Cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies

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General principles of treatment decision for patients with oncology disease

- Multidisciplinary team of specialists
- Precise pathomorphological diagnosis
- Exact staging of the disease

Medications in Oncology

Medical therapy only or as a part of an overall therapeutic strategy:

- Preoperative (neoadjuvant)
- Postoperative (adjuvant)
- Combined with radiotherapy

Medical therapy for metastatic disease

- As combination or monotherapy

Medications in Oncology

Types:

- Classical cytoreductive drugs (cytostatics)
- Targeting agents and antiangiogenic agents
- Hormones
- Immune-checkpoint inhibitors

Medications in Oncology

Assessment of patient-related factors:

1. General condition- ECOG PS (Eastern cooperative Oncology Group performance status)
2. Age
3. Bone marrow status
4. Liver and kidney functions
5. Comorbidities- cardio-vascular, pulmonary, autoimmune diseases etc
6. Additional examinations – hormone receptor state, biomarkers –PD-L1, EGFR, ALK, BRAF, RAS etc.

Cardio-oncology - *Why*

- Development of oncology science related to improved understanding of tumor biology, targeting of various receptors and signaling pathways
- Introduction of new classes of antitumor agents
- Increasing the duration of treatment
- Improved survival of cancer patients
- Improvement of methods for diagnosis of heart damage

Cardiotoxicity

Definition

- Decrease of LVEF below 50% or decrease by more than 10% compared to baseline (below the lower limit of the norm)
- 2D LVEF standard:

54% for women

52% for men

Cardiotoxicity

Factors determining the risk of cardiotoxicity:

- Type of drug agent
- Application method
- Drugs for combination
- Age
- Concomitant diseases
- Previous radiotherapy in the mediastinum

Methods for screening, stratification and monitoring of cardiotoxicity

Initial assessment of cardiovascular risk factors

- Heart failure (with preserved or reduced ejection fraction)
- Asymptomatic LV dysfunction (LVEF <50% or elevated natriuretic peptide)
- CAD data (previous MI, angina)
- Moderate or severe valvular disease - VHD with LVH or LV-disorder
- Hypertrophic, dilated or restrictive cardiomyopathy
- Significant cardiac arrhythmias

Initial assessment

Demographic risk factors:

- Age (pediatric population <18 years,
  age>50 years for Trastuzumab,
  age> 65 years for Anthracyclines)
- Family history of cardiovascular disease

Lifestyle risk factors:

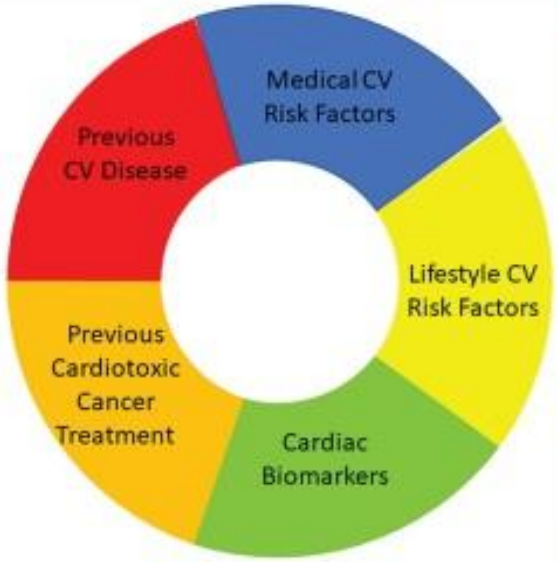
- Smoking
- Obesity
- High alcohol intake
- Immobility

Risk Assessment

There are no validated risk rates for cardiotoxicity

- The risk is determined by the number and severity of risk factors (clinical history), the initial examination of cardiac function
- In addition, cardiac biomarkers (natriuretic peptides or troponin) may be considered
- The risk assessment includes both the initial, baseline assessment and the follow-up of the patient during and after completion of antitumor treatment.

Risk Assessment



Baseline CV Risk Assessment Checklist

Cardiac history
Cancer treatment history
CV risk factors

Blood pressure
HbA1c
Cholesterol profile

*Cardiac troponin**
*BNP or NT-proBNP**

ECG

Echocardiogram

Figure 2 The different risk factors which contribute to baseline cardiovascular (CV) risk in a cancer patient scheduled to receive a cardiotoxic cancer treatment, and a checklist of the clinical history and investigations required at baseline prior to starting a cardiotoxic cancer therapy. *Cardiac biomarkers (troponin and natriuretic peptides) should be measured where available. BNP, brain natriuretic peptide; ECG, electrocardiogram; HbA1c, glycated haemoglobin; NT-proBNP, N-terminal pro-brain natriuretic peptide.

