A practical approach to the 2022 ESC cardio-oncology guidelines: Comments by a team of experts – cardiologists and oncologists

Przemysław Leszek[1]*, Aneta Klotzka[2]*, Stanisław Bartuś[3], Paweł Burchardt[4, 5], Anna M Czarnecka[6, 7], Monika Długosz-Danecka[8], Marek Gierlotka[9], Hanna Koseła-Paterczyk[6], Agata Krawczyk-Ożóg[3], Tomasz Kubiatowski[10, 11], Marcin Kurzyna[12], Adam Maciejczyk[13, 14], Przemysław Mitkowski[2], Aleksander Prejbisz[15], Piotr Rutkowski[6], Ewa Sierko[16, 17], Maciej Sterliński[18], Sebastian Szmit[19, 20], Marek Szwiec[21, 22], Mateusz Tajstra[23], Agnieszka Tycińska[24], Adam Witkowski[25], Wojciech Wojakowski[26], Bożena Cybulska-Stopa[27]

Reviewers: Jacek Mackiewicz[28, 29], Ewa Straburzyńska-Migaj[30]

[1]Department of Heart Failure and Transplantology, Department of Mechanical Circulatory Support and Transplant, National Institute of Cardiology, Warszawa, Poland
[2]1st Department of Cardiology, Poznan University of Medical Sciences, Poznań, Poland
[3]2nd Department of Cardiology, Jagiellonian University Medical College, Kraków, Poland
[4]Department of Hypertension, Angiology, and Internal Medicine, Poznan University of Medical Sciences, Poznań, Poland
[5]Department of Cardiology, J Struś Hospital, Poznań, Poland
[6]Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warszawa, Poland
[7]Department of Experimental Pharmacology, Mossakowski Medical Research Center, Polish Academy of Sciences, Warszawa, Poland
[8]Department of Clinical Oncology, Maria Sklodowska-Curie National Research Institute of Oncology, Kraków, Poland
[9]Department of Cardiology, University Hospital, Institute of Medical Sciences, University of Opole, Opole, Poland
[10]University of Warmia and Mazury in Olsztyn, Olsztyn, Poland
[11]Chemotherapy Department, Grochowski Hospital in Warsaw, Warszawa, Poland
[12]Department of Pulmonary Circulation, Thromboembolic Diseases and Cardiology Center of Postgraduate Medical Education in EHC Otwock, ERN-Lung Member, Otwock, Poland
[13]Department of Radiotherapy, Lower Silesian Center of Oncology, Katowice, Poland
[14]Department of Oncology, Wroclaw Medical University, Wrocław, Poland
[15]Department of Epidemiology, Cardiovascular Prevention and Health Promotion, National Institute of Cardiology, Warszawa, Poland
[16]Department of Radiotherapy I, Maria Sklodowska-Curie Bialystok Oncology Center, Białystok, Poland
[17]Department of Oncology, Medical University of Bialystok, Białystok, Poland
[18]National Institute of Cardiology, Warszawa, Poland
[19]Department of Cardio-Oncology, Center of Postgraduate Medical Education, Institute of Hematology and Transfusion Medicine, Warszawa, Poland
[20]Clinic of Oncological Diagnostics and Cardio-Oncology, Maria Sklodowska-Curie National Research Institute of Oncology, Warszawa, Poland
[21]Department of Surgery and Oncology, University of Zielona Gora, Zielona Góra, Poland
[22]Clinical Department of Oncology, University Hospital of K. Marcinkowski in Zielona Gora, Zielona Góra, Poland
[23]3rd Department of Cardiology, School of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland
[24]Department of Cardiology, Medical University of Bialystok, Białystok, Poland
[25]Departament of Interventional Cardiology & Angiology National Institute of Cardiology, Warszawa, Poland
[26]Division of Cardiology and Structural Heart Diseases Medical University of Silesia, Katowice, Poland
[27]Department of Oncology, Lower Silesian Center of Oncology, Pulmonology and Hematology, Wrocław, Poland
[28]Department of Medical and Experimental Oncology, University of Medical Sciences, Poznań, Poland
[29]Cancer Diagnosis and Immunology Unit, The Greater Poland Cancer Center, Poznań, Polska
[30]1st Chair and Department of Cardiology, Poznan University of Medical Sciences, Poznań, Poland
*Both authors equally contributed to the study

Correspondence to:
Prof. Przemysław Leszek, MD, PhD, Department of Heart Failure and Transplantology, Department of Mechanical Circulatory Support and Transplant, National Institute of Cardiology, Alpejska 42, 04–628 Warszawa, Poland,
e-mail: pleszek@ikard.pl

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INTRODUCTION

The 2022 European Society of Cardiology (ESC) guidelines [1] are a comprehensive document, prepared jointly by experts in cardiology and oncology.

In the case of oncology patients, it is necessary to individualize care in relation to their cardiology condition, stage of cancer, and type of potential anticancer therapy. Cardiac care optimization should be undertaken before the start of oncology therapy and continued during the therapy as well as long after its completion [2].

The published ESC guidelines were supplemented with practical comments from a team of Polish cardiology and oncology experts.

CARDIOVASCULAR TOXICITY RISK STRATIFICATION IN CANCER PATIENTS

Cardiovascular risk stratification should be undertaken in parallel just after cancer diagnosis. This leads to assessment of individual cardiovascular risk, personalization, and optimization of cardiological management during oncological treatment, without unnecessary delays [3].

A careful clinical history (traditional risk factors, prior history of cardiological diseases, cancer, and its therapy) should be supplemented with a physical examination, 12-lead electrocardiogram (ECG), cardiac biomarkers for cancer therapy-related cardiovascular toxicity (CTR-CVT) (baseline assessment and follow-up) of natriuretic peptide (NP) and/or cardiac troponin (cTN) in all patients undergoing cardiotoxic therapy. Cardiovascular imaging, preferably transthoracic echocardiography (TTE), possibly supplemented with 3D echocardiography or GLS (global longitudinal strain) assessment, and in case of doubt cardiac magnetic resonance (CMR) should be considered [4].

The presence of previously diagnosed cardiovascular disease requires individually selected additional tests. Pre-existing cardiovascular disease cannot automatically be a reason to withhold cancer therapy. In such patients, cardiac care is aimed at optimizing cardiovascular treatment, and thus reducing the risk before, during, and after cancer treatment [5].

Practical comment

Commonly used risk scales do not include cancer patients. These patients require complex multidisciplinary care, and need a decision from the Heart Team together with a dedicated oncologist — a multidisciplinary team (MDT) — to qualify them for invasive procedures and cardiac surgery (such as coronary artery bypass, treatment of valvular defects, and others). The common goal of multidisciplinary treatment is complete cardio-oncological assessment, which, in turn, will prolong survival and improve the patient's quality of life.

PREVENTION AND MONITORING OF CARDIOVASCULAR COMPLICATIONS DURING CANCER THERAPY

Appropriate prophylaxis for CTR-CVT (including cancer-therapy-related cardiac dysfunction [CTRCD]) depends on characteristics of particular cancers, potential cardiotoxicity of cancer therapy, and the patient's cardiovascular risk.

Cancer and cardiovascular disease share many common risk factors — potentially modifiable (smoking, etc.) or treatable (hypertension, etc.) [6].

Optimal treatment of cardiovascular disease itself and avoiding adverse drug interactions are important components of basic prevention in cardio-oncology.

In patients with high and very high CV toxicity risk and moderate or severe CTRCD, who require further anthracycline chemotherapy, liposomal anthracycline and dexrazoxane may be considered to reduce the risk of further CV toxicity [7].

Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor antagonists (ARBs) in combination with a beta-blocker should be considered for primary prevention in high- or very high-risk patients during the use of anthracyclines, anti-HER2 therapy, and other molecularly targeted therapies that may cause CTRCD through the "off-target" mechanism [8].

Similarly, statins should be considered as part of primary prevention in adult patients at high/very high cardiovascular risk [9].

The specificity of cardiac monitoring of various cancer therapies should be based on the risk of specific cardiovascular complications associated with a given cancer treatment.

