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Cardiac toxicity in pediatric cancer patients

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Introduction:

- Anthracycline-induced cardiotoxicity was first reported in early **1970s**
- The incidence of cardiotoxicity varies with the type of the treatment.
  - Doxorubicin 3–26 %
  - Trastuzumab in 2–28 %
  - Sunitinib in 2.7–11%

Anthracyclines, **cardiotoxicity** may limit the efficacy of cancer therapies in the:

- **Acute phase** (i.e. during the treatment)
- **Longterm sequelae**, observed years after treatment.

The cardiovascular mortality rates →**tenfold higher** compared to the age matched controls.

2 Mechanisms induced cardiotoxicity

- First is **direct toxicity** and destruction of myocardial cells→**permanent** and possibly **irreversible** myocardial dysfunction (**type I cardiotoxicity)**
  - The classic example: **anthracycline cardiotoxicity**, which is usually **dose dependent**
- The second is **inhibition of the physiological function** of myocardial cells, →'stunned' myocardium and significant but **reversible** myocardial dysfunction **(type II cardiotoxicity).**
  - ✓**Trastuzumab**(HER 2 inhibitor) cardiotoxicity: not dose-depen
  - ✓These two mechanisms frequently overlap

*Molecular mechanism of anthracycline-induced cardiotoxicity

- The inhibition of **topoisomerase IIb** in myocardial cells →**DNA double-strand breaks →(mitochondriopathy(**↓glutation peroxidase **)** with increase in **radical oxygen species and free radical formation)**→ activation of the **apoptotic programme**

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Free radicals→ damage DNA →lipid peroxidation→cells death and large-scale organ damage.

- ***Cardiac muscle is particularly susceptible to free radicals generated by anthracycline antibiotics.***
- **Cardiomyocytes contain low levels of free radical scavengers:**
- **Catalase and glutation peroxidase**
- **which may cause their increased susceptibility to the damage by ROS.**

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Anthracyclines potentially **damage** several major structural **proteins**, which regulate **cardiac muscle contractility**.

1) Titin → regulates cardiac systolic function and sarcomere resting at diastole.

✓**Proteolysis and titin decomposition→ systolic and diastolic dysfunction**

2) Dystrophin →dilated cardiomyopathy

Clinical Manifestation of Anthracycline Cardiotoxicity

The most typical clinical manifestations of cardiac muscle damage are as follows:

- **Asymptomatic ECG abnormalities**
- **Arrhythmias(**Supraventricular and ventricular arrhythmias**)**
- **Electrical conduction dysfunction**
- **Myocarditis**
- **Pericarditis**
- **Acute myocardial infarction**
- **Heart failure**
- **Chronic dilated and/or restrictive cardiomyopathy(**systolic and diastolic cardiac dysfunction **)**
- **Arterial and pulmonary HTN**
- **Coronary artery disease**

❖Chemotherapy- and radiotherapy-related:

- **Endothelial dysfunction**
- **Thrombogenesis**

Classification:

❑ Early-onset Acute or subacute cardiotoxicity(less than 1 %):

- ➢ **usually occurs within :**
- ✓ **Hours to weeks but definitely during the first year after anthracycline administration, and**
- ✓ **Can be reversible with early detection and treatment**
- ✓ **Non-dose dependant**
- ❖ This form of cardiotoxicity is manifested clinically by:
- ➢ **Paroxysmal arrhythmia**
- ➢ **Pericardial effusion**
- ➢ **Myocarditis**
- ➢ **LV dysfunction**
- ➢ **Sudden cardiac death(**acute coronary syndromes **)**

- **Chronic progressive late onset cardiotoxicity(5 up to 57 %):**
  - **Dose dependant**
  - Develops within **more than 1 year**, and often **many years after(**period of 10–20 years after treatment**)**
  - **Irreversible cardiomyocyte loss**
  - **Remains asymptomatic for many year** as the **subclinical anthracycline-induced cardiomyopathy(In most cases)** or symptomatized by the CHF or MI

Risk Factors of Anthracycline Cardiotoxicity:

❑ *Total cumulative dose of anthracyclines:*

- the therapeutic efficacy of anthracyclines increases with the dose→so does their cardiotoxicity.
- **On adults** treated with doxorubicin, the risk for heart failure **was 3–5 %** with the cumulative dose of **400 mg m²** went up to **7–26 %** with the dose below **550 mg/m²** and further increased up to **48 %** with the dose of **700 mg/m².**
- **On childhood** cancer survivors showed that the risk of obvious heart failure increases **11-fold** in patient receiving doses **over 300 mg/m²** as compared to ones treated with doses **below 300 mg/m²**
- However, even low doses (<300 mg/m2) are associated with a non-negligible risk for cardiotoxicity **(1.6 %)→ individual susceptibility to anthracyclines(gene polymorphisms--- Homozygosity** for the major allele (G) in the CBR3 gene **).**

- **Time from cancer diagnosis and the moment of anthracycline treatment commencement:**
  - **Very young or advanced age of patient at the moment of diagnosis:**
  - Age **below 4 years**
- **Sex:**
  - **Female**
    - (mechanism?)sex-based differences in **pharmacokinetics** and **pharmacodynamics** of cytostatic drugs

- **Black ethnicity**
- **Down Syndrome**
- **Chemotherapy combined with radiation therapy to the mediastinum**

poses the highest risk of cardiac complications due **to anatomical heart location** *Early radiation-induced injury* primarily involves the pericardium and manifests as:

- **Acute pericarditis**→develops in several weeks following treatment completion.

