The management of cancer patients with heart disease

Cardiovascular disease and cancer are the two leading causes of death in the world, therefore a patient may have cancer, but also heart disease. Intensive cancer treatment, including chemotherapy and radiotherapy, improves the prognosis, reduces mortality and lengthens patient lives but it is also associated with cardiotoxicity. This paper describes cardiovascular risk factors and methods for the estimation of individual risk before initiation of oncology treatment in subjects at high baseline risk of heart disease. We also describe the way of monitoring patients receiving potentially cardiotoxic treatment and the management of congestive heart failure, coronary artery disease and hypertension in these subjects.


Introduction
Heart disease in patients with cancer or caused by cancer treatment is a very important clinical problem. Progress in the treatment of cancer has essentially improved the outcome of patients. Some forms of cancer that were routinely fatal a few years ago are now thought of as chronic diseases that undergo remission, aggravation and treatment. Thus, survival has become a very important issue in the management of patients with cancer. Paradoxically, many cancer survivors have a higher risk of cardiovascular disease than of cancer recurrence [11, 21], with a sevenfold higher cardiac mortality rate in children surviving cancer [18]. The therapeutic options for patients with cancer include increasingly complex combinations of medications, radiation therapy, and surgical intervention. Many of these treatments have important potential adverse cardiac effects and are likely to have significant effects on patients’ outcomes and quality of life. Preventing cardiovascular disease in oncology patients and cardiac complications of cancer treatment might have dual benefits, allowing cancer patients to be treated more effectively with potentially life-saving cancer therapy, and preventing long-term cardiovascular morbidity and mortality in these individuals long after cancer therapy is completed.

In 2010, the Polish National Team of Cardiologic and Oncologic Supervision on cardiologic safety of patients with breast cancer for the first time presented the recommendations for prevention and treatment of cardiovascular complications in these patients [19]. Here, we summarize the current state of knowledge on the cardiovascular complications of cancer therapy.

Evaluation of cardiovascular risk factors
Prevention of cardiotoxicity begins before the initiation of cancer therapy, with the oncologist and the cardiologist working as a team. Prior to the initiation of oncology treatment, every patient should undergo a complete medical history and a thorough physical examination in order to detect those conditions that may increase the risk for cardiac dysfunction during treatment, and in some cases they may also reveal symptoms and signs of pre-existing cardiac dysfunction [14]. Cardiac assessment should include evaluation of modifiable risk factors such as smoking, hypertension, hypercholesterolemia, diabetes, obesity, low physical activity, excessive alcohol consumption...
or hormonal replacement therapy. Non-modifiable risk factors are: older age, male sex, family history of heart disease, premature menopause as well as previous radiotherapy [9]. The need to assess total risk easily and quickly led to the development of the risk chart called SCORE (Systematic Coronary Risk Evaluation), which is intended to estimate the 10-year risk of a first fatal atherosclerotic event, whether heart attack, stroke, aneurysm of the aorta, or other factors. Everyone with a 10-year risk of coronary artery disease (CAD) death of 5% or more has an increased risk. In Poland the high risk SCORE chart is used (Figure 1).

Every effort must be made to implement lifestyle modification like smoking cessation and regular physical activity, and to control blood pressure, serum lipids and glycaemia. Special attention should be given to risk factor identification and lifestyle modification in women with early breast cancer. An analysis of the Framingham data estimated a 39% lifetime risk of developing cardiovascular disease (CVD) in women at age of 50 years [16]. At this age, 40% of women had at least one existing risk factor, and 17% had two or more risk factors, the latter associated with a 50% lifetime CVD risk. On the basis of this evidence, it is likely that a substantial fraction of breast cancer patients, at the time of diagnosis, will have a significant risk of developing CVD, which increase the risk of adjuvant therapy-associated cardiovascular injury. Independently, many adjuvant therapies used in breast cancer are associated with varying degrees of direct adverse effects on the cardiovascular system. These direct effects occur in the context of concomitant lifestyle perturbations (indirect effects) that combine to reduce cardiovascular reserve and lead to increase CVD and cardiovascular mortality. This phenomenon was called the “multiple-hit” hypothesis (Figure 2) [13].