In the case of therapies with the highest risk of CTRCD (such as anthracyclines/anti-HER2), echocardiography (possibly with GLS

assessment) and biomarker assessment (cTn/NP) are recommended at baseline, during the use of drugs, and within a year after the end of therapy.

In fluoropyrimidine therapy, it is crucial to assess the patient for complications related to ischemic heart disease. In the case of some anti-breakpoint cluster region–Abelson oncogene locus (BCR-ABL) or hormone therapies (prostate/breast cancer), it is important to monitor the complications associated with atherosclerosis.

Blood pressure monitoring is necessary during anti-angiogenic (anti-VEGFR) therapy. Effective control of hypertension is also important during treatment with Bruton kinase inhibitors, proteasome inhibitors, and mitogen-activated extracellular signal-regulated kinase/rapidly accelerated fibrosarcoma (MEK/RAF) inhibitors [8, 9].

Practical comment

The presented document lacks information on the possibility of preventive use — secondary/primary prevention SGLT2 inhibitors and ARNI – which may prove particularly useful in the treatment of heart failure, especially in patients experiencing CTRCD despite ACEI/ARB therapy. Also, the optimal therapeutic position for statins and beta-blockers and the optimal use of liposomal doxorubicin have not been determined.

LONG-TERM FOLLOW-UP AND CHRONIC CARDIOVASCULAR COMPLICATIONS IN CANCER SURVIVORS

Assessment of cancer patients after completion of anticancer therapy includes short-term (up to 12 months) and long-term (over 12 months) management [10].

How to proceed after completion of cancer treatment is determined by cardiac risk, type of cancer, time, and intensity of anticancer treatment (assessed by the Heart Failure Association of the ESC in collaboration with the International Cardio-Oncology Society [HFA-ICOS] risk assessment).

Appropriately individualized procedures are based on assessment of NP and/or cTn and echocardiography. Depending on individual risk assessment, education, lifestyle modification, cardiac rehabilitation, and heart failure therapy are recommended in the group of patients with left ventricular dysfunction during cancer treatment [11].

It is also necessary to raise the awareness of primary care physicians in the case of patients treated with anthracyclines, mitoxantrone (there are no data for trastuzumab), and radiotherapy, due to their increased risk of cardiovascular events [12].

After completion of anticancer treatment, cardiovascular assessment is recommended in women planning to undergo and/or in the first trimester of pregnancy.

Practical comment

The document can be complicated for primary care physicians who will play a key role in the long-term care of cancer patients. Classifying patients into risk groups in long-term follow-up, especially after the end of therapy, may seem problematic. It seems crucial to summarize the most important recommendations on the follow-up procedure after the end of oncological treatment and present them in the form of a general scheme.

HEART FAILURE

Regardless of the type of treatment leading to clinically significant CTRCD, close cardiac monitoring (individualized depending on the patient's risk) in this group of patients should be carried out. Individual surveillance protocol should be composed of TTE, including GLS, and damage markers — cTn and/or NP. In the case of cardiac dysfunction (both asymptomatic and symptomatic), it is necessary to implement the following procedures:

1. Discontinuation/temporary interruption of CTRCD-related treatment — in contact with an oncologist, then working out a future management strategy — depending on both cancer/heart condition
2. Concerning the severity of cardiac dysfunction, (symptomatic/asymptomatic), heart failure treatment should be implemented (initially ACE-Inhibitors/ARBs and/or beta-blockers)
3. In selected patients, after achieving heart function improvement and clinical stabilization, it is possible to return to CTRCD-related treatment under restricted surveillance by the MDT [2, 3].

Practical comment

CTRCD related to the use of individual anticancer drugs has been clearly presented. It should be remembered that in many cases commonly used CTRCD-related regimens contain cardiotoxic drugs administered in a combined or sequential manner.

It is very important to assess the patient before starting CTRCD treatment. In healthy patients, we can easily observe CTRCD if it appears. However, for patients with existing dysfunction, CTRCD supervision seems more difficult.

Moreover, in this group of patients, the refusal of optimal cancer treatment, even with potential cardiac toxicity, may significantly worsen their prognosis. Therefore, heart failure treatment has to be optimized and if implementation of anticancer therapy is considered, CTRCD risk should be carefully monitored.

From a practical point of view, in the case of any cardiac dysfunction, even in asymptomatic patients, all available therapies should be based on all recommendations for heart failure treatment.

An increase in the heart rate (HR) is a negative predictor of prognosis and quality of life; therefore, HR optimization is recommended, especially in patients with sinus rhythm. The mechanisms leading to tachycardia include sympathetic/parasympathetic imbalance related to cancer or, for example, radiation therapy; factors related to cancer, such as stress response to cancer, anemia, de-

pression, pain, reduced physical activity, etc. Appropriate HR control requires causal management and intensive pharmacotherapy.

IMMUNE CHECKPOINT INHIBITORS (ICIs)

ICIs activate the immune response against tumor cells. ICIs are used extensively in a growing number of oncological indications. Among cardiac complications, serious life-threatening complications should be remembered, such as myocarditis (including fulminant), advanced heart blocks, complex ventricular arrhythmias, or sudden cardiac death [5]. They most often develop within the first 12 weeks of treatment although later cases are possible. Other adverse events include takotsubo syndrome, non-inflammatory myocardial dysfunction, vasculitis, acute coronary syndrome, and pericarditis, with or without fluid.

In the event of cardiac complications, in addition to standard cardiological management, ICIs should be withheld, the patient should be monitored, and in severe cases, diagnostic management should not delay high-dose steroid therapy [6]. Details of treatment depend on the type and severity of complications; discontinuation or further continuation of treatment with ICIs depends on the severity of complications, and each case should be analyzed by the MDT to optimize management.

Practical comment

ICIs are drugs that are increasingly used in oncological treatment, therefore, it is important to keep close supervision during therapy. Strong supervision should be applied to patients receiving simultaneously combined immunotherapy (e.g. ipilimumab and nivolumab), previously subjected to other cardiotoxic therapies (e.g. VEGF tyrosine kinase inhibitors), or with a history of cardiovascular diseases (e.g. ischemic heart disease/myocardial infarction/heart failure or others). The occurrence of skeletal myositis or autoimmune disease during ICI therapy should raise vigilance. In the group of patients with current heart disease, it is absolutely necessary to optimize cardiac therapy. In patients without cardiac disease, before starting ICIs, the determination of cTn with subsequent monitoring of their levels during treatment seems to be a minimum requirement. In the group of patients with cardiological burden, strict supervision, especially at the beginning of ICI therapy, should be carried out. It is also important that a significant increase in cTn levels during ICI should be of particular concern to the cardiologist. It can be associated not only with acute coronary syndrome (ACS) but also with myocarditis, which can be a direct threat to the patient's life. To sum up, in ICI therapy, cardiac complications are not very common, but they can occur suddenly, directly threatening the patient's life.

ACUTE CORONARY SYNDROMES (ACS)

Patients with cancer are at increased risk of ACS due to common risk factors, exacerbated by the pro-inflammatory/pro-thrombotic state related to cancer and CTR-CVT. The diagnosis of ACS in cancer patients does not differ significantly from other patients and is based on clinical symptoms, ECG, and serial determination of cTN (in non-ST-segment elevation acute coronary syndrome [NSTE-ACS]) [14]. For patients at high CV risk, treated with CTR-CVT therapy (accelerated atherosclerosis/plaque rupture, vasospasm, and thrombosis), diagnostic vigilance should be increased as the clinical presentation can be atypical due to cancer, cancer-related side effects/therapy, or frailty. Management of ACS in cancer patients is not significantly different compared to patients without cancer. Invasive management is preferred in high-risk patients with ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) if their life expectancy is ≥6 months or if they have acute ACS complications. However, it might be more difficult due to increased frailty syndrome, increased risk of bleeding, and prothrombotic risk. Thrombocytopenia modifies the use of antiplatelet drugs: platelet count <10 000 is a contraindication to the use of aspirin, <30 000 for clopidogrel, and <50 000 for prasugrel and ticagrelor [15]. In low-risk patients (without signs or symptoms of ongoing ischemia or hemodynamic instability), NSTE-ACS patients with poor cancer survival prognosis (<6 months) or very high bleeding risk presenting with STEMI or NSTE-ACS, a conservative non-invasive approach can be attempted.