- **Coronary artery disease** is the most common manifestation of **late** cardiovascular complications of **radiation therapy** with a typical late onset, i.e. in 10–15 years following radiation therapy.

❖*Ion radiation* →induce or **accelerate atherosclerosis**

- **Restrictive cardiomyopathy (diastolic dysfunction)**
- **Systolic heart dysfunction**
- **Valvular heart disease**
- **Cardiac arrhythmias** or conductivity disorder can develop

- **Chemotherapy combined with the administration of other cardiotoxic agents:**

(Cyclophosphamide, iphosphamide, fluorouracil, bleomycin, vincristine, mitoxantrone and trastuzumab)

- **Dose dependent** and usually presents few days after treatment
- High doses **(>140 mg/kg)** are considered very cardiotoxic

- **Cardiotoxicity may be induced or increased by the risk factors for cardiovascular diseases and the comorbidities:**
  - HTN
  - Obesity and overweight
  - Diabetes
  - Dyslipidemia and
  - Imbalanced lifestyle with reduced physical exercise and/or
  - Smoking
  - Alcohol misuse
  - Stress and
  - Unhealthy diet
  - Similarly, other cardiovascular diseases, renal diseases, additional cardiovascular strain due to pregnancy, surgery or increased body weight can trigger cardiovascular symptoms in cancer survivors after a long-term asymptomatic period

Diagnosis and Monitoring of Cardiac Abnormalities

In order to evaluate myocardial abnormalities:

- **laboratory tests**
- **Cardiovascular diagnostic imaging**
- **Genetic tests(rarely)**
- **Biopsy** is **the most sensitive method(**invasive procedure**)**

laboratory tests:

- **T-troponin, I-troponin** and **CKMB** are useful in the **acute phase of myocardial injury,**
- **NT-pro ANP and NT-pro BNP** in detecting **late anthracycline cardiotoxicity)**
- Levels of these oligopeptide neurohormones correlate with the **LVEF** and pulmonary capillary wedge pressure (**PCWP**).
- Excludes heart failure in **over 90 %** of cases
- **New cardiotoxicity markers:**
- Endothelin-1 (ET-1)
- Fatty-acid-binding protein (FABP)
- Cytokines and
- Intercellular adhesion molecule-1 (ICAM-1) being the markers of endothelial damage
- Tissue plasminogen activator (TPA) and plasminogen activator inhibitor-1 (PAI-1) being the components of plasma fibrinolytic system

Diagnostic imaging and LVEF assessment:

- **Echocardiography:**
  - The most commonly available
  - Precise evaluation of heart and large vessel morphology as well as
  - Diagnosis of systolic and diastolic dysfunction
- **3-D echocardiography**
- Quantitative assessment of intrinsic regional myocardial deformation (**strain and strain rate technique**)
- **Tissue Doppler technique** → improve the precision and reproducibility of echocardiographic cardiac function parameters

- Radionuclide angiography (**RNA**)
- **Scintigraphy** →the assessment of **LV** function
  - Multiple-gated acquisition scintigraphy (**MUGA**) with the use of :
  - **Technetium-99m**, or
  - **Indium-111 antimyosin antibody** scintigraphy.
- **SPECT and PET**→Metabolic dysfunction, fibrosis and necrosis
  - ✓They are not commonly used due to limited availability and high cost

Myocardial Dysfunction According to recent cardio-oncology expert consensus

- significant cardiotoxicity after chemotherapy is considered when the following heart echocardiographic criteria are **fulfilled:**

- (i) An absolute decrease of **≥10 %** in LVEF
- (ii) An EF of **<50 %**
- Additionally, LV global longitudinal strain **(GLS)** is proposed as an **early marker of imminent cardiotoxicity** because a reduction in GLS of **>15 %** during chemotherapy is associated with a higher probability of significant LV systolic dysfunction in the near futur

- The EACVI and ASE recommend assessing **GLS** as a routine component of clinical echocardiograms in patients at risk for type 1 or type 2 cardiotoxicity.
- GLS **>15%** →subclinical LV dysfunction
- GLS **<8%** →no evidence of subclinical LV dysfunction
- GLS between **8%** and **15%** is a **gray zone** → closer follow-up

