Cardio-oncology Position Paper

European Society Cardiology

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2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC)

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Why cardioncology?

• Ageing population - suffering of both cancer and CVD
• Increasing incidence of cancer patients
• Increasing incidence of CVD
• Incidence but also survival of cancer increasing
• Most survivors from cancer developing or dying from CVD
• Patients cured for cancer must not become heart failure patients
• Cancer therapy consequences may develop after many years from treatment
• The “sliding doors” concept: different treatment of patients if separate approach to care by oncologists or cardiologists – best treatment if cardiologists and oncologists interact
Trends in incidence of cancer in selected European countries - males
Trends in incidence of cancer in selected European countries - females
Trends in mortality of cancer in selected European countries - males
Trends in mortality of cancer in selected European countries - females
## Relative five year survival (%) in Europe

<table>
<thead>
<tr>
<th>Cancers site</th>
<th>Relative survival</th>
<th>Proportion of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lip, testis, thyroid, malignant melanoma, Hodgkin’s lymphoma</td>
<td>&gt; 80%</td>
<td>4%</td>
</tr>
<tr>
<td>Breast, prostate, bladder, cervix, uterus, larynx</td>
<td>60-79%</td>
<td>30%</td>
</tr>
<tr>
<td>Colon, rectum, kidney, non-Hodgkin lymphoma</td>
<td>40-59%</td>
<td>20%</td>
</tr>
<tr>
<td>Stomach, ovarian cancer, multiple myeloma</td>
<td>20-39%</td>
<td>10%</td>
</tr>
<tr>
<td>Lung, pancreas, oesophagus, brain, liver</td>
<td>&lt; 20%</td>
<td>25%</td>
</tr>
</tbody>
</table>
The “SLIDING DOORS” Concept

PATIENT WITH HEART FAILURE AND CANCER

ONCOLOGIST
- Cancer diagnosis and staging
- Surgical intervention
- Anthracyclines followed by signalling inhibitors
- Cardiotoxicity
- Worsening of HF

CARDIOLOGIST
- Diagnostic work-up of HF
- Optimization of HF therapy
- Coronary lesion: PCI + BMS
- Delay in Cancer diagnostics, stadiation and treatment
- Cancer progression

ONCOLOGIST-CARDIOLOGIST COORDINATION
- Optimal timing of cancer diagnostics and stadiation and HF diagnostic work-up
- Optimal timing of cancer intervention and selection of chemotherapy with “cardioprotection”
- Optimal management of coronary lesion and of HF treatment
- Long survival with optimal QoL
Physiopathology and toxic Heart effects of CT drugs – General Principles

- Type I toxicity (cell necrosis - permanent cardiac damage)
- Type II toxicity (cell dysfunction - reversible cardiac damage)
- **Potentiation** of toxic effect by un-correct timing of association of type I and II drugs
- Shift from high doses chemotherapy in advanced stages of cancer to modulated chemotherapy with combinations of different agents (type I and II), lower doses and prolonged administration
- Shift from prolonging survival to side effects and QoL
- Paediatric and Older patients
- Not only Heart Failure
DIFFERENT TOXIC EFFECTS OF CHEMOTHERAPY

- MYOCARDIAL DISFUNCTION
- HEART FAILURE
- HYPERTENSION
- THROMBO-EMBOLISM
- CORONARY DISEASE
- LONG QT ARRHYTHMIAS

OTHER COMPLICATIONS

CV RISK FACTORS

PRO COAGULATION CONDITION

PRO-ARRHYTMIC CONDITIONS

CV RISK FACTORS
Relationship cancer therapy – cardiovascular diseases

- Myocardial Dysfunction and Heart Failure (HF)
- Coronary Artery Disease (CAD)
- Valvular Heart Disease (VHD)
- Arrhythmias – LQT acquired
- Arterial Hypertension
- Thromboembolic Disease (TE)
- Peripheral Vascular Disease (PAD) and stroke
- Pulmonary Hypertension (PAH)
- Pericarditis
Myocardial Dysfunction and Heart Failure

- Strict control of cardiovascular risk factors
- LVEF assessment before and periodically during CT – same imaging method with good quality
- Lower limit of LVEF < 50%
- If reduction of LVEF > 10% but not under the lower limits repeat assessment during and shortly after CT
- If reduction of LVEF > 10% under the lower limit: ACE-Is (or ARBs) + Beta-Blockers to prevent further LV dysfunction
- ACE-Is (or ARBs) + B-Blockers in symptomatic HF or asymptomatic LV dysfunction
Myocardial Dysfunction and Heart Failure