In justified cases, fractional flow reserve (FFR) and intracoronary ultrasound (IVUS) should be used. In patients undergoing percutaneous coronary intervention (PCI), due to a potentially higher bleeding risk (especially in patients with active gastrointestinal (GI) cancer, the duration of dual antiplatelet therapy (DAPT with aspirin and clopidogrel, instead of newer $P2Y_{12}$ antagonist) should not exceed 1–3 months [16]. If vitamin K antagonists (VKAs) or non-vitamin K antagonist oral anticoagulants (NOACs) are required, triple therapy after PCI should be limited to 1 week. Coronary artery bypass grafting (CABG) should be reserved for patients with ACS who are not candidates for PCI and whose survival is estimated at >1 year. A temporary interruption of cancer therapy is recommended in patients where cancer therapy is suspected to be a contributing ACS cause [17].

Practical comment

The basic principles of ACS treatment are presented in relation to the ESC guidelines for the diagnosis and treatment of STEMI and NSTE-ACS. At the same time, they draw attention to possible complications related to the impact of cancer itself and related drugs, especially bleeding caused by, among others, thrombocytopenia, which is common in this group of patients. Therefore, attention should be paid to the length of DAPT after PCI procedures. The role of the MDT should be emphasized in making decisions about the treatment method (also with the use of distance communication and image data transmission), especially in difficult and ambiguous cases, where cardiotoxicity is

suspected as a possible ACS trigger and while assessing expected survival of the cancer patient.

CHRONIC CORONARY SYNDROMES (CCS)

Cancer patients who present new angina symptoms, especially under cancer treatments associated with increased risk of angina should have thorough clinical evaluation. Patients with symptoms should be diagnosed in accordance with the ESC guidelines and have conservative treatment, and their cardiovascular risk factors should be substantially modified. Decisions regarding revascularization procedures (PCI, CABG) in oncology patients should be carefully considered by the MDT [16, 17]. Importantly, PCI procedures in cancer patients with CCS and ACS are associated with increased risk of bleeding, re-infarction, and the need for subsequent revascularization, depending cancer type. Therefore, DAPT should be individualized and as short as possible (1–3 months).

Practical comment

The guidelines are quite brief on the problems faced by CCS patients. The main principles of CCS treatment are the same for all patients, regardless of comorbidities. The MDT is necessary to individualize both conservative therapy and, in particular, coronary revascularization procedures depending on cancer type and treatment, careful balancing of the risk of bleeding associated with anticoagulant treatment vs. the benefits that the patient may get from revascularization, assessment of the expected length of survival, or temporary discontinuation of anticancer drugs.

CARDIAC ARRHYTHMIAS

The most clinically relevant are atrial fibrillation (AF) and ventricular arrhythmias or rather, the potential threat of malignant tachyarrhythmias ventricular tachyarrhythmias cardiac/oncological disease and ncological treatment). Arrhythmias most often manifest themselves in advanced stages of both diseases or as a side effect of anticancer treatment [18].

Atrial fibrillation is the most common arrhythmia in cancer patients. Due to the overlapping risk of thromboembolic complications, presence of cancer with its treatment, and specificity of arrhythmias, early determination of anticoagulant management in this group of patients is very important. The CHA_2DS_2-VASc scale does not include cancer patients; therefore, the decision threshold for anticoagulant treatment in oncology patients should be significantly reduced [19]. Anticoagulant management in cancer patients should be individualized; in the absence of contraindications, in a long-term anticoagulant strategy, preference should be given to NOACs, with assessment of the risk of bleeding complications.

Practical comment

There are few reports on evidence-based medicine (EBM) antiarrhythmic and anticoagulant management in oncology patients. CHA_2DS_2-VASc assessment has not been sufficiently validated in cancer patients. Chronic anticoagulant therapy is recommended in patients with AF and cancer for the prevention of ischemic stroke/other thromboembolic complications, in line with the current general guidelines for AF treatment. Anticoagulant therapy should be considered in patients with appropriately lower CHA_2DS_2-VASc scores; continuous anticoagulation may be considered even in patients without thromboembolic risk factors (except 1 point for females) after prior assessment of bleeding risk.

The risk of serious ventricular arrhythmias in cancer patients is increased [20], which is associated with the use of drugs that can prolong the QTc interval. The occurrence of malignant ventricular arrhythmias or absolute prolongation of the QTc interval >500 ms requires at least temporary discontinuation of treatment if cancer therapy is suspected to contribute to QTc prolongation.

Practical comment

The occurrence of ventricular arrhythmias in the vast majority of cases is associated with the iatrogenic effect of cancer therapy, less often with the inflammatory/infiltrative process. Statistically, the risk of torsade de pointes (TdP) is associated with an increase in the QTc interval ≥500 msec. Non-modifiable factors associated with ventricular arrhythmia (VA) risk include age, sex, history of coronary/structural heart disease, and baseline QTc prolongation. Discontinuation of anticancer therapy and ECG monitoring is recommended in patients who have a QTc interval ≥500 msec. Evaluation/correction of electrolyte disturbances is always necessary. ECG is recommended with each increase in the dose of a drug that may prolong the QTc interval. In antiarrhythmic prophylaxis, beta-blockers are the preferred drug group. It should be remembered that most antiarrhythmic drugs (including amiodarone) can prolong the QTc interval. Long-term prognosis in some oncology patients is significantly improved; therefore, in the case of a high risk of malignant ventricular arrhythmias, the use of an implantable cardioverter defibrillator may be justified.

BRADYCARDIA AND IMPLANTATION OF CARDIAC IMPLANTABLE ELECTRONIC DEVICES (CIEDs)

Oncology therapy-induced bradycardia is the most common disorder after immunotherapy and immunomodulatory treatment (Table 1) [21, 22].

Practical comment

The indications for implantation of cardiac implantable electronic devices (CIEDs) do not differ from those in the non-cancer patient population. The stage of cancer should not affect treatment decisions related to CIEDs. This does not apply to terminal stages of the disease, where a deci-

Table 1. Bradyarrhythmia as a possible complication of oncology treatment

Therapy	Symptoms requiring intervention	Treatment
Immunotherapy with immune checkpoint inhibitor (ICI) drugs	With and without the presence of myocarditis: 1. occurrence of new AV block I° 2. PQ interval > 300 ms	1. Monitoring with serial ECG recordings 2. Hospitalization, ECG monitoring, intravenous methylprednisolone
Immunomodulatory drugs (IMiD): thalidomide, pomalidomide; anaplastic lymphoma kinase inhibitors (ALKi, anaplastic lymphoma kinase inhibitors): crizotinib, alectinib, brigatinib, ceritinib	Loss of consciousness, pre-fainting states, decreased exercise tolerance: Holter test (sinus inhibition, sinus bradycardia)	1. Well tolerated in patients without organic heart disease 2. Test withdrawal of cancer therapy to confirm the association of symptoms with therapy 3. Evaluation of the possibility of alternative therapies 4. No alternative – pacemaker implantation.

sion has been made to introduce palliative therapy to make the patient's life more comfortable.

Cancer patients have an increased perioperative risk (bleeding and systemic infections). This is due to leukopenia, anemia, thrombocytopenia, and increased susceptibility to infection.

The choice of implanted device should be dictated by the patient's ability to undergo magnetic resonance imaging [23, 24].

To reduce hematomas or infections, it is worth considering modern medical devices: electrodeless pacemakers and fully subcutaneous defibrillators.

IMPLANTABLE CIED DEVICES AND RADIATION THERAPY

The use of radiation therapy (RT) in patients with CIEDs can cause irreversible damage to the device. The risk of an adverse RT/CIED interaction is increased by the cumulative dose per device (>2 Gy for a pacemaker, >1 Gy for a implantable cardioverter defibrillator [ICD], and >10 MV for the beam energy). Ignorance of the implications of RT effect on CIEDs puts patients at risk of disqualification from RT or misclassification for removal/relocation of existing CIEDs before RT [25].

