Cardiological adverse events after oncological treatment in women

Powiklania kardiologiczne leczenia onkologicznego u kobiet

Introduction
Oncological treatment causes a number of organ complications, including cardiological ones, which are related to the characteristics of the given drugs and patients. Positive cardiological medical history, female sex and old age are the basic factors responsible for cardiotoxicity development. There are no differences in mechanism and duration of cardiotoxicity between men and women. Temporary dysrhythmia, heart failure and cardiomyopathy are the most often adverse effects after oncological treatment. Pathomechanism of cardiomyopathy is related to the presence of free radicals. Prevention against cardiological adverse effects is very important because of the limited options to reverse them. Prevention includes not exceeding the cumulative dose, the anthracycline dose fractionation, adequate qualification for cardiotoxic treatment, liposomal doxorubicins use or dextrazosine administration to restrict free radicals.

Cardiotoxicity
Cardiotoxicity is most often observed during and after anthracycline treatment. Cardiotoxicity, from the time of chemotherapy administration to the appearance of symptoms of adverse effects, are divided into:
1. acute cardiotoxicity (hypotonia, temporary dysrhythmia) - during or directly after treatment administration,
2. subacute cardiotoxicity (pericarditis or myocarditis) - a few weeks to a few months after treatment completion; it occurs very seldom in oncology,
3. chronic cardiotoxicity - within the first year after anthracycline therapy, usually in the form of dilated cardiomyopathy,
4. late cardiotoxicity - many years after treatment discontinuation resulting in dysrhythmia or left ventricular failure.

Anticancer drugs influence cardiovascular system in a few different ways. They induce arrhythmia and conduction disturbances (paclitaxel and adriamycin), hypertension (bevacizumab), increasing risk of thromboembolic events (hormonotherapy).

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Radiotherapy delivered to the left side of the chest, hypertension, coexisting heart disease as well as the concurrent use of cardiotoxic agents heavily increase the risk of anthracycline cardiotoxicity. 

Postchemotherapy cardiac events often occur more frequently in females but the cause of this phenomenon is still unknown. Other factors which increase cardiotoxicity risk are age (65 years and above) and exceeding the cumulative dose of anthracyclines [6].

The maximum life dose of adriamycin is 550 mg/m². This decreases to 450 mg/m² when delivered concurrently with radiotherapy of the left-side of the chest. The concurrent use of taxanes requires a further decrease in adriamycin dose to 360 mg/m². The cumulative dose of epirubicin was estimated at 1100 mg/m².

Breast cancer and cytostatics

Adriamycin is a classic example of cytostatic causing cardiotoxicity. Its use can result in dysrhythmia, dilated cardiomyopathy and heart failure. Pathomechanism of postanthracycline cardiomyopathy is mainly based on the presence of free radicals, which are produced during enzymatic reactions and the complex doxorubicin-Fe³⁺ formation. Myocardium is particularly sensitive to the disruptive activity of free radicals due to its low content of catalase and dismutase and increased concentration of peroxidase in cardiomyocytes [6].

Temporary dysrhythmia (mainly bradycardia) and left ventricular dysfunction can be caused by the combination of paclitaxel and anthracyclines. Hypotension and fluids retention with oedemas, pleural and pericardial effusion can occur during treatment with docetaxel. Treatment with cyclophosphamide can lead to asymptomatic myocarditis, pericarditis and fully symptomatic heart failure. The intensity of a single dose of cyclophosphamide is the most important cardiotoxic factor in opposition to the cumulative dose crucial for anthracycline toxicity. The administration of a single dose of 180-200 mg/body mass can be responsible for cardiomyopathy, as well as within 2-4 days.

Cisplatin may cause arrhythmias and chest pain with an increase in the level of troponins suggesting acute coronary syndrome. Cisplatin administration increases the risk of heart infarction to 1.9 when compared with untreated individuals. Life threatening arrhythmias associated with post-cisplatin hypoglycaemia were reported in 35% of patients. Intensive hydration with the subsequent duration rate 100-150 ml/min is recommended when the cisplatin dose exceeds 40 mg/body mass. This recommendation can be problematic for patients with impaired heart efficiency.

Some authors associate the administration of 5Fluorouracil (5FU) with coronary angiospasm (1-18%). They suggest prolonging the drug infusion to diminish the risk of angiospasm. 5Fluorouracil is an active metabolite of capecitabine and induces 3% risk of cardiovascular complications in patients pretreated with taxans.