A.R. Lyon *et al*, European Journal of Heart Failure (2020) **22**, 1945–1960

Screening and follow-up

- ECG
- Image methods

- echocardiography
- nuclear imaging
- cardiac magnetic resonance
- computed tomographic coronary angiography

- Biomarkers

-troponin
-natriuretic peptides

Imaging modalities

Echocardiography

- 3D-evaluation of LVEF
- Simpson's 2D method for LVEF estimation
- GLS-Global longitudinal strain

Advantages: wide availability, lack of radiation, assessment of hemodynamics and other cardiac structures

Disadvantages: variations in ratings between different performers, image quality

Imaging modalities

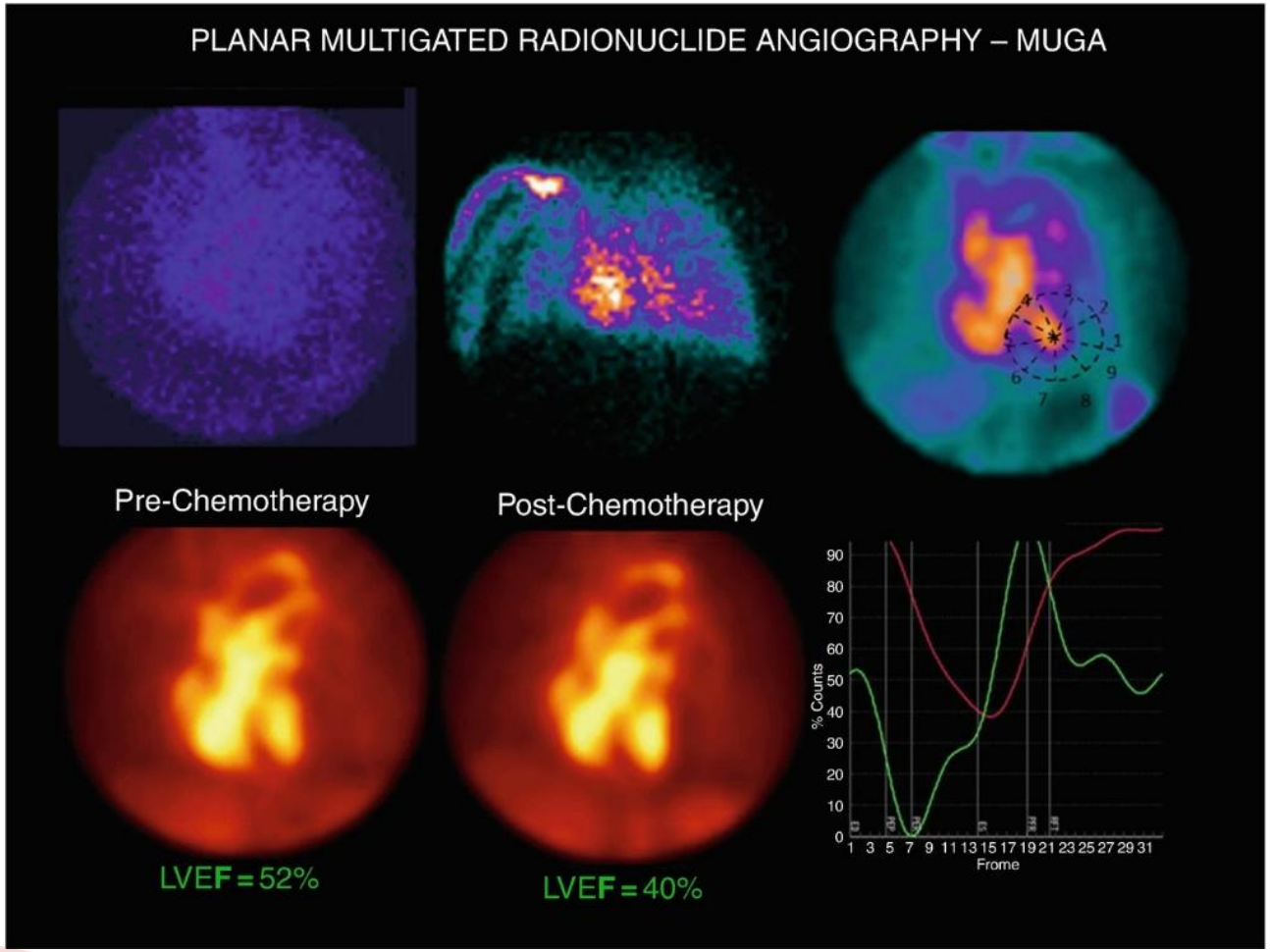
Nuclear imaging

- MUGA (multigated radionuclide angiography)
- Cardiac FDG-PET (F- fluorodeoxyglucose positron emission tomography- CT scan)
- SPECT MUGA (single photon emission computed tomography)