Risk Factors for cardiotoxicity following anthracyclines

- Cumulative dose
- Female sex
- Age
  - >65 years old
  - Paediatric population (<18 years)
- Renal failure
- Concomitant or previous radiation therapy involving the heart
- Concomitant chemotherapy
  - alkylating or antimicrotubule agents
  - immuno- and targeted therapies
- Pre-existing conditions
  - Cardiac diseases associating increased wall stress
  - Arterial hypertension
  - Genetic factors
Myocardial Dysfunction and Heart Failure

<table>
<thead>
<tr>
<th>Technique</th>
<th>Currently available diagnostic criteria</th>
<th>Advantages</th>
<th>Major limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiography:</td>
<td>• LVEF: &gt;10 percentage points decrease to a value below the LLN suggests cardiotoxicity.</td>
<td>• Wide availability.</td>
<td>• Inter-observer variability.</td>
</tr>
<tr>
<td>3D-based LVEF</td>
<td>• GLS: &gt;15% relative percentage reduction from baseline may suggest risk of cardiotoxicity.</td>
<td>• Lack of radiation.</td>
<td>• Image quality.</td>
</tr>
<tr>
<td>2D Simpson’s LVEF</td>
<td></td>
<td>• Assessment of haemodynamics and other cardiac structures.</td>
<td>• GLS: inter-vendor variability, technical requirements.</td>
</tr>
<tr>
<td>GLS</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Nuclear cardiac imaging (MUGA)</td>
<td>• &gt;10 percentage points decrease in LVEF with a value &lt;50% identifies patients with cardiotoxicity.</td>
<td>• Reproducibility.</td>
<td>• Cumulative radiation exposure.</td>
</tr>
<tr>
<td>Cardiac magnetic resonance</td>
<td>• Typically used if other techniques are non-diagnostic or to confirm the presence of LV dysfunction if LVEF is borderlines.</td>
<td>• Accuracy, reproducibility.</td>
<td>• Limited structural and functional information on other cardiac structures.</td>
</tr>
<tr>
<td>Cardiac biomarkers:</td>
<td></td>
<td>• Detection of diffuse myocardial fibrosis using T1/T2 mapping and ECVF evaluation.</td>
<td>• Limited availability.</td>
</tr>
<tr>
<td>- Troponin I</td>
<td></td>
<td></td>
<td>• Patient’s adaptation (claustrophobia, breath hold, long acquisition times).</td>
</tr>
<tr>
<td>- High-sensitivity Troponin I</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>- BNP</td>
<td>• A rise identifies patients receiving anthracyclines who may benefit from ACE-Is.</td>
<td>• Accuracy, reproducibility.</td>
<td>• Insufficient evidence to establish the significance of subtle rises.</td>
</tr>
<tr>
<td>- NT-proBNP</td>
<td>• Routine role of BNP and NT-proBNP in surveillance of high-risk patient needs further investigation.</td>
<td>• Wide availability.</td>
<td>• Variations with different assays.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• High-sensitivity.</td>
<td>• Role for routine surveillance not clearly established.</td>
</tr>
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</table>
Coronary Artery Disease

• Assessment of CAD considering CT as a risk factor and based on age, gender and history
• Clinic evaluation and diagnostic tests for ischemia detection indicated to diagnose pre-existing CAD and guide the choice of CT drugs
• CT with pyrimidine analogues requires close monitoring for ischemia with regular ECGs – STOP CT if ischemia occurs
• Drug re-challenge may be considered if no alternatives (eventually pre-treatment with TNG and/or Channel blockers
• Long term F-U and ischemia tests useful for detection of CAD after CT and mainly RT
Valvular Heart Disease

- CT agents do not directly affect cardiac valves.
- VHD for pre-existing valve lesions, infective endocarditis and LV dysfunction.
- RT-induced VHD in 10% of treated patients: fibrosis and calcification of the aortic root and cusps, mitral valve annulus and base and mid portions of the leaflets.
- Mediastinal RT with 20-30 Gy, 30-year risk increased by 1.4%.
- Echocardiography assessment method of choice, at baseline and at follow-up.
- CMR and CT may be used. CT useful for calcifications of the ascending aorta.
- Cardiac surgery challenging because of mediastinal fibrosis, associated CAD, myocardial and pericardial disease and impaired wound healing. TAVI of choice.
Arrhythmias

