Review article

Cardiovascular complications of selected antibodies used in oncological immunotherapy

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ABSTRACT

Immunotherapy supports other therapeutic methods and is an important element in the fight against cancer. Its main tasks include stimulation and guidance of the immune system to fight cancer, inhibition of the mechanisms that block the immune system, and direct destruction of neoplastic cells. Different from chemotherapy or hormonal therapy, its mechanism of action is associated with a different profile of adverse events. HER2 receptor inhibitors may cause symptoms of heart failure, which usually recede, once the treatment has been discontinued. Bevacizumab, an anti-VEGF antibody, induces numerous cardiovascular complications, including arterial hypertension, arterial embolism, haemorrhage and haemoptysis as well as venous thromboembolism.

Key words: immunotherapy, monoclonal antibodies, trastuzumab, bevacizumab, pertuzumab, trastuzumab-emtansine, vascular endothelial growth factor

INTRODUCTION

Next to surgery, chemotherapy, radiotherapy, and hormone therapy, immunotherapy constitutes an important tool in the fight against neoplastic diseases. Its main tasks include enhancing and targeting the immune response against the tumour, reversing the mechanisms blocking anti-cancer response, and inhibiting or destroying cancer cells. Active immunotherapy enhances the function of the immune system. Anti-cancer vaccines mainly consist of neoplastic cells or their modified antigens, and it is not their role to prevent disease, as in the case of anti-infectious vaccines, but to exert therapeutic influence.

One type of active immunotherapy involves administration of modified antigen presenting cells, dendritic cells, or antibodies that inhibit the mechanisms which suppress the immunological response. A new solution also involves antibodies which recognize cancer antigens, binding to them at one end, and stimulating immune system's lymphocytes at the other.

In passive immunotherapy, immune system components are used, including those acting in a non-selective manner (e.g. cytokines) and those acting in a targeted way (e.g. antibodies). Some antibodies may additionally carry cytotoxic drugs or radioactive isotopes. Another form of immunotherapy is adoptive immunotherapy, making use of specially modified lymphocytes [1].

The different mechanism behind immunological drugs, as compared to cytotoxic medications, inevitably involves new adverse events. Some of them are associated with all antibodies, while others are strictly related to the drugs' targets. Due to the rapid development of immunotherapy, and the growing number of drugs used in daily practice and in clinical studies, it is impossible to analyse all cardiovascular complications associated with them. Hence, further on, you will be presented with the mechanisms behind the development of adverse events related to some selected antibodies only.

MONOCLONAL ANTIBODIES

Targeted action of monoclonal antibodies is aimed at cancer cell apoptosis, while sparing the healthy tissues. Initially, the idea behind it was that monoclonal antibodies do not involve immune system mechanisms, but apart from inhibiting signal transmission pathways that lead from membrane receptors to the inside of cells, and apart from stimulating pro-apoptotic mechanisms, monoclonal antibodies do stimulate the immune system, e.g. by means of complement-dependent or antibody-dependent cytotoxicity [2].

Trastuzumab

Trastuzumab is a human monoclonal antibody which inhibits HER2 receptor dimerization with another receptor from the EGFR (epidermal growth factor receptor) family, thus blocking signal transmission to the inside of cells, and suppressing cell cycle progress, and stimulating antibody-dependent cytotoxicity.

The HER2 receptor belongs to the family of EGFR receptors, and in nearly 20% of cases, it is overexpressed on the surface of breast cancer and gastric cancer cells, worsening patient prognosis, but at the same time constituting a good target for targeted therapy with the use of antibodies and tyrosine kinase inhibitors.

Initially, trastuzumab was used in the treatment of advanced breast cancer together with anthracyclines, which resulted in the symptoms of heart failure in 27% of the patients treated with the AC regimen (doxorubicin, cyclophosphamide) and trastuzumab at the same time. In 16% of those treated simultaneously with anthracyclines and trastuzumab, NYHA grade 3 and 4 heart failure developed. In most patients, high doses of anthracyclines were used (6 chemotherapy courses), with cardiac safety assessed retrospectively, but due to the significant cardiotoxicity, simultaneous administration of anthracyclines was abandoned altogether [3].