Polish guidelines recommend aggressive management of risk factors and consider angiotensin-converting enzyme inhibitors (ACEis) treatment in all women with breast cancer therapy [19]. These recommendations are based on the results of a randomized trial conducted after high-dose chemotherapy [2]. One hundred fourteen adults who had elevated troponin I after high-dose chemotherapy (one quarter of the treated population) were randomized to enalapril (20 mg/day) or open-label control. Treatment was started one month after chemotherapy and continued for one year. Cardiac evaluation was performed at baseline, and at 1, 3, 6, and 12 months after oncology treatment. The results were impressive: 43% of the control and none of the enalapril group had a more than 10% decrease in ejection fraction, and clinical cardiac events were likewise nearly eliminated with enalapril, from 30 events in the control population to only two in the enalapril. This was primary attributable to reductions in heart failure and arrhythmias.

Heart failure in oncology patients

The most frequent manifestation of cardiotoxicity is dilated-hypokinetic cardiomyopathy, and at the beginning its symptoms might be unnoticed or treated as the side effect of chemotherapy. Recent data clearly shows that the time elapsing from the beginning of chemotherapy to the development of left ventricular dysfunction and the onset of heart failure therapy, including ACEI and β-blockers, is an important determinant of the extent of recovery from chemotherapy-induced cardiomyopathy [1]. This highlights the need for an early and real-time diagnosis of cardiac injury in cancer patients receiving potentially cardiotoxic drugs. The most important risk factor for the development of cardiotoxic effects of anthracycline-based chemotherapy is cumulative drug dosage. The incidence of cardiotoxicity seems to increase substantially at dosage greater than 550 mg/m² [15]. The very young and very old patients experience cardiotoxic effects at lower cumulative dosage of anthracyclines than the rest of the treated population. Other important risk factors include mediastinal radiotherapy, pre-existing heart disease, and hypertension. Cardiotoxicity might also be increased when anthracyclines are used with other chemotherapeutic agents with potential cardiotoxicity, such as trastuzumab or taxanes [22]. It is vital to assess these risk factors aside from treatment related parameters when deciding on treatment strategy.

The presentation of heart disease due to anthracycline is typical of congestive heart failure, with orthopnea, fatigue, dyspnea, and lower-extremity edema representing the cardinal signs and symptoms. The standard method of cardiac monitoring is left ventricular ejection fraction (LVEF) assessment by echocardiography, MUGA (Multi Gated Acquisition) scan or cardiac MRI [28]. Echocardiography additionally allows for differentiation of LVEF decrease mechanism and provides a wide spectrum of information on cardiac morphology and its systolic and diastolic function. The Polish National Team of Cardiologic and Oncologic Supervision recommends performing echocardiography before anthracycline and taxane therapy in all patients, and then at regular intervals, that is 1-2 months after treatment, one year after treatment, and afterwards every year [19]. Additionally, echocardiography must be performed after doxorubicin 200 mg/m² in patients with increased risk, and regardless of treatment phase always if heart failure symptoms occur [19]. During trastuzumab treatment echocardiography should be done before treatment, every 3 months during the first year, and after treatment every year [19]. However, LVEF measurement may miss early heart damage, and LVEF decrease is detected when the damage is mostly irreversible. An earlier sign of cardiotoxicity is diastolic dysfunction assessed by Doppler echocardiography and tissue Doppler imaging, including strain and strain rate. Natriuretic peptides, being released into the circulation as a result of cardiomyocyte damage, natriuretic peptides are secreted in response to myocardial stress. Thus, their assessment may be more sensitive in diagnosis of early (reversible cell loss) cardiac dysfunction, also due to their correlation with early-occurring diastolic, rather than systolic dysfunction. However, available data based on the results of observational studies, which assessed usefulness of natriuretic peptides as a marker of cardiotoxicity, do not allow for a clear statement. Cil et al. observed 33 newly diagnosed breast cancer patients after high-dose doxorubicin dosage of 240 mg/m² over four treatment cycles as part of adjuvant chemotherapy for curative breast surgery [4]. Venous NT-proBNP levels were measured before and at the end of doxorubicin therapy. LVEF was measured by echocardiography performed 3 weeks after surgery and at the end of doxorubicin at the time of the treatment. Levels were significantly higher in patients with decreased LVEF. There was no difference in LVEF or NT-proBNP levels between the patients who had high NT-proBNP levels and those who had normal NT-proBNP levels before doxorubicin chemotherapy. None of the studied factors (breast cancer grade, estrogen receptor status, progesterone receptor status, human epidermal growth factor receptor 2 status, age) was found to be significantly related to NT-proBNP. Similar results were presented by Sandri et al. [20]. They evaluated the predictive role of NT-proBNP in patients treated with high-dose chemotherapy. NT-proBNP was measured.
in 52 patients affected by aggressive malignancies before the start of chemotherapy, at the end of chemotherapy administration, and 12, 24, 36 and 72 hours thereafter. In these subjects, echocardiogram was performed regularly during one-year follow-up. Seventeen patients had persistently increased NT-proBNP. 19 patients had only transient increases (concentrations went back to baseline at 72 hours), and 16 had no NT-proBNP increase. Only patients with persistently increased NT-proBNP had a significant worsening of the left ventricular diastolic indexes from baseline to 12 months and of LVEF. Although nearly all studies demonstrated that the increase in NT-proBNP is predictive for the development of cardiac dysfunction with a good correlation between NT-proBNP levels and systolic and diastolic function, the heterogeneity of data (small sample size, different populations, cut-offs, duration of follow-up, cardiac end-point) makes comparison of study results difficult, and does not yet allow for conclusions regarding the use of these markers in clinical practice. The National Team of Cardiologic and Oncologic Supervision suggests that natriuretic peptides should be measured before cardiotoxic therapy, but currently routine assessment is not recommended in early diagnosis and monitoring complications, however it may be helpful in patients with decreased LVEF [19].