Risk stratification should be performed by the attending cardiologist/electrophysiologist and should be based on: CIED location (thoracic vs. external), cumulative dose per CIED and/or beam energy, and the presence of pacemaker dependence or frequent ICD therapies.

1. Any patient with CIED undergoing RT should have an interrogation and full device check just before starting RT (if the last CIED check was > 3 months after starting RT) and up to two weeks after finishing it. Whether and how often a CIED check should be performed during RT depends on baseline risk assessment (every week of RT for high-risk patients, no check during RT for low-risk patients).
2. High-risk patients should be monitored with ECG and pulse oximetry during each RT session. An external pacing kit should also be available.

Device extraction/relocation may occur if the CIED prevents effective RT of tumor and/or it is situated directly in the delivered radiation beam and the risk of damage to the CIED is very high. Such decisions should be made on a case-by-case basis taking into account the risk/benefit balance, patient age, pacemaker dependency, prognosis, type of RT (palliative vs. radical), risk of CIED infection (e.g., immunosuppressive therapy), and possibility of dose/energy reduction of RT [26, 27].

Practical comment

The guidelines do not explicitly address whether the recommendations apply to other implantable devices such as arrhythmia recorders (ILRs, implantable loop recorders), leadless pacemakers (LPs), cardiac contractility modulation (CCM) systems, subcutaneous ICDs (S-ICDs), or phrenic nerve stimulators. This is probably due to the lack of data from clinical trials. The qualification and care during and after RT for patients with one of the above-mentioned devices should take place in centers with extensive experience in caring for CIED patients treated with RT.

PULMONARY EMBOLISM THROMBOSIS AND ANTICOAGULANT TREATMENT

As part of venous thromboembolism (VTE) prophylaxis during oncological treatment, patients undergoing major open or laparoscopic abdominal surgery who have a low risk of bleeding and a high risk of VTE are recommended for prolonged prophylaxis with low-molecular-weight heparin (LMWH) for 4 weeks after surgery [28]. Prophylactic administration of LMWH for primary prevention of VTE is indicated in hospitalized cancer patients as well as in cases of prolonged immobilization, if there is no bleeding or other contraindications.

The recommendations highlight the possibility of using apixaban, edoxaban, or rivaroxaban to treat symptomatic or incidentally detected VTE in cancer patients. For the treatment of symptomatic or incidentally detected VTE in cancer patients with a platelet count >50 000/µl, LMWH is recommended. However, when the platelet count is 25 000–50 000/µl, anticoagulation with half a dose of LMWH can be considered. In patients with cancer and catheter-related VTE, anticoagulation treatment should be continued for at least 3 months or longer if the catheter remains *in situ*.

Practical comment

Venous thromboembolism is the second most common cause of death in cancer patients. The presence of cancer is associated with a 5-fold increase in the risk of VTE, and

cancer-related VTE accounts for 30% of all VTE cases [29, 30]. Unprovoked VTE may be the first clinical manifestation of malignant neoplasm, and the rate of cancer diagnosis in the following 12 months is 5%.

Risk factors for VTE in patients with cancer are related to both the patient's clinical characteristics (older age, comorbidities, female sex, inherited coagulation disorders, functional status/ability of the patient, history of VTE), tumor (type, genetic characteristics [JAK2 or KRAS gene mutations], histological type [adenocarcinoma], initial period after diagnosis, primary focus [pancreas, stomach, ovary, brain, lung, myeloma], stage of disease [advanced, metastatic] as well as treatment [oncology, central venous catheters, surgery and hospitalization itself]) [29].

Patients with multiple myeloma have an increased risk of thrombosis. Risk factors for VTE in these patients are (1) patient-related: previous VTE, acute infections, autoimmune diseases, central venous catheter, chronic kidney disease, smoking, cardiovascular disease, diabetes, general surgery, history of hereditary thrombophilia, immobilization, surgery, trauma, obesity (BMI >30 kg/m^2); and (2) myeloma-related: advanced disease, erythropoiesis-stimulating drugs, high-dose dexamethasone, treatment with thalidomide, lenalidomide or ponalidomide. Recommendations related to VTE prophylaxis during plasmacytic myeloma treatment include therapeutic doses of LMWH after VTE and prophylactic doses of LMWH, at least during the first 6 months of treatment, in patients with risk factors for VTE (excluding prior VTE).

In acute pulmonary embolism, we follow the 2019 ESC guidelines and the second ESC expert position statement on the diagnosis and treatment of acute deep vein thrombosis (DVT). Incidentally detected proximal DVT or PE should be treated in the same way as symptomatic VTE, as the recurrence rate and risk of death are similar. The minimum duration of anticoagulant treatment is 6 months, and prolonged anticoagulant treatment is suggested in cases of active cancer, metastatic disease, or the use of chemotherapy.

PREGNANT WOMEN

Improvements in cancer treatment in recent years have led to an increase in the number of women who become pregnant after anticancer treatment. Most have a history of exposure to radio- and chemotherapy, particularly anthracyclines, which increase the risk of cardiovascular complications. The 2022 ESC guidelines recommend cardiovascular evaluation before pregnancy or during the first trimester [1]. Such evaluation includes at a minimum, patient's previous medical history, ECG, assessment of natriuretic peptide levels, and performance of echocardiography (ECHO). Follow-up is worth considering in patients at high cardiovascular risk who have received cardiotoxic chemotherapy.

A separate issue is when cancer is diagnosed during pregnancy (1:1 000 pregnancies) [30]. Cardiac evaluation with regular follow-up every 4–8 weeks or every 2 cycles of anthracycline drug infusion is recommended before the initiation of such oncological treatment. Serial evaluation of left ventricular ejection fraction and determination of natriuretic peptide levels are used to monitor drug cardiotoxicity. Pregnant women with cancer have a higher risk of VTE. Low-molecular-weight heparins are preferred for treatment and prophylaxis.

Practical comment

The main risk factors that are associated with the occurrence of cardiovascular incidents in pregnant women with a history of cured cancer, i.e. young age of cancer diagnosis, longer period from the start of anticancer treatment to the first pregnancy, cardiovascular complications developed during treatment, and the cumulative dose of anthracyclines used.

Breast cancer, melanoma, and cervical cancer are most commonly diagnosed in pregnancy. Echocardiographic evaluation plays an important role. An increase in stroke volume, heart rate, preload, and total peripheral resistance are typical hemodynamic changes in pregnant women, resulting in an 80%–85% increase in cardiac output by the end of pregnancy. Left ventricular mass and volume increase, as well as right ventricular volume. The ejection fraction (EF) of the left ventricle, which is a parameter for monitoring cardiotoxicity, remains unchanged. Cardiologists should keep in mind that there are higher cutoff values for NT-proBNP (<300 pg/ml) and BNP (<100 pg/ml) in pregnancy [31]. Measurement of high-sensitivity troponin, as a parameter for monitoring myocardial damage, may be considered before and during anthracycline therapy in pregnant women with cancer [32, 33].

ARTERIAL HYPERTENSION

Arterial hypertension (AH) in cancer patients may result from:

- older age;
- anticancer drugs used: VEGFi, BCR-ABL, second- and third-generation tyrosine kinase inhibitor (TKIs) (birganitib, ibrutinib, fluoropyrimidines, cisplatin, abirsterone, bicalutamide, enzalutamide);
- glucocorticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs);
- stress, pain.

Drugs that inhibit the angiotensin renin system (ACEI/ARB) are recommended as the mainstay of hypotensive therapy in oncology patients. Combination treatment of ACEI/ARB with a dihydropyridine calcium antagonist is recommended for patients with cancer and systolic blood pressure (BP) ≥160 and/or diastolic BP ≥100 mm Hg. Patients with BP values ≥180 and/or ≥110 mm Hg should have their oncology therapy causing AH temporarily stopped.

Additional medications if indicated include

- spironolactone, nitrates in transdermal preparations, and/or dihydralazine in patients with refractory AH associated with cancer therapy;
- beta-blockers in patients with sympathetic nervous system activation due to stress and/or pain symptoms;
- diuretics (preference for spironolactone) in patients with fluid retention.