Follow-up and Treatment of Myocardial Dysfunction

- After **baseline clinical evaluation** and **heart echo**→follow up→ **every 3 months for the first year** of therapy
- For anthracyclines in particular, a **repeat echo** is also advisable at a **cumulative dose of 240 mg/m2** or even **earlier if clinical symptoms and/or an increase in cardiac enzymes** is observed
- **For higher anthracycline doses:**
  - Routine echocardiograms are recommended **before** each anthracycline cycle
- For **less cardiotoxic** chemotherapy, follow-up assessments should be **individualised**

❑Long-term clinical follow-up is mandatory for anthracyclines

❖Routine **heart echos** are recommended at **6**, **24** and **36** months after the **last anthracycline cycle**

- In particular, for patients who received **anthracyclines before** adolescence **(<15 years old) or** those exposed to **high doses (>240 mg/m2),** follow-up monitoring should extend to **4** and probably **10** years after therapy.
- Anthracyclines are **contraindicated** in patients with baseline severe systolic dysfunction **(EF <30 %)**
- A **strong indication** for temporary **cessation of anthracyclines** is an absolute EF decline of **>10 %**

- In patients receiving **trastuzumab**, the detection of a mildly decreased **EF (45–50 %)** after therapy:
  - Start of **heart failure treatment** and
  - **Re-assessment after 3 weeks without** modification of trastuzumab **dose**
- However, trastuzumab should be **discontinued** when:
  - EF drops **below 45%,** or
  - To **45–50 % with an absolute decrease** of at least **≥10 %** compared with baseline.

Anthracycline Cardiotoxicity Prevention

- The **main purpose** of all preventive strategies:
  - ✓ Minimize cardiotoxicity
  - ✓ Improve the efficacy of cancer treatments
- The currently used **anthracycline cardiotoxicity-preventive strategies include**:

❑ Limited cumulative anthracycline dose:

- Therefore, the recommended highest **doxorubicin** dose should fall within the range of **400–550 mg/m²** and should not exceed **240 mg/m²** in most children and adolescents
- **However, it should be emphasized that there is no completely safe dose of anthracyclines and even the lowest dose can induce severe cardiotoxicity.**

- **Another subject for a discussion is the route of Administration:**
  - Short **quick bolus or**
  - **Slow infusion**
- Heart injury does not depend on the:
  - **Cumulative dose** only but also on
  - **Peak serum** anthracycline levels as well.
- Anthracycline administration as a long-term (**over 48 h**), **continuous infusion→cardioprotective effect** by means of **decreasing the maximum serum drug concentration**.
- Based on this assumption, many paediatric treatment protocols recommend **continuous infusion**

The use of anthracycline analogues and liposomal anthracyclines:

- **Analogues:**

(**epirubicin, idarubicin or mitoxantrone** are characterized by the weaker toxic effect on the cardiac muscle)

- **liposomal anthracyclines(third-generation anthracyclines: pegylated liposomal doxorubicin):**

➢ Transport the doxorubicin on a liposomal carrier and to prolong the time it remains within the circulation, just like the **continuous infusion**

❖ **Liposomes** →transporting the active substance selectively to the neoplastic tissue→limits the anthracycline contact with healthy cells and tissues→limiting their toxicity to the cardiac muscle

✓ **But very expensive, which limits their use**

Cardioprotective agents:

- **Drug interactions** in order to decrease anthracycline cardiotoxicity
  - **Beta-blockers(nebivolol and carvedilol)**
  - **ACE inhibitors**
- **Antioxidant properties**
  - **Q10 coenzyme**
  - **Vitamin E and**
  - **Carnitine**
- **Dexrazoxane (Cardioxane)** which exerts its effect as **iron chelator** and **inhibitor of free radical formation in the heart→ ↓superoxide radicals** produced by anthracyclines →in patients treated with **high doses of doxorubicin (>300 mg/m2) or** previous administration of anthracyclines/trastuzumab, baseline **EF <50 % use in early stages of treatment**)#controversial
  - The long-term effect, though, still has to be confirmed
  - It has been reported that this substance **may reduce the efficacy of cancer therapies.**

- **statins**?
- **Interestingly,** modification of **traditional risk factors** together with **regular aerobic exercise** may prevent cardiotoxicity

Conclusion:

It should be emphasized that the **effective cancer treatment(70-100%)** in children and adolescents is a **huge success of modern medicine**.

As a result, the population of **childhood cancer survivors is becoming more numerous each year.**

Considering the anticipated progression-free survival, the measures should be taken in order to **limit the late effect of cancer treatment on other organs and systems**, including cardiovascular system.

That is why, having in mind the **quality of life** of cancer survivors, it is so important to understand the key mechanisms of toxic effect of anthracyclines on cardiovascular system

Develop effective prevention and treatment strategies as well as cardiovascular monitoring system.

Thank you