The management of heart failure in oncologic patients does not differ from others and should follow the European Society of Cardiology guidelines [5]. Figure 3 provides a treatment strategy for the use of drugs and devices in patients with symptomatic heart failure and systolic dysfunction. It is essential to withdraw cardiotoxic treatment and treat other common cardiovascular and non-cardiovascular co-morbidities.

Despite advances in drug therapy, the prognosis of patients with heart failure remains poor. As compared with the patients with idiopathic cardiomyopathy, the patients with cardiomyopathy due to cardiotoxic chemotherapy have significantly worse survival [7]. Long-term survival of women with congestive heart failure (6 years, 33%) approximates that of women with breast cancer and distant metastases (5 years, 22%), it is far worse than for women with breast cancer and regional metastases (5 years, 77%) or women without identifiable metastases (5 years, 97%) [6]. Heart failure may develop in 28% of women receiving the combination of trastuzumab and anthracycline therapy [6]. Although most subjects who developed heart failure had symptomatic improvement with appropriate therapy, heart failure, like many cancers, is a progressive disease, and mortality remains high despite improvement in symptoms.

**Coronary artery disease in oncology patients**

Chemotherapy might also result in cardiac ischemia, which has been most commonly described in patients who received 5-fluorouracil, topoisomerase inhibitors, and antitumor antibiotics [10]. It is proposed that coronary vasoispasm is the most important effect of cancer therapy that leads to myocardial ischemia and infarction [15]. The risk of cardiac ischemia appears to vary, ranging from 1% to 68% in the subjects treated with high-dose infusion of 5-fluorouracil, and patients with established CVD might be at increased risk of developing myocardial ischemia during drug infusion [10].

Thoracic radiation is the most important cause of CAD or myocardial infarction related to cancer therapy. Modern radiotherapy techniques reduce the volume of the heart and major coronary vessels exposed to high doses, but some exposure is often unavoidable. Radiation-induced damage of coronary artery endothelium seems to be the main mechanism of CAD induced by radiotherapy [24]. This leads to thrombus formation and occlusion of vessels, reduced vascular density, perfusion defects and focal ischemia, which is followed by progressive myocardial cell death and fibrosis. The risk of fatal cardiovascular disease increases with younger age, longer follow-up, higher dose volumes of exposure to the heart and with the presence of traditional risk factors, especially diabetes mellitus [15]. Nowadays, there are no specific recommendations regarding the screening of patients at high-risk of radiation-induced CAD. In high-risk patients with symptoms of angina, the standard stress testing or coronary angiography is compulsory.

Patients who suffer from myocardial ischemia due to 5-fluorouracil treatment often respond to temporary therapy termination [15]. Additionally, administration of cal-
Hypertension in oncology patients

Hypertension is one of the most frequent comorbidities in cancer patients [19]. Treatment of myocardial infarction is more complicated and guidelines are often difficult to apply because of higher risk of bleeding or presence of intracranial malignancy which is an absolute contraindication to the use of thrombolytic therapy. Subjects undergoing percutaneous coronary angioplasty also receive heparin, aspirin and clopidogrel which significantly increase the risk of major bleeding. In oncology patients the decision to use bare metal or drug-eluting stents is also more complex and stents must be selected individually according to oncologic prognosis, risk of restenosis and platelet counts [19]. When bare metal stents are implanted, patients should receive aspirin and clopidogrel for a minimum of one month to prevent subacute thrombosis, but with drug-eluting stents this period must be prolonged to at least one year.