Advantages: reproducibility

Disadvantages: cumulative radiation exposure, limited structural and functional information on other cardiac structures

Imaging modalities



L. T. Dompieri et al, Nuclear Cardiology, 2021

Imaging modalities

Cardiac magnetic resonance imaging

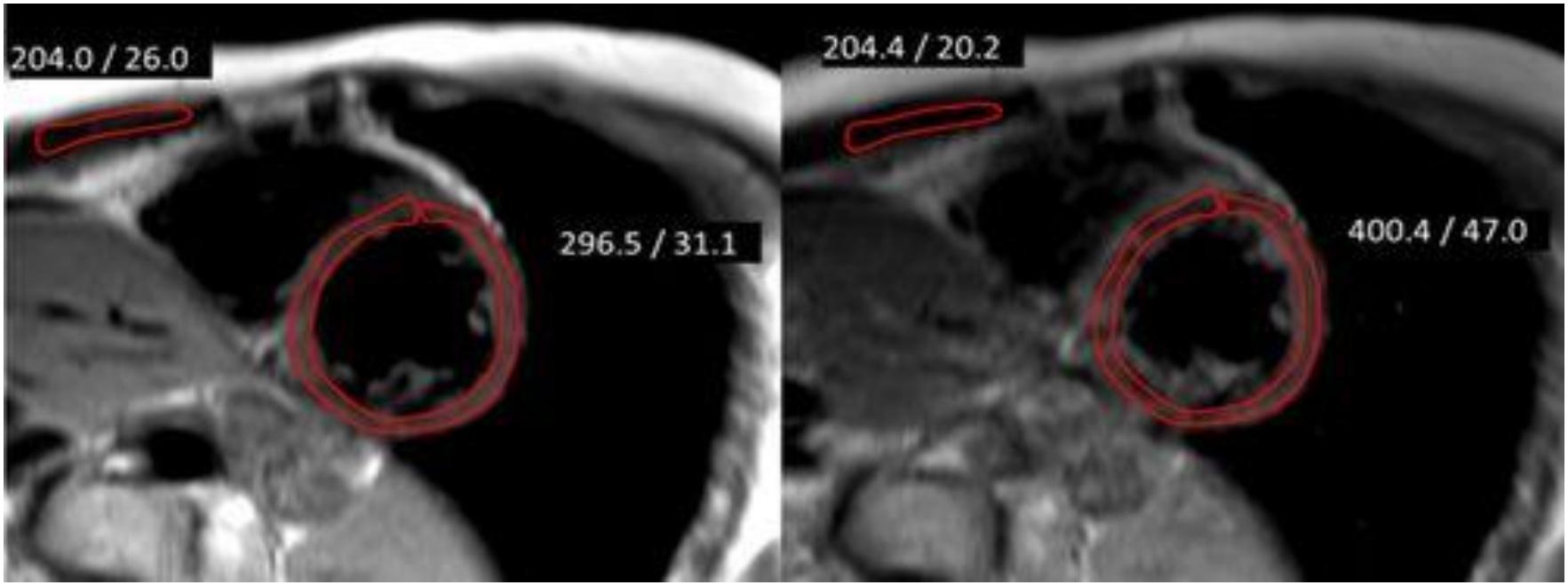
Advantages:

- accuracy
- reproducibility detection of diffuse myocardial fibrosis

Disadvantages:

- limited availability
- time to receive the data

Imaging modalities



Early gadolinium enhancement in a patient with breast cancer receiving adjuvant trastuzumab therapy referred with concern of cardiotoxicity. Left ventricular ejection fraction by cardiac MRI was 54%. Signal intensity measurements (mean/SD) in the myocardium and skeletal muscle precontrast (left) and postcontrast (right) illustrated. Calculated early gadolinium enhancement ratio was 16.3 (abnormal), suggestive of capillary leak/inflammation.