Practical comment

The recommendations are quite conservative concerning the intensity of treatment (combination therapy only in NT stage 2) — this is in contrast to the current guidelines, which favor starting treatment with combination therapy when BP values reach ≥140/90 mm Hg [34, 35].

The omission of thiazide/thiazide-like diuretics and preference for spironolactone as a diuretic, in the guidelines, is hard to understand [36].

The guidelines indicate the possibility of using the following drugs in the treatment of refractory AH: dihydralazine and nitrates in transdermal form – both groups of drugs are not available in Poland. They also mention the vasodilator beta-blockers: carvedilol and nebivolol. However, highly cardioselective beta-blockers, such as bisoprolol, are preferred [37, 38].

PULMONARY HYPERTENSION

Pulmonary arterial hypertension (PAH) (group 1) can be caused by toxic effects of anticancer drugs on small pulmonary arterioles. The best-documented effect is that of the TKI, dasatinib [39, 40]. Other drugs include carfilzomib, bosutinib, ponatinib, and interferon alfa. Alkylating agents, such as cyclophosphamide and mitomycin C, can lead to the development of pulmonary venous obliterative disease (PVOD). Pulmonary hypertension associated with left heart failure (group 2) is most often caused by damage to the left ventricular muscle during anticancer therapy with drugs such as anthracyclines. Pulmonary hypertension dependent on lung damage or hypoxia (group 3) occurs in lung cancers and metastatic tumors occupying a large volume of lung tissue or after surgical resection of the lung. Anticancer therapies, such as bleomycin or thoracic radiotherapy, can lead to lung fibrosis and give PAH through this mechanism. Active cancer is a risk factor for the development of thromboembolic pulmonary hypertension (Group 4). Central catheters and vascular ports can also be a source of recurrent embolism. The diagnostic and treatment management of an oncology patient with PH is not significantly different from that of patients without cancer.

Practical comment

From a practical point of view, prompt diagnosis of pulmonary embolism appears to be the most important issue, as it is an acute disease requiring immediate initiation of anticoagulant therapy. Oncology patients may require consultation from the acute pulmonary embolism response team (PERT) due to the numerous contraindications to thrombolytic therapy [41]. For dasatinib-induced NP, the drug should be discontinued, and another TKI should be used. For NP of thromboembolic etiology in patients with an oncological history, the preferred forms of treatment are riociguat pharmacotherapy and balloon pulmonary angioplasty [42, 43].

PERICARDIAL DISEASES

The most common cause of pericardial fluid is cancer of the lung, breast, ovary, and esophagus, as well as leukemia and lymphoma [44]. Both cancer drugs and radiation therapy can cause pericardial disease. Progression of cancer can involve pericardial infiltration, pericardial metastasis, or disruption of lymph flow from the heart. The pericardium can also be the site of primary cardiac tumors (sarcomas, lipoma, lymphomas, endothelioma) [45].

Pericarditis may be the first sign of cancer. Standard treatment is nonsteroidal anti-inflammatory drugs (e.g., ibuprofen) and colchicine for about three months. In refractory cases, steroids should be used. Pericardial effusions of low to moderate severity (4–20 mm) can be treated conservatively under echocardiographic guidance. Cardiac tamponade requires urgent pericardial puncture. In the case of recurrent pericardial fluid or if a puncture is not possible, surgical treatment (creation of a pericardial window) should be considered. Intrapericardial administration of drugs (cytostatics) may also be considered [46].

Pericarditis associated with ICI immunomodulatory drugs has a worse prognosis and may co-occur with myocarditis. Hence, the need for expanded diagnosis with CT and/or MRI and biomarkers is emphasized. High doses of methylprednisolone and colchicine and withholding ICIs are recommended. A refractory course may be an indication for immunosuppressive therapy. A benign course allows for continued treatment with ICIs along with anti-inflammatory drugs.

Practical comment

Pericarditis can occur even years after radiation therapy, and its risk increases in proportion to the radiation dose. Modern anticancer drugs, especially ICIs (ipilimumab), can cause pericarditis associated with a 20% mortality rate, while others (nivolumab, atezolizumab, durvalumab, avelumab, cemiplimab) carry a mortality rate of up to 50% for myocarditis. Patients receiving ICIs should have serial echocardiography.

ANTIPLATELET AND ANTICOAGULANT TREATMENT IN THE CARDIO-ONCOLOGY PATIENT

The oncology population is more likely to require anticoagulant treatment than the general population. The strategy

of antiplatelet treatment especially in the oncology patient requires analysis of the risk of bleeding and thrombotic complications [47, 48]. The authors of the guidelines recommend:

1. Antiplatelet treatment with clopidogrel, a $P2Y_{12}$ inhibitor, as the drug of choice.
2. NOACs should be considered in patients with atrial fibrillation for stroke prophylaxis instead of LMWH and VKAs (excluding patients with mechanical heart valves or moderate-to-severe mitral stenosis) in patients without high bleeding risk, significant drug interactions, or severe renal impairment. LMWH should be considered in patients with active cancer and atrial fibrillation in whom NOACs cannot be used.
3. Apixaban, edoxaban, or rivaroxaban are recommended for the treatment of symptomatic or incident thromboembolism (VTE) in patients with cancer without contraindications. LMWHs are recommended for the treatment of symptomatic or incident VTE in cancer patients with platelet counts <50 000/μl.

Practical comment

1. The preferred dual antiplatelet therapy (DAPT) drugs are acetylsalicylic acid and clopidogrel. Clopidogrel, a $P2Y_{12}$ inhibitor, is the drug of choice. The duration of DAPT should be as short as possible (1–3 months) [48]. Antiplatelet drugs should be withheld: for acetylsalicylic acid, if the platelet count is below 10 000/μl and for clopidogrel, below 30 000/μl. An invasive PCI strategy can be considered if the platelet count is above 30 000/μl. If the platelet count is less than 20 000/μl and coronary angiography is necessary, platelet transfusions are recommended before the angiography procedure and a lower dose of heparin (30–50 U/kg) is used.
2. The use of VKAs in the oncology patient remains the only option in patients with atrial fibrillation and moderate-to-severe mitral stenosis or with a mechanical heart valve.

   In most oncology patients, LMWH is a short-term anticoagulation option. It is the treatment of choice in patients with inoperable gastric/colorectal cancer, concomitant gastric disease, severe renal impairment (eGFR by CrCl <15 ml/min, interactions between administered drugs and NOACs, and platelet counts <50 000/μl. For eGFR <15 ml/min, it may be necessary to dose LMWH under anti-Xa measurement guidance or switch to VKA [49].
3. NOACs have been evaluated as a potential alternative to LMWH for cancer-related VTE based on randomized trials (HOKUSAI, SELECT-D, CARAVAGGIO) comparing edoxaban, rivaroxaban, or apixaban with dalteparin [70, 71]. NOACs are no worse than dalteparin in reducing the risk of recurrent VTE, with a similar risk of major bleeding. However, a higher risk of clinically significant non-serious bleeding was observed, especially in patients with luminal gastrointestinal and genitourinary malignancies (SELECT-D trial with rivaroxaban). Edoxaban, rivaroxaban, and apixaban are recommended for the treatment of VTE (DVT and PE) in cancer patients without the following bleeding risk factors: unoperated gastrointestinal or genitourinary malignancies, recent history of bleeding or within 7 days of major surgery, significant thrombocytopenia (platelet count, 50 000/μl), severe renal impairment (creatinine clearance CrCl, 15 ml/min), or gastrointestinal-related comorbidities [50, 51].

CHEMOTHERAPY (ANTHRACYCLINES, 5-FU, AND OTHERS). OTHER ANTICANCER DRUGS

Recommendations to reduce the cardiovascular risk during chemotherapy indicate the need for a cardiological consultation in patients at high or very high risk of cardiovascular disease before starting oncological treatment and cardiac care during anticancer therapy. Cardiac ultrasound is also recommended in all patients before starting anthracycline therapy and one year after treatment.