In the studies on trastuzumab as adjunctive treatment in breast cancer, administered after the completion of anthracycline treatment, the cardiovascular system was prospectively assessed. Symptoms of heart failure were reported in 7–34% of patients, and severe symptoms of NYHA grade 3 or 4 heart failure were observed in 0–4% of them. The findings indicate that anthracyclines increase the risk of cardiovascular complications [4–7].

In advanced gastric cancer, treated with trastuzumab combined with alkylating drugs or antimetabolites, cardiovascular complications were observed in ca. 1–5% of the patients involved [8]. Differences in the incidence of cardiovascular complications as presented in different clinical studies stem from the different cardiovascular status of the patients, the time interval between the completion of anthracycline treatment and initiation of trastuzumab therapy, and duration of the antibody therapy itself.

Trastuzumab-related cardiotoxicity is usually reversible, it does not depend on the cumulative dose, and it rarely develops following treatment completion. It mainly involves structural and functional changes in mitochondrial contractile proteins, rarely leading to cell death, though. Once heart failure or cardiotoxicity symptoms have developed, most frequently manifested as

a drop in the left ventricular ejection fraction (LVEF), discontinuation of the drug and initiation of cardiovascular treatment often leads to recovery. Angiotensin convertase inhibitors are most commonly applied, just as in the case of anthracycline-induced heart failure [9, 10].

Cardiovascular risk factors include [11]:

- prior anthracycline treatment
- short interval between the use of anthracyclines and trastuzumab
- elderly age
- arterial hypertension
- low baseline value of the left ventricular ejection fraction.

Presently, high doses of anthracyclines are avoided, and in the case of a positive cardiovascular history, chemotherapy regimens without anthracyclines are used.

T-DM1, pertuzumab

The remaining drugs targeting the HER2 receptor have a similar cardiovascular safety profile.

Combination of trastuzumab with emtansine (T-DM1), a cytotoxic drug, is aimed at blocking the HER2 receptor activity, while delivering emtansine directly to the neoplastic cells showing HER2 receptor overexpression, and sparing the healthy tissue. In the EMILIA study, involving patients with advanced breast cancer who had previously been treated with chemotherapy and trastuzumab, a reduction in the left ventricular ejection fraction was observed in 1.7% of them, and NYHA grade 3 heart failure symptoms in 0.2% of the patients [12].

Pertuzumab is a humanized monoclonal antibody, which binds to the extracellular domain of the HER2 receptor, inhibiting its dimerization, and thus blocking its function. It is currently used together with trastuzumab and docetaxel in neoadjuvant and palliative treatment breast cancer. In phase I–III clinical studies on pertuzumab, cardiotoxicity was observed in 4.5–14.5% of the patients, but no cases of severe (NYHA grade 3 or 4) heart failure were reported. Most of the events developed during concurrent use of the two anti-HER2 antibodies, but adding pertuzumab to trastuzumab did not result in an increased rate of cardiovascular complications [12].

Bevacizumab

Bevacizumab is an anti-VEGF (vascular endothelial growth factor) antibody which inhibits the process of angiogenesis, binding to the VEGFR-1 and VEGFR-2 receptors, located on the surface of vascular endothelial cells. It also has immunosuppressive activity, inhibiting the activity of antigen-presenting dendritic cells in lymph nodes, and constituting an essential element in terms of stimulating the immune response against cancer cells.

Preventing VEGF binding to the VEGF receptors, bevacizumab compromises the function of endothelial cells, increases the permeability of blood vessels, and stimulates the natural bodily defences against cancer. On the one hand, the drug enhances the vascularization of the tumour, thus facilitating penetration of cytostatic drugs, and on the other hand, it destroys the fine blood capillaries, which is conducive to the reduction in tumour size, and inhibits its further development [13].

It is used in the treatment of different neoplasms, including breast cancer, cervical cancer, colorectal, ovarian and fallopian tube cancers, primary peritoneal cancer, non-small-cell lung cancer, renal cancer, and glioblastoma.

One of the complications observed during bevacizumab treatment is arterial hypertension. In a meta-analysis covering 20 studies involving patients with different neoplastic diseases, arterial hypertension was reported in 23.6% of them, and in 7.9% of the subjects it was grade 3 or 4 arterial hypertension. It is believed that the risk of hypertension might have been underestimated due to the threshold value of 150/100 mmHg. Presently, hypertension is diagnosed once the threshold value of 140/90 mmHg is reached.