P. Thavendiranathan et al, AHA Journals, 2013

Cardiac biomarkers

- Troponin I
- Highly sensitive troponin I
- B-type natriuretic peptide
- N-terminal fragment of B-type natriuretic peptide

Advantages: accuracy, reproducibility, accessibility, high sensitivity

Disadvantages: the role of routine follow-up is not clearly established

Screening and monitoring - general recommendations

- Use of the same imaging methods and / or laboratory biomarker analyzes throughout the treatment / follow-up period
- Use of methods / tests with the best reproducibility
- Use of imaging methods to provide additional clinical information
- Use of imaging methods without radiation, if possible

Cardiotoxicity – clinical manifestations

- Direct cytotoxic effect of chemotherapy leading to pumping chamber dysfunction
- Myocardial ischemia
- Arrhythmias
- Pericarditis
- Repolarization disorders
- Drug-induced severe hypertension
- Coronary spasm
- Thromboembolic complications

Cardio-oncology team

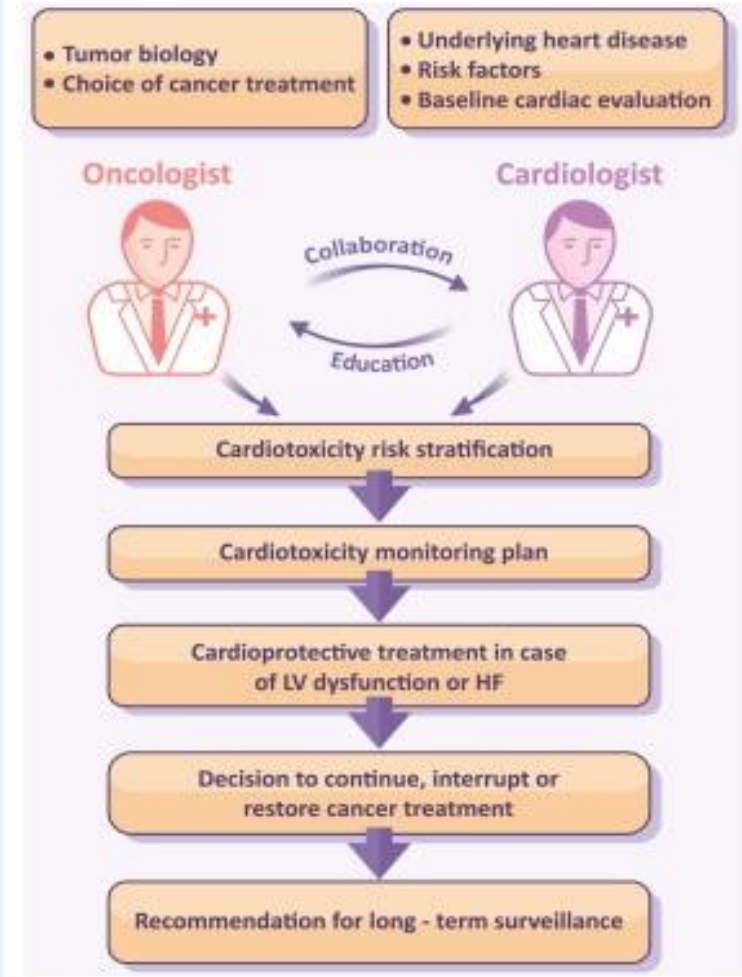


Figure 2 Cardio-oncology interactions. HF, heart failure; LV, left ventricular.

J. Čelutkienė *et al*, European Journal of Heart Failure (2020) **22**, 1945–1960

Assessment of cardiotoxicity risk

Table 1 Assessment of cardiotoxicity risk

Therapy-related factors	Patient-related factors
Low risk of cardiotoxicity	
Lower dose AC (e.g. doxorubicin <200 mg/m^2, epirubicin <300 mg/m^2), liposomal formulations	Age >18 and <50 years
Trastuzumab without AC	
Medium risk of cardiotoxicity	
Modest-dose AC (doxorubicin 200–400 mg/m^2 and epirubicin 300–600 mg/m^2)	Age 50–64 years
AC followed by trastuzumab	1–2 CV risk factors such as hypertension, dyslipidaemia, obesity, insulin resistance, smoking
VEGF tyrosine kinase inhibitors	
Second- and third-generation Bcr-Abl tyrosine kinase inhibitors	
Proteasome inhibitors	
Combination immune checkpoint inhibitors	
High risk of cardiotoxicity	
Simultaneous AC and trastuzumab	Age ≥65 years
High-dose AC (doxorubicin ≥400 mg/m^2 or epirubicin ≥600 mg/m^2)	>2 CV risk factors as hypertension, dyslipidaemia, obesity, smoking
Modest-dose AC plus left chest radiation therapy	Diabetes
Elevated cardiac troponin post-AC prior to HER2-targeted therapy	Underlying CV disease: CAD, PAD, CMP, severe VHD, heart failure
High-dose radiation therapy to central chest including heart in radiation field ≥30 Gy	
VEGF tyrosine kinase inhibitors following previous AC chemotherapy	Reduced or low-normal LVEF (50–54%) pre-treatment
	Prior cancer therapy