Practical comment

Anthracyclines are commonly used in oncology as the basis of systemic treatment of many cancers, including breast cancer, sarcomas, and lymphomas, while fluoropyrimidines are the basis of treatment of gastrointestinal cancers. These drugs have a proven effect on prolonging survival in cancer patients, but often balancing the undeniable benefits and risks of their use is difficult. Appropriate and frequent cooperation with cardio-oncologists is important, which is not easy due to the limited number of these specialists.

BRAF AND MEK INHIBITORS — RECOMMENDATIONS FOR REDUCING CARDIOVASCULAR RISK DUE TO IBRAF AND/OR IMEK

According to the recommendations, blood pressure monitoring is indicated at each clinical visit and weekly during the first 3 months of treatment, then monthly, and in patients treated with cobimetinib/vemurafenib, ECG is also recommended after 2 and 4 weeks from the start of treatment, and every 3 months thereafter. Echocardiography is recommended in all high- and very high-risk patients before initiating BRAF/MEK inhibitor combination therapy and may be considered in low- and moderate-risk patients before initiating BRAF/MEK inhibitor combination therapy.

Practical comment

The mitogen-activated protein kinase (MAPK) pathway in cardiomyocytes is a protective signaling pathway, and its inhibition interferes with the mechanisms of intramyocyte repair by inhibiting extracellular signal-regulated kinases 1/2; therefore, cardiac complications may occur during therapy with BRAF inhibitors and MEK inhibitors (iBRAF/iMEK). The recommendations do not include assessment of cardiovascular risk in patients with seri-

ous cardiovascular diseases before iBRAF/iMEK therapy. Patients receiving previous oncological treatment also deserve special attention. Asymptomatic cardiotoxicity after immunotherapy or radiotherapy-induced myocardial damage may increase the risk of significant left ventricular systolic dysfunction or even heart failure during iBRAF and iMEK treatment.

QT interval prolongation may also occur during iBRAF therapy. The presented ESC recommendations indicate the need to perform ECG only during therapy with vemurafenib and cobimetinib, but there is no mention of the need to perform ECG before and during therapy with other BRAF inhibitors, such as dabrafenib or encorafenib. It seems important to note that ECG should be performed before and during therapy with any BRAF inhibitor, not only vemurafenib.

iBRAF/iMEK treatment is associated with a significant risk of cardiac damage, including heart failure, and cancer therapy-related cardiac dysfunction (HF/cardiomyopathy/CTRCD); therefore, it is recommended that left ventricular ejection fraction be assessed before initiating iBRAF and iMEK therapy. The ESC recommendations do not indicate the need to determine the level of troponins and B-type natriuretic peptide (NT-proBNT, N-terminal pro-B--type natriuretic peptide) in blood serum before or during iBRAF/iMEK therapy. It seems, however, that in patients with serious cardiovascular diseases and at significant cardiovascular risk, especially in the case of qualification for adjuvant treatment, these tests can be considered.

Combination therapy with a BRAF inhibitor and an MEK inhibitor is associated with increased risk of VTE compared to BRAF inhibitor monotherapy. Pulmonary embolism has been reported in 1% to 2% of patients treated with iBRAF/iMEK, which should be taken into consideration during iBRAF/iMEK therapy. Other follow-up examinations during iBRAF and iMEK therapy should be scheduled based on risk factors, clinical symptoms, and laboratory findings [1, 52].

CHECKPOINT INHIBITORS. IMMUNOTHERAPY CAR-T — GENETICALLY MODIFIED T LYMPHOCYTES. HEMATOPOIETIC CELL TRANSPLANTATION

ICIs are drugs that use the activation of the immune response against cancer cells as their mechanism of action. Among the cardiac complications, one should remember serious, life-threatening complications, such as myocarditis (including fulminant myocarditis), advanced heart blocks, complex ventricular arrhythmias, or sudden cardiac death. These severe complications, associated with high mortality, most commonly develop within the first 12 weeks of treatment, although late cardiac toxicity (after 20 weeks) is also possible.

In the case of cardiac complications, in addition to typical cardiac procedures, oncological treatment should be stopped, the patient should be monitored, and diagnostic procedures should be immediate. Concomitant treatment with steroids in high doses (in life-threatening cases, methylprednisolone — bolus 500–1000 mg intravenously once daily for the first 3–5 days) should not be delayed while waiting for the results of diagnostic tests. The method of treatment depends on the type and severity of complications, and the decision about interruption or continuation of treatment with ICIs depends on the severity of complications. Each case should be analyzed by the MDT to optimize the procedure.

Practical comment

In ICI therapy, it is important to remember to conduct cardiac monitoring, especially at the beginning of therapy. It should be emphasized that special checks are carried out in patients receiving simultaneous combined immunotherapy (e.g. ipilimumab and nivolumab), previously subjected to other cardiotoxic therapies (e.g. tyrosine kinase inhibitors, VEGF), or with a history of cardiovascular diseases (e.g., ischemic heart disease, myocardial infarction, heart disease, heart failure, or others). The occurrence of skeletal myositis or a history of autoimmune disease (e.g. systemic lupus erythematosus, rheumatoid arthritis, sarcoidosis, or others) during ICI therapy should be noted. In the group of patients with current heart disease, it is absolutely necessary to optimize cardiac therapy and achieve clinical stability. Before starting ICIs in the group of patients without cardiac diseases, determining the troponin level followed by monitoring during ICI treatment seems to be an absolute minimum requirement. In the group of patients with cardiac diseases, cardiological supervision should be more frequent at the beginning of ICI therapy. On the other hand, it should be remembered that, especially during ICI treatment, a significant increase in troponin concentration requires further diagnostics. In addition to coronary syndrome, an increase in troponin may be associated with myocarditis.

In patients treated with immunotherapy, cardiac toxicity may occur in the form of myocarditis, pericarditis, and conduction abnormalities, which can develop within only a few weeks of starting treatment with immune checkpoint inhibitors [53–55].

CARDIOVASCULAR COMPLICATIONS IN PATIENTS WITH PROSTATE CANCER DURING HORMONE THERAPY

The recommendations indicate the need to assess the baseline risk of cardiovascular complications and to estimate the 10-year risk of life-threatening and non-life-threatening cardiovascular complications using the SCORE2 or SCORE-OP scales in patients undergoing hormone therapy with no history of cardiovascular disease. In addition, it is recommended to perform baseline and periodic ECG examinations in patients who are at risk of prolongation of the corrected QT interval (QTc) during hormone therapy. Given that the use of drugs from the group of antagonists of the

gonadotropin-releasing hormone (GnRH) is associated with significantly lower risk of death and incidence of cardiovascular complications compared to GnRH agonists, the use of GnRH antagonist drugs is suggested in patients with current cardiovascular disease, who require hormone therapy.

Practical comment

About 40% of prostate cancer patients are treated with hormone therapy. The most commonly used drugs are GnRH agonists, which increase the risk of cardiovascular complications and death, especially in the group of men >60 years of age. Therefore, using drugs from the group of GnRH antagonists (instead of GnRH agonists) in patients with coexisting cardiovascular diseases is a very important suggestion.

It seems not feasible for oncologists, radiotherapists, or urologists to use the extensive (4-page algorithm) SCORE2 or SCORE-OP scales developed by cardiologists in outpatient settings during hormone therapy. These scales are based on numerous clinical and laboratory parameters: sex, age, smoking, BP, and non-HDL cholesterol. Few oncology or urology centers can determine non-HDL cholesterol. In addition, it should be emphasized that these scales can only be used in patients without any cardiovascular disease, diabetes, or chronic kidney disease. They are not used in patients after strokes, percutaneous revascularizations, coronary angioplasty, etc. Moreover, prostate cancer patients are mostly elderly patients with numerous comorbidities, including cardiovascular diseases. Therefore, it seems that baseline assessment of the risk of cardiovascular complications and estimation of the 10-year risk of life-threatening and non-life-threatening cardiovascular complications, as well as annual assessment of these complications should be performed by a cardiologist.