Breast cancer and hormonotherapy

Tamoxifen is an antiestrogen agent with low estrogen activity used for breast cancer treatment. Tamoxifen increases the risk of cardiovascular disorders and thrombotic events. Total cholesterol and LDL cholesterol reduced level was observed in the course of tamoxifen therapy. The ATAC trial as well as the BIG 1-98 study elicited, that hypercholesterolemia occurs more often during aromatase inhibitors treatment [2,13,14,15]. The IES trial brought similar results [3]. Generally, the tamoxifen toxicity profile seems to be more favorable when compare with aromatase inhibitors (tables number I, II, III).

Breast cancer and targeted therapy

Bevacizumab is a humanized monoclonal antibody against VEGF (vascular-endothelial growth factor). This drug induces hypertension and thromboembolic events. Trastuzumab is a humanized monoclonal antibody against the HER2 receptor (human epidermal growth factor receptor 2). The NSABP B-31 study revealed cardiotoxicity among 4.1% of women treated with trastuzumab [7,12].

Symptomatic heart failure, regardless of the grade according to NYHA, was diagnosed in 1.7% of women with breast cancer treated with adjuvant trastuzumab in a 12-month follow-up (HERA study) [8].

The Intergroup N9831 study revealed, that serious cardiological events, defined as heart deaths and heart failure, were observed in 0.3% of patients receiving adjuvant chemotherapy (adriamycin plus cyclophosphamide). This percentage increases to 3.3%, when trastuzumab is given subsequently [7,12].

Adriamycin and trastuzumab are the most frequent cardiotoxic drugs used in breast cancer treatment. Differences between the cardiotoxicity of both agents are shown on table 4 [5].

Other cancers and cardioxic treatment

Irradiation combined with cisplatin is the radical treatment of cervical cancer. The risk of cardiological side effects is related to cisplatin (discussed above).

Cardioxic drugs such as: cisplatin and bevacizumab are used in the treatment of advanced ovarian cancer. The risk factors of endometrial cancer are similar to those responsible for heart diasease. Palliative treatment includes anthracycline and derivants of progestagens, which are responsible for body gain and thromboembolic events.

There are a few complications related to lung cancer treatment: cardiotoxicity (cisplatin), vein damage (vinorelbine) and thromboembolic events (bevacizumab).

Multi byroso acid (sphingosine, sorafenib, sunitinib) and mTOR inhibitors (mamalian target of rapamycin) (temsirolimus, everolimus) are responsible for hypertension during the anticancer treatment of advanced/metastatic renal cancer. In these cases careful monitoring of the arterial blood pressure value with frequent modification of hypertension treatment is necessary. Additionally, sorafenib can cause stagnant heart failure and myocardial infarction. Thrombo-phebitis is a known side effect of temsirolimus treatment.

Potentially cardioxic agents such as: 5fluorouracil, cisplatin, adriamycin, trastuzumab, taxans are wide used in the systemic treatment of gastric cancer.

5fluorouracil is the essential cytostatic used in colorectal cancer management. This agent can induce coronary angiospasm. The cardiotoxicity of capecitabine during colorectal cancer treatment is incidental. Irinotecan and monoclonal antibodies against EGFR (cetuximab and panitumumab) cause diarrhea leading to electrolytic disorders and subsequently life-threatening arrhythmia. Cetuximab may also induce hypomagnesemia.

Radiotherapy

Radiotherapy is a method widely used in oncology. It is also an integral part of breast cancer treatment.

The probability of cardiotoxicity following radiotherapy depends on factors related to irradiation and the patient’s characteristics. The location of neoplasm in the chest, the total radiotherapy dose, fraction dose and irradiated heart volume belong to the risk factors related to radiation therapy. Moreover, using radiotherapy concurrently with cardiotoxic systemic treatment (adriamycin, cisplatin) and molecular targeted therapy (trastuzumab, cetuximab) may result in the radiation cardiac changes [10].

Patient age, obesity, smoking and the presence of concomitant diseases (hypertension, diabete mellitus, hyperlipidemias) increase risk of radiation-induced cardiac complications. Changes in coronary vessels are a consequence of the direct action of radiation. The main types of damage caused by postradiotherapy in the heart include myocardial ischaemia and structural/functional changes in the endothelial cells of coronary vessels [10].

Ischaemic heart disease is the most common side effect of breast cancer treatment [11]. Furthermore, radiotherapy can cause damage heart valves, conductions disturbances, radiation-induced cardiomyopathy and pericarditis [1].

Modern and very efficient radiotherapy techniques like 3D conformal radiation or intensity modulated radiation therapy have resulted in the substantial reduction of postradiotherapy damage.

Diagnostics

A structural and functional heart assessment with an evaluation of the left ventricular ejection fraction should be performed prior to starting cardiotoxic oncological treatment in order to define the cardiovascular risk. Furthermore, the initial cardiac troponins level should be measured. The initial concentration of natriuretic peptide should be estimated in the case of a diminished left ventricular ejection fraction.