Abr, active Bcr-related; AC, anthracycline; Bcr, breakpoint cluster region; CAD, coronary artery disease; CMP, cardiomyopathy; CV, cardiovascular; HER2, human epidermal growth factor receptor 2; LVEF, left ventricular ejection fraction; PAD, peripheral artery disease; VEGF, vascular endothelial growth factor; VHD, valvular heart disease.

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Assessment of cardiotoxicity risk

Risk of cardiotoxicity

- Low risk <2%
- Moderate risk 2- 9%
- High risk 10-19%
- Very high risk> 20%

Assessment of cardiotoxicity risk

- The current risk assessment recommendations have been formulated by the Cardio-Oncology Study Group from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) in collaboration with the International Cardio-Oncology Society (ICOS) and concern **7 classes** of anticancer drugs.

Baseline risk assessment

Cancer treatment class	Cancer indication	Treatment-related CV toxicity
Anthracycline chemotherapy (doxorubicin, epirubicin, daunorubicin, idarubicin)	Breast cancer, lymphoma, acute leukaemia, sarcoma	Heart failure Asymptomatic LVSD Atrial and ventricular arrhythmias
HER2-targeted therapies (trastuzumab, pertuzumab, trastuzumab emtansine (T-DM1), lapatinib, neratinib, tucatinib)	HER2+ breast cancer HER2+ gastric cancer	Heart failure Asymptomatic LVSD Hypertension
VEGF inhibitors TKIs (sunitinib, pazopanib, sorafenib, axitinib, tivozanib, cabozantinib, regorafenib, lenvatinib, vandetinib) and antibodies (bevacizumab, ramucirumab)	VEGF TKIs: renal cancer, hepatocellular cancer, thyroid cancer, colon cancer, sarcoma, GIST Antibodies: breast cancer, ovarian cancer, gastric cancer, gastro-oesophageal cancer, colon cancer	Hypertension Heart failure Asymptomatic LVSD Myocardial ischaemia and infarction QTc prolongation
Multi-targeted kinase inhibitors: second and third generation BCR-ABL TKIs (ponatinib, nilotinib, dasatinib, bosutinib)	Chronic myeloid leukaemia	Arterial thrombosis (myocardial infarction, stroke and PAOD[a]) Venous thromboembolism Hypertension Heart failure and asymptomatic LVSD Atherosclerosis[b] QTc prolongation[b] Pulmonary hypertension[c]

A.R. Lyon *et al* European Journal of Heart Failure (2020) **22**, 1945–1960

Proteasome inhibitors (carfilzomib, bortezomib, ixazomib) **Immunomodulatory drugs** (lenalidomide, pomalidomide)	Multiple myeloma	Heart failure[d] Asymptomatic LVSD[d] Myocardial ischaemia and infarction Atrial and ventricular arrhythmias Venous thromboembolism Arterial thrombosis Hypertension
Combination RAF and MEK inhibitors (dabrafenib + trametinib, vemurafenib + cobimetinib, encorafenib + binimetinib)	Raf mutant melanoma	Heart failure and asymptomatic LVSD Hypertension QTc prolongation[e]
Androgen deprivation therapies **GnRH agonists** (goserelin, leuprorelin) **Antiandrogrens** (abiraterone)	Prostate cancer ER+ breast cancer[f]	Atherosclerosis Myocardial ischaemia and infarction Diabetes mellitus Hypertension
Immune checkpoint inhibitors: **anti-programmed cell death 1 inhibitors** (nivolumab, pembrolizumab) **anti-cytotoxic T-lymphocyte-associated protein 4 inhibitor** (ipilimumab) **anti-programmed death-ligand 1 inhibitors** (avelumab, atezolizumab, durvalumab)	Melanoma (metastatic and adjuvant) Metastatic renal cancer, non-small cell lung cancer, small cell lung cancer, refractory Hodgkin's lymphoma, metastatic triple negative breast cancer, metastatic urothelial cancer, liver cancer, MMR-deficient cancer	Myocarditis including fulminant myocarditis Pericarditis Non-inflammatory heart failure Ventricular arrhythmias AV block Acute coronary syndromes including atherosclerotic plaque rupture and vasculitis