• Basal 12 leads ECG and QTc in all patients at baseline
• Repeated periodical ECGs in patients with history of LQT, organic heart disease, other QT prolonging drugs, bradycardia, thyroid dysfunction and electrolytes abnormalities
• Discontinue treatment /alternative treatment if QTc > 500 msec or increase > 60 msec or arrhythmias development
• Careful assessment and avoid conditions favoring torsades de pointes, mainly hypokalaemia and extreme bradycardia
• Minimize exposition to other QTc prolonging drugs during CT with potentially chemotherapy at risk
  - see

http://www.crediblemeds.org
## Table 10 Risk factors for QT prolongation in cancer patients

<table>
<thead>
<tr>
<th>Risk factors for QT prolongation</th>
<th>Correctable</th>
<th>Non-correctable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Electrolyte imbalance</strong></td>
<td></td>
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<tr>
<td>Nausea and emesis</td>
<td></td>
<td>Family history of sudden death (occult congenital LQTS or genetic polymorphisms)</td>
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<tr>
<td>Diarrhoea</td>
<td></td>
<td>Personal history of syncope</td>
</tr>
<tr>
<td>Treatment with loop diuretics</td>
<td></td>
<td>Baseline QTc interval prolongation</td>
</tr>
<tr>
<td>Hypokalaemia (≤3.5 mEq/L)</td>
<td></td>
<td>Female gender</td>
</tr>
<tr>
<td>Hypomagnesaemia (≤1.6 mg/dL)</td>
<td></td>
<td>Advanced age</td>
</tr>
<tr>
<td>Hypocalcaemia (≤8.5 mg/dL)</td>
<td></td>
<td>Heart disease</td>
</tr>
<tr>
<td><strong>Hypothyroidism</strong></td>
<td></td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td><strong>Concurrent use of QT-prolonging drugs</strong></td>
<td>Antiarrhythmic</td>
<td>Impaired renal function</td>
</tr>
<tr>
<td>Anti-infective</td>
<td></td>
<td>Impaired hepatic drug metabolism</td>
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<tr>
<td>Antibiotic</td>
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<tr>
<td>Antifungal</td>
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<tr>
<td>Psychotropic</td>
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<tr>
<td>Antidepressant</td>
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<tr>
<td>Antipsychotic</td>
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<tr>
<td>Antiemetic</td>
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<tr>
<td>Antihistamine</td>
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</tbody>
</table>

**Note:** This table is an excerpt from a larger discussion on arrhythmias and includes examples of risk factors for QT prolongation in cancer patients. The table categorizes factors into correctable and non-correctable to aid in understanding the potential implications for patient care.
Arterial Hypertension

- Monitor blood pressure before and during CT
- Management of Hypertension according to current GLs
- Early and aggressive antihypertensive treatment to prevent CV complications
- Prefer ACE-Is /ARBs, beta-blockers, dihydropyridine calcium channel blockers – Avoid due to possible drug interactions non-dihydropyridine channel blockers
- Reinforce hypotensive therapy and reduce or discontinue VEGF inhibitors if BP not controlled.
- Restart VEGF if BP controlled.
Thromboembolic Disease

**Table 11 Clinical factors associated with increased risk of cancer-associated venous thromboembolism (modified from Khorana et al. 182)**

<table>
<thead>
<tr>
<th>Cancer-related factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Primary site of cancer (mostly pancreas, brain, stomach, kidney, lung, lymphoma, myeloma)</td>
</tr>
<tr>
<td>• Histology (specially adenocarcinoma)</td>
</tr>
<tr>
<td>• Advanced stage (metastatic)</td>
</tr>
<tr>
<td>• Initial period after cancer diagnosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient-related factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Demographics: older age, female sex, African ethnicity</td>
</tr>
<tr>
<td>• Comorbidities (infection, chronic kidney disease, pulmonary disease, atherothrombotic disease, obesity)</td>
</tr>
<tr>
<td>• History of venous thromboembolism, inherited thrombophilia</td>
</tr>
<tr>
<td>• Low performance status</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment-related factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Major surgery</td>
</tr>
<tr>
<td>• Hospitalization</td>
</tr>
<tr>
<td>• Chemotherapy and anti-angiogenic agents</td>
</tr>
<tr>
<td>• Hormonal therapy</td>
</tr>
<tr>
<td>• Transfusions</td>
</tr>
<tr>
<td>• Central venous catheters</td>
</tr>
</tbody>
</table>
Peripheral Vascular Disease and Stroke