Cardiac troponins should be monitored during cardiotoxic chemotherapy. Patients with increased cardiac troponins at baseline should be referred to cardiologist [12].
Table I  Cardiovascular side effects during hormonotherapy (ATAC study).

<table>
<thead>
<tr>
<th>side effect</th>
<th>tamoxifen (n=3 125)</th>
<th>anastrozole (n=3 116)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>myocardial infarction</td>
<td>34 (0.27%)</td>
<td>33 (0.27%)</td>
<td>ns</td>
</tr>
<tr>
<td>cerebral stroke</td>
<td>20 (0.16%)</td>
<td>34 (0.28%)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>cardiovascular deaths</td>
<td>67 (2.0%)</td>
<td>66 (2.0%)</td>
<td>ns</td>
</tr>
<tr>
<td>deaths due to cerebral stroke</td>
<td>25 (0.8%)</td>
<td>29 (0.9%)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Table II  Cardiovascular side effects during hormonotherapy (IES study).

<table>
<thead>
<tr>
<th>side effect</th>
<th>exemestane (n=2320)</th>
<th>tamoxifen (n=2338)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>cardiovascular events</td>
<td>382 (16.5%)</td>
<td>350 (15.0%)</td>
<td>0.16</td>
</tr>
<tr>
<td>ischemic heart disease</td>
<td>185 (8.0%)</td>
<td>162 (6.9%)</td>
<td>0.17</td>
</tr>
<tr>
<td>hypertension</td>
<td>830 (35.8%)</td>
<td>772 (33.0%)</td>
<td>p=0.05</td>
</tr>
<tr>
<td>thromboembolic events</td>
<td>28 (1.2%)</td>
<td>54 (2.3%)</td>
<td>p=0.004</td>
</tr>
</tbody>
</table>

Table III  Cardiovascular side effects during hormonotherapy (BIG1-98 study).

<table>
<thead>
<tr>
<th>side effects</th>
<th>letrozole (n=2448)</th>
<th>tamoxifen (n=2447)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>cardiac events</td>
<td>134 (5.5%)</td>
<td>122 (5.0%)</td>
<td>0.48</td>
</tr>
<tr>
<td>ischemic heart disease</td>
<td>54 (2.2%)</td>
<td>41 (1.7%)</td>
<td>0.21</td>
</tr>
<tr>
<td>heart failure</td>
<td>24 (1.0%)</td>
<td>14 (0.6%)</td>
<td>0.14</td>
</tr>
<tr>
<td>other cardiovascular events</td>
<td>19 (0.8%)</td>
<td>6 (0.2%)</td>
<td>0.014</td>
</tr>
<tr>
<td>cerebral stroke/ transient brain ischemia</td>
<td>34 (1.4%)</td>
<td>35 (1.4%)</td>
<td>0.90</td>
</tr>
<tr>
<td>thromboembolic events</td>
<td>50 (2.0%)</td>
<td>94 (3.8%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table IV  Classification of heart failure in oncology according to Ewer and Lippman (from J. Clin. Oncol. 13, 2900-2902).

<table>
<thead>
<tr>
<th></th>
<th>type I</th>
<th>type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>typical drug</td>
<td>adriamycin</td>
<td>trastuzumab</td>
</tr>
<tr>
<td>clinical duration</td>
<td>durable and unreversible lesion</td>
<td>return to normal heart function</td>
</tr>
<tr>
<td>dose relation</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>mechanism</td>
<td>creating of free radical</td>
<td>blocking of Erb2</td>
</tr>
<tr>
<td>ultrastructural changes</td>
<td>necrosis of cardiomyocytes</td>
<td>non observed</td>
</tr>
<tr>
<td>echocardiography</td>
<td>Low LVEF, hipokinesia</td>
<td>Low LVEF, hipokinesia</td>
</tr>
<tr>
<td>repeated treatment</td>
<td>NO</td>
<td>YES?</td>
</tr>
<tr>
<td>late side effects</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>

Prevention

Prevention against cardiological adverse effects is very important because of the limited options to reverse them. The prevention includes not exceeding the cumulative dose, anthracycline dose fractionation, adequate qualification for cardiotoxic treatment, the use of liposomal doxorubicins or dextrasofoxane administration to restrict free radicals.

Therapy with convertase inhibitors can be considered in females who are qualified for chemotherapy and/or radiotherapy. These drugs are effective in the prevention of cardiovascular complications in patients at high risk of heart disease. In the case of intolerance of convertase inhibitors, sartans should be taken into consideration [4].

References

15. The ATAC Trialists' Group. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 100-months analysis of the ATAC trial. Lancet Oncol. 2009, 8, 45.