A.R. Lyon *et al* European Journal of Heart Failure (2020) **22**, 1945–1960

Cardiotoxicity

Anthracycline antitumor antibiotics:

- Daunorubicin, Doxorubicin, Epirubicin, Idarubicin and others.
- Main indications: breast cancer, sarcomas, ovarian cancer, etc.
- Mechanism of cardiotoxicity - damage of myocytes by iron-dependent free radicals and oxidation processes, apoptosis

Cardiotoxicity

Time of occurrence

- Acute - occurring immediately after the infusion (<1%)
- Early chronic toxicity - during the first year after treatment (1.6-2.1%)
- Late-onset chronic cardiotoxicity - (10-30 years after the last dose of anthracycline)

Cardiotoxicity

Main manifestations of cardiotoxicity:

- Heart failure
- Asymptomatic LVSD
- Supraventricular and ventricular arrhythmias.
- Left ventricular dysfunction associated with anthracycline therapy is ***dose-dependent, cumulative, and progressive***

Cardiotoxicity

The risk of cardiotoxicity and HF increases:

- With increasing cumulative dose of anthracyclines
- In old age
- When co-administered with other potentially cardiotoxic drugs (Taxanes, Trastuzumab, etc.)
- Presence of valve abnormalities, congenital heart disease, cardiomyopathy

Recommendations for follow-up of patients treated wih anthracycline

- Initial assessment of cardiac function, at high risk discussing a change in therapeutic regimen
- The cumulative dose
- Initial study of biomarkers - highly sensitive troponin or natriuretic peptide, monitoring of troponin levels in each anthracycline containing a course of therapy