Hypertension in oncology patients

Hypertension is one of the most frequent comorbid conditions in cancer patients and observed side-effects of systemic inhibition of vascular endothelial growth factor (VEGF) [22]. The incidence and severity of hypertension in cancer patients are dependent on the type of drugs, dose, age of patients, as well as the presence of coexisting cardiac disease. The recognition of this side-effect is an important issue because poorly controlled hypertension could lead to serious cardiovascular events. On the other hand, hypertension induced by anti-VEGF agents may be a predictive factor for oncologic response [25]. The prevalence of hypertension in cancer patients is not clear. The data from the metaanalysis revealed a 22.5%-57.7% incidence of hypertension under angiogenic inhibitors associated with a 7.5, 6.1, and 3.9 relative risks for developing hypertension with bevacizumab, sorafenib, and sunitinib, respectively [27]. The recently published metaanalysis of randomized controlled trials on safety of bevacizumab revealed that bevacizumab was associated with a fourfold higher risk for hypertension [8].

Hypertension de novo or worsening control of a preexisting one after the introduction of antiangiogenic treatment may indicate many possible underlying mechanisms: renal thrombotic microangiopathy, glomerular lesion, but more commonly it is isolated hypertension secondary to treatment itself [12]. These drugs may lead to increased systemic vascular resistance by endothelial dysfunction associated with decrease in nitric oxide production and an increase in oxidative stress [12]. Patients suitable to angiogenic inhibitor treatment should be assessed at baseline for existing kidney disease with a screening for blood pressure, urine analysis for proteinuria, and a glomerular filtration rate. Repeat screening should be carried out every week for the first eight weeks and before any infusion [12]. Hypertension caused by antineoplastic drugs is usually treated with standard methods (ACEIs, β-blockers, calcium channel blockers, diuretics). It has been postulated that in hypertension related to nitric oxide dysfunction ACEIs may be the best treatment option.

Another very important issue associated with hypertension is the statement that elevated blood pressure increases the risk for renal cell carcinoma. In 2007 the results of the European Prospective Investigation into Cancer and Nutrition (EPIC) study were published [26]. Blood pressure was measured in almost 300 000 patients in 1992-1998. During a mean follow-up of 6.2 years, 250 cases of renal cell carcinoma were diagnosed. The authors reported that blood pressure was independently associated with risk for developing cancer. The relative risks for the highest versus the lowest category of systolic (160 mmHg vs. <120 mmHg) and diastolic (100 mmHg vs. <80 mmHg) blood pressures were 2.48 (95% confidence interval: 1.53, 4.02) and 2.34 (95% confidence interval: 1.54, 3.55). Risk estimates did not significantly differ according to sex or use

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of anti hypertensive medication. Individuals taking anti hypertensive drugs were not at a significantly increased risk unless blood pressure was poorly controlled. These results support the hypothesis that hypertension, rather than its treatment, increases the risk of renal cell carcinoma in both sexes, while effective blood pressure control may lower the risk.

**Decalogue of cardiac management in women with breast cancer**

The National Team of Cardiologic and Oncologic Supervision on cardiologic safety of patients with breast cancer summarized ten of the most important recommendations which help in providing care for women with breast cancer [19]:

1. Smoking is prohibited;
2. Optimal hypertensive treatment;
3. Proper cholesterol levels;
4. Optimal body weight, and
5. Optimal glucose level are necessary;
6. ACEIs should be considered before chemotherapy and/or radiotherapy, irrespective of blood pressure;
7. In case of left ventricular dysfunction dual treatment with ACEIs and β-blockers should be considered in all during cancer treatment and until the end of life;
8. Trime thazine, Q10 and melatonin seem safe during treatment but there are no randomized trials;
9. Thromboembolic risk factors and indications for anticoagulation treatment should be considered;
10. Aspirin 75 mg/d should be administered in all patients at increased cardiovascular risk, whereas chronic treatment should be considered in all women after the end of therapy.

**Conclusions**

Nowadays close interactions between the cardiologist and the oncologist are required for the optimal care of many patients with cancer. The early identification of patients at risk for cardiotoxicity is a current need both for the oncologist and the cardiologist in order to counteract the development of left ventricular impairment and to optimize the treatment of patients undergoing chemotherapy. In view of the significance of the heart failure side effects, it is imperative that physicians perform long-term cardiac follow-up of patients receiving cardiotoxic treatment and that more be learned about the drug’s cardiotoxicity to ensure that patients do not trade one lethal disease for another.

**References**