It should be emphasized that all hormone therapy drugs in patients with prostate cancer can lead to QTc prolongation, but it is rare. However, QTc prolongation increases the risk of sudden death. Prostate cancer patients treated with hormone therapy may simultaneously take other drugs leading to prolongation of this segment, e.g. amiodarone, sotalol, or psychotropic drugs. Therefore, during hormone therapy, it is worth monitoring this parameter (by ordering ECG with QTc assessment), and when it is prolonged, the patient should be referred for a cardiological consultation to modify the dose of cardiological drugs or replace them.

CARDIOVASCULAR COMPLICATIONS IN BREAST CANCER PATIENTS TREATED WITH ANTI-HER2, CDK4/6 INHIBITORS, AND/OR HORMONE THERAPY

The recommendations indicate the need to perform left ventricular ejection fraction and global systolic fraction tests before starting anti-HER2 treatment and every three months during it. In patients who have completed treatment, echocardiography should be performed 12 months after the end of treatment. In palliative patients, assessment of cardiac function should be performed every 3 months during the first year of treatment. In the absence of cardiac symptoms suggestive of increasing damage to myocardial function, control examinations may be performed every 6 months. In breast cancer patients previously treated with anthracycline-containing systemic regimens, it is recommended that cardiac troponin (cTn) levels be determined before initiation of anti-HER2 therapy. Detection of elevated cTn levels may allow identification of patients at high risk of developing cardiac function damage in the course of anticancer therapy with anti-HER2 drugs. However, in patients requiring systemic therapies in combination with anti-HER2 treatment, anthracycline-free regimens should always be considered. In addition, if anthracycline-based regimens and anti-HER2 therapy are necessary, sequential use of these therapies is recommended, as such treatment has been shown to significantly reduce the incidence of cardiac dysfunction in the course of anticancer therapies.

Practical comment

Referring to the recommendations regarding modern therapies used in the treatment of breast cancer, it can be stated that, despite using the term "anti-HER2 therapies", they focus mainly on patients receiving trastuzumab in the perioperative treatment or in the treatment of disseminated disease. There is no direct reference to the validity and scope of cardiological assessment in patients receiving therapies based on anti-HER2 antibodies combined with cytostatics (e.g. trastuzumab-emtansine, trastuzumab-derukstecan, etc.). These recommendations also do not contain a provision relating to anti-HER2 therapies based on small-molecule kinase inhibitors that block the function of the intracellular domain of the receptor (e.g. lapatinib, tucatinib, etc.). It would be extremely important to include a recommendation about the risk of cardiovascular complications while using this group of drugs and about appropriate cardiological management. Cardiological management does not differ from that recommended in the case of antibodies blocking the extracellular domain of the receptor; however, from the oncologist's point of view, such data should be included. One aspect of breast cancer treatment not described in the ESC recommendations is the use of antibodies blocking receptors other than HER2, most of which are conjugated with a cytostatic (sacituzumab, govitekan, and others). Perhaps it would be worth referring to this group of new therapies in Polish recommendations. In addition, the question remains whether a patient receiving anti-HER2 therapy in the next line of treatment for disseminated disease after previous therapies blocking the HER2 receptor should be monitored in the same way as patients receiving first-line treatment for disseminated disease.

It should be remembered, however, that in Poland, anti-HER2 therapies are prescribed as part of a drug program

imposing a specific method of monitoring treatment complications. Therefore, in the event of discrepancies between the cardiological recommendations and the drug program regarding the monitoring of cardiovascular complications, there should be a clear provision informing about the superiority of the drug program. It would be optimal to achieve consistency between the ESC guidelines and the drug program.

Recommendations for the diagnosis and monitoring of cardiovascular complications in breast cancer patients treated with hormonal therapy are based on the extensive SCORE2 and SCORE2-OP scales assessing several clinical and laboratory parameters. With the current number of patients admitted to oncology centers every day, it is impossible to conduct accurate assessment based on the above scales. In addition, patients can be treated for disseminated disease or receive hormone therapy in the next line of treatment; they may have been exposed to drugs with potentially cardiotoxic effects during previous therapies or received several drugs indicated for organ dysfunction in the course of the neoplastic process. What cardiac surveillance should be applied to these patients? Is it really safe to extend the intervals between individual assessments?

Considering all the above doubts, it seems advisable to create guidelines for the cardiac care of oncology patients at every stage of treatment.

ANTI-ALK TYROSINE KINASE INHIBITORS AND EPIDERMAL GROWTH FACTOR RECEPTOR (eGFR) INHIBITORS

The ESC guidelines regarding treatment with a tyrosine kinase inhibitor directed against the ALK protein (anaplastic lymphoma tyrosine kinase) recommend assessment of cardiac risk before treatment, which includes physical examination, BP measurement, ECG, lipid profile, and measurement of glycated hemoglobin HbA1c.

Practical comment

Treatment with ALK inhibitors

Recommendation for cardio-oncological management before starting treatment based on ALK inhibitors and safety monitoring during treatment introduces the need for additional examinations before and during therapy. Currently, we have the option of using crizotinib, alectinib, cerinib, brigatinib, and loratinib. In terms of examinations, before inclusion in treatment, we are obliged to conduct a physical examination, whose integral part is measurement of heart rate and BP, as well as electrocardiography. The current ESC guidelines recommend determination of the lipid profile and level of glycated hemoglobin as part of initial cardiac risk assessment. So far, it has not been necessary to perform these two tests in everyday clinical practice. In the clinical trials that were the basis for the registration of crizotinib, alectinib, cerinib, brigatinib, and loratinib, and in post-registration studies, hyperglycemia and diabetes were not listed as significant side effects of the treatment [3, 55–62]. Therefore, the need to determine HbA1c in all patients starting treatment is not justified in the summary of product characteristics and published registration documents. The test may be justified in selected clinical situations (glucose intolerance, diabetes). Also, determination of the lipid profile in patients before starting treatment with all ALK kinase inhibitors are not justified by the incidence of lipid disorders. Assessment of the lipid profile and its monitoring are justified in the case of lorlatinib, where this complication is very common. In the registration study, hypercholesterolemia occurred in 70% of patients and hypertriglyceridemia in 64%, while in the case of crizotinib, the frequency of lipid metabolism disorders was low and amounted to 4% for hypercholesterolemia and 6% for hypertriglyceridemia [59]. Analyzing the above data, it is reasonable to assess a lipid profile before starting treatment and to monitor it during treatment every 3-6 months only for lorlatinib. Due to the low incidence of lipid disorders in the case of crizitonib, monitoring of lipid disorders and assessment of the lipid profile before starting treatment seems to be unjustified in everyday clinical practice [59]. Due to the high prevalence of hypertension with brigantinib (23%, including 10% in grade 3) and lorlatinib (18%, including 10% in grade 3), constant BP monitoring should be performed [57, 59]. A side effect of treatment with ALK kinase inhibitors was symptomatic bradycardia with a heart rate below 50/min. Therefore, heart rate control is necessary during treatment with ALK kinase inhibitors [60].

TREATMENT WITH EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) INHIBITORS

Also in the case of epidermal growth factor receptor inhibitors, as part of initial cardiac risk assessment, testing of the lipid profile and level of glycated hemoglobin should be performed. In the clinical trials that were the basis for the registration of EGFR kinase inhibitors, hyperglycemia, and diabetes were not listed as significant side effects of the treatment [62–67]. Therefore, the need to test HbA1c in all patients starting treatment is not justified in the summary of product characteristics and published registration papers. Also, testing the lipid profile in patients before starting treatment is not justified by the prevalence of lipid disorders. On the other hand, the recommendation to perform echocardiography before and during osimertinib treatment is related to the observed decrease in left ventricular stroke volume below 10 percentage points from baseline to an absolute value of 50% and below in 3.1% and 5.5% of patients in the FLAURA and AURA3 studies [62–64], respectively. Most events were asymptomatic and resolved without treatment or discontinuation of osimertinib. Patients with poorly controlled hypertension

and elderly patients have an increased risk of myocardial insufficiency [66]. Based on the above data, it is reasonable to perform an echocardiographic examination before and during the treatment with osimertinib.