Recommendations for follow-up of patients treated wih anthracycline

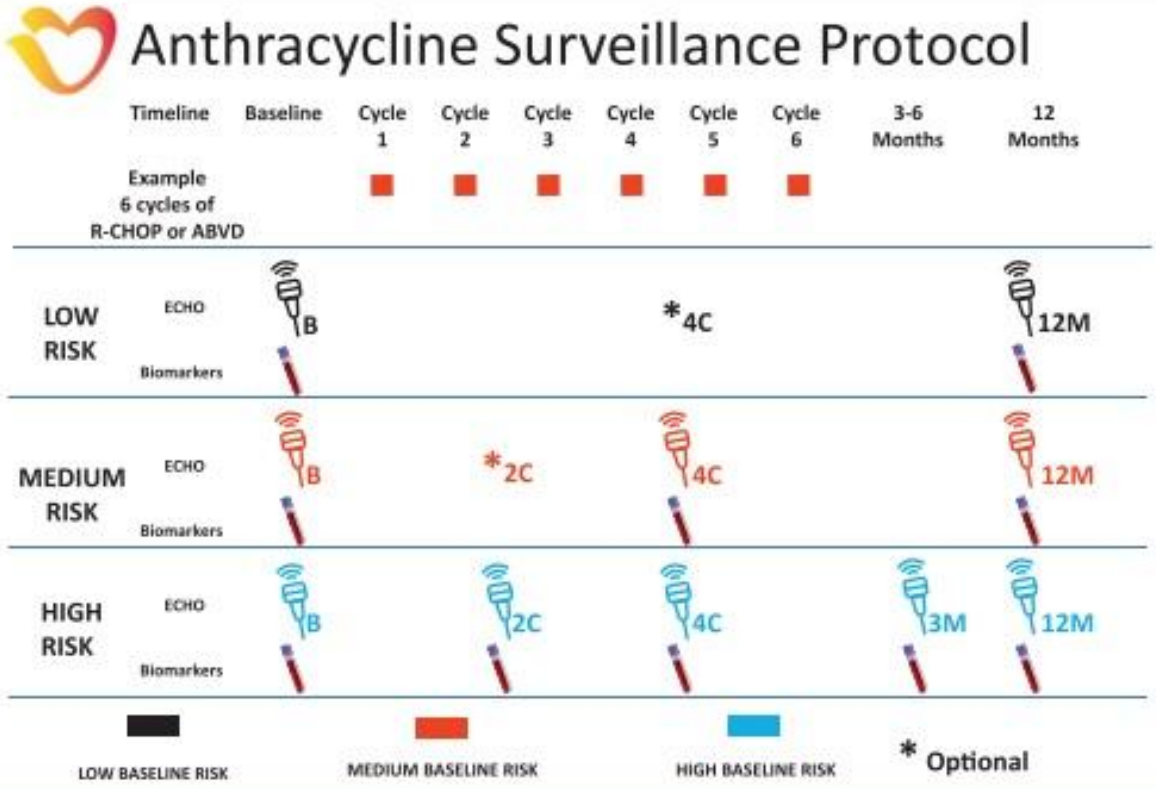

Figure 3 A surveillance pathway using biomarkers and echocardiography for cancer patients receiving six cycles of anthracycline chemotherapy with timing based upon baseline cardiovascular risk. Pathways for low risk, medium risk and high risk are presented. ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; B, baseline pre-treatment; C, cycle of chemotherapy; M, months post-final cycle; R-CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone with rituximab. *Optional additional assessment timepoints.

J. Čelutkienė *et al*, Europ[illegible]ournal of Heart Failure (2020) **22**, 1945–1960

Cardiotoxicity

Trastuzumab

Monoclonal antibody, HER2 / neu receptor inhibitor

Indications: breast cancer, in neoadjuvant, adjuvant aspect and in the treatment of metastatic disease

- Frequency of therapeutically induced heart damage - up to 30%
- Cardiac decompensation - 2-7% is ***not dose-dependent***
- Arterial hypertension, reversible left ventricular dysfunction and heart failure

Cardiotoxicity

Other HER2 inhibitors

- Trastuzumab emtansine T-DM1 - conjugate antibody drug, trastuzumab covalently connected with DM1 microtubule inhibitor
- Pertuzumab- monoclonal antibody
- Lapatinib, Neratinib, Tucatinib - tyrosine kinase inhibitors
- Cardiotoxic effects similar to those described with Trastuzumab
- Frequency 2-5%

Cardiotoxicity

Risk factors associated with cardiotoxicity with anti-HER2 drugs:

- Prior or concomitant treatment with anthracyclines
- Age> 65 years
- BMI> 30
- Previous LV dysfunction
- Previous radiotherapy
- Arterial hypertension

Recommendations for follow-up of patients treated with Trastuzumab

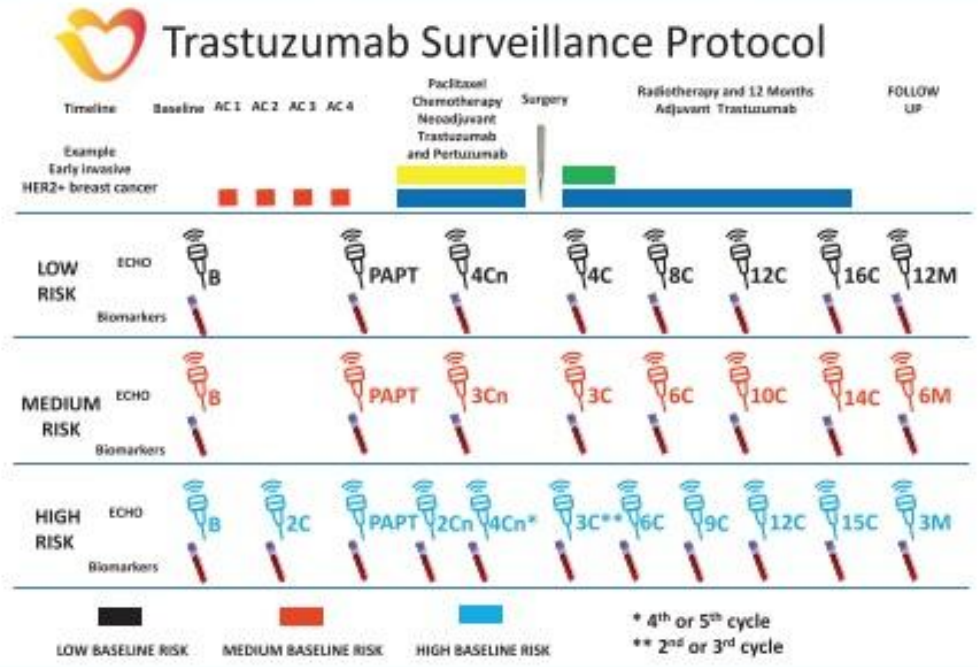

Figure 5 A surveillance pathway using biomarkers and echocardiography for patients receiving neoadjuvant anthracycline (AC) chemotherapy (doxorubicin or epirubicin) and trastuzumab followed by 12 months of adjuvant trastuzumab for HER2+ early breast cancer with timing based upon baseline cardiovascular risk. Pathways for low risk, medium risk and high risk are presented. B, baseline pre-treatment; C, cycle of chemotherapy or adjuvant trastuzumab; Cn, neoadjuvant cycle of trastuzumab; M, months post-final cycle; PAPT, post-anthracycline chemotherapy pre-trastuzumab. *, **Optional additional assessment timepoints.