- Up to 30% of treated with nilotinib, ponatinib, and other TKI develop from first months to many years severe lower limb PAD.
- Antiplatelet drugs and, if severe PAD, revascularization
- Raynaud phenomenon
- Risk for ischaemic stroke doubled after mediastinic, cervical or cranial RT.
- Cerebrovascular ultrasound screening 5 years after irradiation and at least every 5 years.
- Aorta, other sovra-aortic vessels and iliac arteries involved
Other Conditions

- Pericardial disease
- Pleural effusion
- Autonomic dysfunction
- Pulmonary hypertension

- Pediatric cancer population
- Elderly cancer population
- Pregnant Women
Cardiac Radiation Toxicity targets

- **Myocardium**
  - Damage microcirculation
  - Interstitial fibrosis
  - Conduction tissue fibrosis

- **Pericardium**
  - Damage microcirculation
  - Fibrin and collagen substitution

- **Valves**
  - Fibrinosis
  - Calcification

- **Coronary Artery**
  - Smooth muscle media thinner
  - Extensive fibrosis
  - Fibrointimal hyperplasia
  - Thrombosis
  - Lipid deposition

- **Cardiac Devices**
  - Endocardial damage
  - Neo-vascularization

- **Conduction Defects**
  - Systolic dysfunction
  - Diastolic dysfunction

- **Other**
  - Thickening
  - Adhesion
  - Fluid effusion
  - Stenosis insufficiency

- **Proximal Location**
  - Coronary atherosclerosis
Shifting paradigm of Radiotherapy

REGIONAL RT (ie, MANTLE RADIATION)  INVOLVED-FIELD RT  INVOLVED-NODE RT
Multiple radiation sources

- Radiation Source 1
- Radiation Source 2
- Radiation Source 3
- Radiation Source 4
- Radiation Source 5
- Radiation Source 6

- Sternum
- Heart
- Oesophagus
- Aorta
Multi-leaf Collimator

- **Radiation Source**
- **Radiation Beam**
- **Multi-Leaf Collimator**
- **Modified Radiation Beam**
- **Thungsten Leaves**

Diagram showing the path of a modified radiation beam through a multi-leaf collimator.
Rotating Radiation Source
Long-term Surveillance Programs for cancer survivors

- Myocardial dysfunction
- Coronary disease
- Vascular disease
- Valvular disease
Long-term Surveillance Programmes for cancer survivors
Long-term Surveillance Programmes for cancer survivors

- GENERAL PRACTITIONER
- ONCOLOGIST
- CARDIOLOGIST
- PATIENT
Long-term Surveillance Programmes for cancer survivors
Long-term Surveillance Programs for cancer survivors – Critical points

• Very few organized Cardio-Oncology Services
  o In Italy is starting a poll to know how many really they are: Candiolo (TO) IRCCS, Milan IEO, Napoli IRCCS Fondazione G. Pascale, Padua IOV, Bari IRCCS G.Paolo II, Aviano (PN) CRO
  o In Spain University Hospitals La Paz in Madrid and Bellvitge in Barcelona with C-O structures
  o In Portugal University Hospital Santa Maria, Lisbon C-O with specialized cardiologist - 3 oncology hospitals with general cardiologists.
  o In France C-O service in Marseille, Hopital Bichat Paris, Hospital St Joseph et St Luc Lyon active collaboration with Oncology Centres
  o In Belgium, Germany, Czech Republic, Norway, Rumania, Switzerland not apparently structures
Long-term Surveillance Programs for cancer survivors – Critical points

• Who is interested in Cardio-Oncology?
  o In Italy C-O WG of ANMCO – AIOM - AICO (?) -
  o In Spain C-O WG of Spanish Society of Cardiology
  o In Portugal, France, Belgium, Germany, Czech Republic, Norway, Rumania, Switzerland no apparently WGs or associations about C-O
Long-term Surveillance Programs for cancer survivors – Critical points

• Enhance Knowledge:
  o Patients
  o General Practitioners
  o Cardiologists
  o Oncologists
  o Community

• Communication

• Organization

• Resources

• Common Paths for Follow-Up an Management
What Essential Messages

• Reduce common CVD risk factors
• Careful elimination of risk conditions
• Does the proposed CT or RT have a cardiac toxicity?
• What kind of CVD problem may have a specific cancer treated patient?
• How frequent is a complication with a specific therapy?
• Has the patient specific risk factors for a specific therapy?
• Right balance risk/benefit of treatment (‘sliding door’) concept
• Every cancer patient may be at risk of a CVD during or after long time with CT or RT
• Long term follow-up with watch-full care