CARDIOVASCULAR TOXICITY INDUCED BY ANTITUMOUR THERAPY

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DISCLOSURES

• Consultant / Advisory Boards / Speaker: Tesaro, Sanofi, Roche, MSD, TEVA, Norgine, Prostrakan, Leo pharma, Janssen, Hospira, Boehringer, AMGEN, Pierre Fabre Oncologie, Vifor Pharma

• Associations: ESMO, ASCO, MASCC, AFSOS, AESCO
Cumulative incidence curves of cardiovascular disease events

Pediatric experience

15-Year Cumulative Mortality

- 1970s: 3.1% (2.7 – 3.5)
- 1980s: 2.4% (2.2 – 2.7)
- 1990s: 1.9% (1.6 – 2.2)

Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

CARDIAC SURVIVOR FLOWSHART

Overarching clinical questions addressed in the clinical practice guideline

Cancer diagnosis

Which cancer patients are at increased risk for developing cardiac dysfunction?

Recommendation 1

Start of treatment

What strategies minimize risk before initiation of therapy?

Recommendation 2

What strategies minimize risk during potentially cardiotoxic therapy?

Recommendation 3

End of treatment

What are the preferred surveillance / monitoring approaches during treatment in patients at risk for cardiac dysfunction?

Recommendation 4

What are the preferred surveillance / monitoring approaches after treatment in patients at risk for cardiac dysfunction?

Recommendation 5

SH. Armenian et al. JCO 2017, 35, 893-911.
THE CARDIOLOGIST !!!!!

**Ischemic events**
- Baseline ECG
- BNP Troponin 1 monitoring
- Anamnesis

**Hypertension**
- Anamnesis
- Comorbidities
  - angiotensin-converting enzyme inhibitors
  - Calcium channel blockers

**QT prolongation**
- Arrhythmias
- Torsade de pointes

**Cardiac Heart Failure**
- Congestive Heart Failure
- Left Ventricular Dysfunction
- Pericardial effusions
- Myopericarditis
Assess Prevalence of Cardiovascular Diseases by type of malignancy

Assess Cardiac Risk Factors

Individual risk factors
- Tobacco use
- Hypertension
- Diabetes
- Dyslipidemia
- Obesity
- Age (> 60 years)
- Cardiac history

Treatment related risk factors
- Anthracyclines
- Radiotherapy (heart area)
- Monoclonal antibody
- Other cardiotoxic drugs
### Assess Prevalence by Anticancer Treatment (Heart Failure)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type of CV failure</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines</td>
<td>Anthracycline induced cardiomyopathy</td>
<td>3-26% (≤ 550 mg/m²) Acute 1% 1 year after Tt completion</td>
</tr>
<tr>
<td>Alkylating agents (cyclophosphamide)</td>
<td>Left Ventricular Dysfunction Pericardial effusions Myopericarditis</td>
<td>7 – 28% Dose related (≥ 1,5 g/m²/day)</td>
</tr>
<tr>
<td>inhibitors of microtubule polymerization</td>
<td>Congestive Heart Failure</td>
<td>0.7% - 1.6% Depends co-drugs</td>
</tr>
<tr>
<td>Monoclonal antibodies and targeted agents</td>
<td>Cardiac Heart Failure</td>
<td>3 – 34%</td>
</tr>
<tr>
<td>Tyrosine Kinase Inhibitors (HER2-EGFR)</td>
<td></td>
<td>1.4% symptomatic cardiac failure ≥10% asymptomatic drop LVEF</td>
</tr>
</tbody>
</table>

- Doxorubicin >500 mg/m²
- Liposomal doxorubicin >900 mg/m²
- Epirubicin >720 mg/m²
- Mitoxantrone >120 mg/m²
- Idarubicin >90 mg/m²

Curigliano et al. Annals Oncol 2012; 23 (7)
Cardiac Toxicity Induced by Trastuzumab

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Asymptomatic drop in LVEF (≥10 percentage-points to &lt;55%)</th>
<th>Severe CHF/cardiac events (NYHA class III/IV CHF or death)</th>
<th>Discontinued for cardiac reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B31 [18] n = 2043</td>
<td>AC + TH + H versus AC + T</td>
<td>34% versus 17%</td>
<td>4.1% versus 0.8%</td>
<td>19% a</td>
</tr>
<tr>
<td>NCCTG N9831, n = 2766 [19]</td>
<td>AC + TH + H versus AC + T + H versus AC + T</td>
<td>5.8–10.4% versus 4.0–7.8% versus 4.0–5.1%</td>
<td>3.3% versus 2.8% versus 0.3%</td>
<td>n/a a</td>
</tr>
<tr>
<td>BCIRG 006, n = 3,222 [14]</td>
<td>AC + T versus AC + TH + H versus TCaH b</td>
<td>11% versus 19% versus 9%</td>
<td>0.7% versus 2.0% versus 0.4%</td>
<td>n/a</td>
</tr>
<tr>
<td>HERA, n = 5,102 [20]</td>
<td>Adj chemo ≥H versus Adj chemo alone</td>
<td>7.1% versus 2.2%</td>
<td>0.6% versus 0.06%</td>
<td>4.3%</td>
</tr>
<tr>
<td>FinHer, n = 232 [21]</td>
<td>V or T + H versus V or T ≥FEC×3</td>
<td>3.5% versus 8.6%</td>
<td>0% versus 3.4%</td>
<td>n/a</td>
</tr>
</tbody>
</table>

A, anthracycline; C, cyclophosphamide; T, taxane; H, trastuzumab; Ca, carboplatin; V, vinorelbine; F, 5-flourouracil; E, epirubicin; n/a, information not available.

