much smaller quantities.[5]

Systemic use of anti-VEGF agents in oncology is associated with increased risk of arterial hypertension, cardiovascular events and arterial embolism. However, it is not established whether also their intravitreal administration increases these risks.[5] Moreover, it would be important to increase pharmacosurveillance, to uncover complications arising from the administration of these drugs in real life.[5]

In a previous study, Rasier et al., attempted to determine the short-term effect of intravitreal bevacizumab administration on systemic blood pressure levels of patients and to evaluate the safety of the drug in these patients.[6] They found that blood pressure was increased in both groups at week three following the injection, and normalized at week six in patients without medication, while it persisted in some of the patients on antihypertensive medication.[6] They concluded that there is a risk of dysregulation of blood pressure levels or persistence of hypertension in hypertensive patients after intravitreal bevacizumab injections.[6] They also recommended a cardiological consultation before intravitreal bevacizumab injections, especially for hypertensive patients.[6]

There has been controversy concerning the possible association between Intravitreal bevacizumab (IVB) injections and thromboembolic accidents. Some studies reported no association between IVB injections and cerebrovascular accidents (CVAs) or myocardial infarction (MIs), but others reported that IVB injections are associated with an increased risk of CVAs or MI.[7]

Kwon et al. retrospectively reviewed the charts of patients who had received IVB injection in 2016 at a single center, and grouped them according to whether they received the injection for age-related macular degeneration (AMD), diabetes-related complications, or retinal vein occlusion (RVO).[7] Then they investigated the prevalence of MI within two months after IVB injection and analyzed the possible association of IVB with MI.[7] In 2016, 724 patients were enrolled and received a total of 1870 IVB injections. Seven patients were diagnosed with MI within two months after receiving an IVB injection; of 274 patients with AMD, two were diagnosed with MI; of 311 patients with diabetes-related complications, three were diagnosed with MI; and of 139 patients with RVO, two were diagnosed with MI (p=0.785). All MIs occurred between three days and three weeks after IVB injection (mean=14.00 ± 6.45 days). The average age of patients diagnosed with MI after the IVB injection was 64.42 ± 13.22 years (6 males and one female). The prevalence of MI was 0.73% in patients with AMD, 0.96% in patients with DM, and 1.44% in patients with RVO. The MIs after receiving IVB were associated with previous history of MI or cerebrovascular infarction in multivariate logistic regression analysis (p=0.005). There was no significant difference in MI prevalence after IVB injection according to the reason for receiving the injection.[7]

In the present study, dedicated to the ''investigation of the effect of intravitreal bevacizumab treatment on left heart function using speckle tracking echocardiography'', the researchers point out that the dose of bevacizumab used is significantly lower than that used in cancer treatments and there is a slight decrease in GLS with statistical significance.

Although intravitreal bevacizumab is administered at a dose of 1.0–2.5 mg (150 times less than the systemic dose used in cancer), it has been suggested that VEGF inhibition may cause systemic adverse effects that may be serious for patients with diabetes or elderly patients at high risk of cardiovascular adverse events.[8]

The study was conducted due to the lack of information on detailed evaluation of the cardiac effects of intravitreal anti-VEGF applications.[8] More comprehensive randomized controlled studies are needed to obtain more information on this subject and to guide the treatment.[8] During the course of the study, the newly diagnosed hypertension in two patients was thought to be drug-related.[8]

It is difficult to interpret these results due to the sample size (44 patients included) in a single center. The results were assessed early (at three months), and there was very slight decrease in GLS; however, the study aims to draw attention to the fact that there may be cardiovascular repercussions with intravitreal bevacizumab injections use and Cardiology practitioners should be aware of these treatments.

Cardiological evaluation may be recommended in the context of intravitreal bevacizumab injections, especially for hypertensive patients, for patients with diabetes, elderly patients at high risk of cardiovascular adverse events and patients with a history of myocardial infarction or stroke.

Conflicts of interest

The author has no conflicts of interest to declare.

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