Bevacizumab shows a multidirectional mechanism of hypertension induction. Inhibition of the normal growth of endothelial cells leads to a reduced production of prostaglandins and nitric oxide, which both have vasodilation effects. Contraction of the blood vessels in the kidneys increases the absorption of sodium ions, while peripheral vascular contraction increases peripheral resistance [14]. Proteinuria is also more often observed in patients with arterial hypertension. It was reported in 0.7–54.7% of the subjects involved in bevacizumab studies, and it was usually considered as clinically non-significant [15].

Another cardiovascular complication associated with bevacizumab is heart failure. In the BEATRICE study, bevacizumab was added to conventional chemotherapy in some of the patients with early triple negative breast cancer without oestrogen and progesterone receptor expression, and without HER2 receptor overexpression. Symptoms of heart failure developed in 2% of the subjects, with grade 3 or 4 observed in only 1% of them. In most cases, the complication was transient.

Cardiovascular risk factors include:

- prior anthracycline treatment
- diagnosis of heart failure
- advanced ischaemic heart disease
- chronic ischaemic cardiomyopathy
- compromised function of the left heart valves.

Damage to the coronary vascular endothelial cells may lead to their contraction, increased permeability, and embolism, eventually resulting in myocardial infarction or ischemia-induced arrhythmia. In the BEATRICE study, such complications occurred in ca. 1% of the study subjects [16]. On the other hand, in a meta-analysis of 5 randomized trials, involving 1745 patients with metastatic colorectal cancer, breast cancer or non-small-cell lung cancer treated with chemotherapy or chemotherapy combined with bevacizumab, embolic lesions developed in the coronary vessels of 3.6% of the study subjects. The increased risk of arterial embolic complications was also associated with cerebral incidents. Embolic complications were reported more frequently in patients with a positive medical history. The meta-analysis did not demonstrate an increased risk of venous thromboembolism, though [17]. In a group of patients with advanced cervical cancer, on the other hand, venous thromboembolic complications were observed 6 times more frequently in those treated with chemotherapy combined with bevacizumab than in those on chemotherapy alone (18% vs. 3%) [18].

Haemorrhagic complications and haemoptysis were reported more often in patients treated for non-small-cell lung cancer with bevacizumab and chemotherapy than in those on cytostatic drugs alone (19% vs. 3%). 15 (out of 305) patients receiving bevacizumab died of treatment-related complications, and in 10 of them there had been haemorrhagic episodes or thromboembolic incidents [19].

CONCLUSIONS

Immunotherapy is a source of new possibilities, but it is also associated with a new profile of adverse events. Appropriate assessment of the cardiovascular system prior to the initiation of treatment as well as prophylactic and therapeutic actions undertaken to improve the patient's cardiac condition are essential for the selection of patients who will clinically benefit from treatment, without running the risk of serious cardiotoxicity.

Most of the cases of heart failure associated with anti-HER2 therapy are reversible, provided the condition is diagnosed and treated early on. Angiotensin receptor inhibitors are usually administered in clinical practice, just as in the treatment of anthracycline-induced heart failure. International literature includes case reports involving chronic cardiovascular complications, which is why it is important to monitor patients both during and after the treatment.

The multidirectional anti-VEGF treatment is associated with a broad spectrum of adverse events. They most common ones include:

- arterial hypertension
- fatigue and weakness (often associated with immunotherapy)
- diarrhoea and abdominal pain.

The most severe complications include:

- GI tract perforation
- haemorrhage and haemoptysis (in patients diagnosed with lung cancer)
- arterial embolism.

Confirmed arterial hypertension that is well-controlled with angiotensin convertase inhibitors, angiotensin receptor blockers, β-blockers or dihydropyridine calcium channel blockers should not be a factor which restricts anti-cancer therapy [20].

The profile of adverse events associated with the discussed antibodies is extensive, depending primarily on the role of the target site as well as, inter alia, on the impact exerted on the immune system, on the patient's condition, concomitant diseases and previously administered treatment.

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