BCR-ABL INHIBITORS, BRUTON KINASE INHIBITORS, MULTIPLE MYELOMA DRUGS

Recommendations regarding the reduction of cardiovascular risk due to BCR-ABL inhibitors propose assessment of baseline cardiovascular risk in patients requiring therapy with second or third-generation BCR-ABL tyrosine kinases. In patients treated with nilotinib or ponatinib, it is recommended to assess the cardiovascular risk every 3 months in the first year, and then every 6–12 months, while QTc interval measurement should be considered before the start of therapy, then in the 2nd and 4th week of treatment with nilotinib, and 2 weeks after any dose increase. Echocardiography should be considered in all patients before starting treatment with second- and third-generation BCR-ABL tyrosine kinases. Echocardiography is recommended in all patients before starting dasatinib therapy. In high and very high-risk patients receiving dasatinib or ponatinib, echocardiography every 3 months for the first year should be considered. Echocardiography may be considered every 6–12 months in patients requiring long-term (>12 months) therapy with ponatinib or dasatinib. Assessment of the ankle-brachial index may be considered to detect subclinical peripheral vascular disease.

Practical comment

In the treatment of multiple myeloma, multi-drug regimens are mainly used, which include, among others, glucocorticosteroids, which significantly increase the risk of hypertension. For this reason, it is advisable to systematically control BP during each medical visit, as well as recommend patient self-monitoring with daily BP measurements and keeping a measurement diary.

Among the drugs used in multiple myeloma, special attention should be paid to the potential risk of cardiotoxicity of proteasome inhibitors (bortezomib, ixazomib, carfilzomib). Proteasomes, protein complexes responsible for degradation of dysfunctional or unnecessary proteins, perform an important stabilizing function in cardiomyocytes, and if this function is impaired, myocardial dysfunction can occur. The greatest risk of cardiotoxicity is seen with carfilzomib. The incidence of myocardial dysfunction during treatment with bortezomib is relatively low (up to 4%) compared to carfilzomib, although the toxicity of bortezomib may be increased by concomitant use of steroids. Carfilzomib is a more potent and irreversible proteasome inhibitor with a much higher risk of myocardial damage (up to 25%).

Another challenge in patients diagnosed with multiple myeloma is the high risk of thromboembolic complications resulting from the disease itself (hyperviscosity, renal failure, light chain disease) or treatment (polychemotherapy, high doses of dexamethasone, use of immunomodulatory drugs such as thalidomide, lenalidomide, pomalidomide, use of recombinant erythropoietin). Based on the analysis of risk factors, the European Myeloma Network guidelines recommend 100 mg/day aspirin for thrombosis prophylaxis in patients with one or two risk factors, and LMWH or full-dose warfarin in patients with three or more risk factors.

Treatment with thalidomide, lenalidomide, or pomalidomide significantly increases the incidence of thrombotic complications. The risk of thrombosis is lowest when the patient receives only an immunomodulatory drug, while it increases up to 3–5 times in the case of combination therapy or high doses of dexamethasone. Randomized studies have shown that the risk of thrombotic complications was lower in patients treated with bortezomib and immunomodulatory drugs compared to the group treated without a proteasome inhibitor. In addition, the combined use of thalidomide, aspirin, and warfarin was found to be comparable to LMWH in the prevention of thrombosis in myeloma patients, except in older patients where warfarin was less effective than LMWH.

LMWH remains the drug of choice in the treatment of thromboembolic complications in patients with multiple myeloma.

In the case of light chain (AL) amyloidosis, in approximately 80% of patients, amyloid deposits in the myocardium, which leads to restrictive heart failure, in which normal left ventricular ejection fraction persists until late stages of the disease despite the presence of severe clinical symptoms. Cardiac involvement is diagnosed on the basis of imaging tests (ECHO, MRI of the heart) and biochemical tests (assessment of troponin T or I and NT-proBNP levels). Resting ECG is also helpful in the diagnosis – some patients have low QRS complex voltage.

ESC RECOMMENDATIONS ON ASSESSMENT OF CARDIOVASCULAR RISK ASSOCIATED WITH RADIOTHERAPY IN CANCER PATIENTS

The guidelines recommend baseline assessment of cardiovascular risk and estimation of the 10-year risk of cardiovascular disease, including fatal cardiovascular disease, using the SCORE2 or SCORE2-OP scale. Non-invasive screening for coronary artery disease should be considered in asymptomatic patients who have received >15 Gy mean heart dose (MHD), 5 years after completion of radiotherapy and every 5–10 years thereafter. Carotid ultrasound examination should be considered in asymptomatic patients after radiotherapy of the head/neck region, 5 years after the end of radiotherapy, and every 5–10 years thereafter. Renal artery ultrasonography should be considered in patients after radiotherapy to the abdominal and pelvic regions who have worsening renal function and/or hypertension.

Practical comment

The assessment of the incidence of cardiovascular diseases associated with radiotherapy (RT) is very difficult to deter-

mine. This is mainly due to the long time from exposure to the onset of clinical symptoms in the cardiovascular system, concomitant use of cardiotoxic systemic therapy, constant progress in radiotherapy techniques, changes in the treated population, and physicians not linking emerging cardiovascular diseases with previous radiation therapy. For the same reasons, it is very difficult to clearly identify possible cardiovascular diseases that are the result of radiotherapy. Radiation damage to the heart can manifest itself as pericarditis, pericardial fibrosis, diffuse myocardial fibrosis, and finally coronary artery disease (CAD), but none of these changes is specific to radiation and can occur for a variety of reasons. It should also be noted that radiotherapy usually does not cause direct damage to myocytes because they are highly differentiated and quite resistant to radiation. Radiation-induced heart failure is primarily due to myocyte ischemia, which is caused by the destruction of capillaries. Coronary atherosclerosis develops slowly over several to several dozen years, while capillary damage occurs within a few months of irradiation. It seems, therefore, that the increased incidence of myocardial infarctions after radiotherapy results from the accelerated development of atherosclerosis (normally associated with age, but here it causes illness in younger people), and the increased number of deaths as a result of myocardial infarctions is a consequence of reduced myocardial tolerance to acute ischemia due to the already existing radiation-induced chronic ischemia of myocytes. The evolution may be rapid, with acute coronary syndrome or sudden death as the first manifestation of the disease, but more often the disease remains asymptomatic for a long time [26, 76, 77].

It is essential to identify patients with pre-existing CAD and other cardiovascular diseases before initiating cancer treatment. Available data indicate that pre-existing CAD significantly increases the risk of developing CAD associated with oncological treatment; therefore, it is important to determine the patient's condition before starting radiotherapy. There is typically a long latency period after radiotherapy, during which CAD is asymptomatic, and symptoms may occur up to 10 years after original therapy. New evidence suggests that adults exposed to high cumulative doses of anthracyclines and/or undergoing radiotherapy targeted at the chest should be offered lifelong surveillance. It should also be noted that there is an increasing number of patients who underwent oncological treatment in childhood, and the risk of severe CVD in this group is increased by as much as 8-fold, which means that in long-term follow-up, heart disease is one of the most common causes of death in people who underwent oncological treatment in childhood. Cardiotoxicity of cancer treatment in childhood is most often associated with the use of anthracyclines and radiotherapy. Lifetime follow-up is recommended for patients who have received anticancer therapy in childhood and have received anthracyclines, high-dose thoracic radiotherapy, or both [26, 76, 77].

Guidance in cardio-oncology developed under the auspices of the ESC is an extremely valuable and important initiative. It significantly influences the organization of diagnostic activities aimed at early detection of cardiovascular complications in the course of modern anticancer therapies. These recommendations clearly emphasize the importance of creating Multidisciplinary Therapeutic Teams providing direct care at every stage of anticancer treatment. These teams, which include not only oncologists, radiotherapists, or surgeons but also, as needed, cardiologists, gastroenterologists, and endocrinologists, play a key role in proper selection of therapeutic options, in the context of comorbidities and monitoring of treatment-related complications. Regardless of the formulation of the provisions of individual recommendations, it is extremely important to support cardiologists in acquiring further expertise in the field of cardio-oncology, which is all the more important in the context of the constantly increasing number of cancer patients and introduction of new drugs based on the latest achievements in molecular biology and clinical immunology.

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