I. Čelutkienė *et al*, European Journal of Heart Failure (2020) **22**, 1945–1960

Recommandaions for risk assesment and follow-up of treatment with HER2-agents

- Initial assessment cardiac examination / echocardiography
- Every three months during treatment and at the end,
- 6-12 months after the last dose
- Troponin test every three months, at high risk - every cycle

Cardiotoxicity

Bevacizumab

- Recombinant humanized antibody that blocks angiogenesis by inhibiting vascular endothelial growth factor A (VEGF-A)
- Frequency of left ventricular dysfunction - 1.7-3%
- Main cardiotoxic effects

- Hypertension
- Thromboembolic complications - arterial and venous thromboembolism

Cardiotoxicity

Bevacizumab- indications:

- Metastatic carcinoma of the colon
- Metastatic breast cancer
- Non-small cell lung cancer
- Ovarian carcinoma, fallopian tubes
- Primary peritoneal carcinoma
- Cervical cancer
- Hepatocellular carcinoma

Cardiotoxicity

Tyrosine kinase inhibitors:

- Sunitinib, Pazopanib, Sorafenib, Axitinib, Neratinib, Afatinib, Regorafenib and others
- Indications:
  - Renal cell carcinoma
  - NSCLC
  - Hepatocellular carcinoma
  - Thyroid carcinoma
  - Sarcomas
  - GIST
  - Colorectal cancer

Cardiotoxicity

- Significant increase in the risk of developing congestive heart failure (2.69-fold increase)
- Cardiotoxic effects:
- Arterial hypertension
- HF
- Asymptomatic LVSD
- Myocardial ischemia and MI
- QT prolongation.

Recommandaions for risk assesment and follow-up of treatment with VEGF-inhibitors

- Initial assessment
- In case of initial high risk - discussion of early clinical control during the first 2-4 weeks
- Echocardiography every six months
- Biomarkers every 2-3 months

Cardiotoxicity

- Combination of RAF and MEK inhibitors

Dabrafenib + Trametinib

Vemurafenib + Cobimetinib

- Indications:
  - Malignant melanoma, RAF M +
- Cardiotoxic effects:
  - Asymptomatic LVSD
  - Heart failure
  - Hypertension
  - Prolonged QT

Cardiotoxicity

- **Androgen deprivation therapies**
  - GnRH agonists (Goserelin, Leuprorelin)
  - Antiandrogens (Abirateron, Enzalutamid)
- Indications: prostate cancer
- Cardiotoxic manifestations:
  - Myocardial ischemia and infarction
  - Hypertension
  - Atherosclerosis
  - Diabetes mellitus

Cardiotoxicity

Immune checkpoint inhibitors:

- Anti- programmed cell death 1 inhibitors
  - Nivolumab
  - Pembrolizumab
- Anti- cytotoxic T-lymphocyte- associated protein 4 inhibitor
  - Ipilimumab
- Anti- programmed death- ligand 1 inhibitors
  - Avelumab
  - Atezolizumab
  - Durvalumab

Immune checkpoint inhibitors

Indications:

- Malignant melanoma
- NSCLC
- SCLC
- Metastatic triple-negative breast cancer
- Metastatic urothelial carcinoma
- Hepatocellular carcinoma

Immune checkpoint inhibitors

Cardiotoxic manifestations:

- Myocarditis (including fulminant myocarditis)
- Pericarditis
- Ventricular arrhythmias
- AV block
- Acute coronary syndrome (incl. Atherosclerotic plaque rupture, vasculitis)
- Non-inflammatory HF

Conclusion

- Risk assessment, cooperation between an oncologist and a cardiologist is already a mandatory, inevitable part of the multidisciplinary approach in the treatment of cancer patients, a manifestation of modern personalized medicine.
- The aim of the presented recommendations is for the patient with oncological care to receive the optimal antitumor treatment, without worsening his general condition and specifically cardiovascular status (benefit / risk assessment), both during the treatment and after its completion.

ANK YOU FOR THE ATTENTION!