Curigliano et al. Annals Oncol 2012; 23 (7)
### Assess Prevalence by Anticancer Treatment (Cardiac Ischemia)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type of CV failure</th>
<th>Frequency Delay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimetabolites: 5FU</td>
<td>Cardiac Ischemia</td>
<td>1 – 68%</td>
</tr>
<tr>
<td></td>
<td>Coronary artery thrombosis</td>
<td>Within 2-5 days of starting therapy</td>
</tr>
<tr>
<td></td>
<td>Arteritis, Vasospasm</td>
<td></td>
</tr>
<tr>
<td>inhibitors of microtubule polymerization:</td>
<td>Myocardial ischemia</td>
<td>5%</td>
</tr>
<tr>
<td>paclitaxel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrine Agents: Aromatase Inhibitors</td>
<td>Myocardial infarction</td>
<td>0.5%</td>
</tr>
<tr>
<td></td>
<td>Cardiac failure</td>
<td></td>
</tr>
<tr>
<td>Targeted Agents (VEGF): sunitinib</td>
<td>Modest increase in cardiac troponins</td>
<td>18%</td>
</tr>
</tbody>
</table>

Curigliano et al. Annals Oncol 2012; 23 (7)
Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines†

G. Curigliano¹, D. Cardinale², T. Suter³, G. Plataniotis⁴, E. de Azambuja⁵, M. T. Sandri⁶, C. Criscitiello¹, A. Goldhirsch¹, C. Cipolla² & F. Roila⁷, on behalf of the ESMO Guidelines Working Group*
Algorithm for the management of cardiotoxicity in patients receiving anthracyclines

Baseline cardiologic evaluation, ECHO

Anthracycline-CTh

Tnl evaluation at each cycle

Tnl POS

Enalapril for 1 year

ECHO end CTh, 3-6-9 months

ECHO 12 m

ACE + BB

ECHO every 6 months for 5 years

Clinical Follow-up

ECHO every year

Tnl NEG

ECHO 12 m

Clinical Follow-up

LVD

ECHO at end CTh

No LVD

ECHO 3 months

No LVD

ECHO 6 months

No LVD

ECHO 9 months

No LVD

ECHO 12 months

No LVD

ECHO every year

ACE = angiotensin-converting enzyme inhibitors
BB = betablocking agents

CTh, chemotherapy; Tnl, Troponin I

Curigliano et al. Annals Oncol 2012; 23 (7)
Algorithm for continuation and discontinuation of trastuzumab based on LVEF assessments

Curigliano et al. Annals Oncol 2012; 23 (7)
Elevated baseline troponin I (> 40 ng/L) (13.6% - 56 of 412 pts)

Elevated baseline troponin T (> 14 ng/L), (24.8% - 101 of 407 pts)

Increased significant LVEF drop risk

HR = 4.52; (P = 0.001)

HR = 3.57; (P = 0.001)
CHECPOINT INHIBITORS AND CARDIAC SAFETY
CLINICAL PRACTICE GUIDELINES

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

J. B. A. G. Haanen¹, F. Carbonnel², C. Robert³, K. M. Kerr⁴, S. Peters⁵, J. Larkin⁶ & K. Jordan⁷, on behalf of the ESMO Guidelines Committee*
• Cardiac AEs Incidence <1%, (higher with IT combination)

• Wide range of toxicities:
  • Myocarditis,
  • Pericarditis,
  • Arrhythmias,
  • Cardiomyopathy
  • Impaired ventricular function

• Early consultation with a cardiologist is recommended [V, B].

• High-dose corticosteroids and Immunosuppressive drugs successful

Cardiac toxicity
• When a myocarditis is suspected, admit the patient and immediately start high-dose (methyl)prednisone (1–2 mg/kg). In the case of deterioration, consider adding another immunosuppressive drug (MMF or tacrolimus) [V, B].
FIRST CASE REPORT: Acute Coronary Syndrome

Acute coronary syndrome as a possible immune-related adverse event in a lung cancer patient achieving a complete response to anti-PD-1 immune checkpoint antibody

Y. Tomita et al. Annals Oncology 2017; 28; 11: Letter to the editors. 2893-95

Activated T cells produce pro-atherogenic cytokines such as IFN-c and TNF-a that contribute to both growth and destabilization of lesions resulting in rupture [1]. This leads to a hypothesis that PD-1 blockade therapy might be involved in provoking the growth and destabilization of atherosclerotic lesions and causing ACS by immune activation in the coronary atherosclerotic lesions.
Cardiac Toxicity in Patients Treated With Immune Checkpoint Inhibitors
It Is Now Time for Cardio-Immuno-Oncology*

Carlo G. Tocchetti, MD, PhD, Maria Rosaria Galdiero, MD, PhD, Gilda Varricchi, MD, PhD
• Common in patients with cardiovascular risk factors, especially diabetes and combination ICI therapy.
• PD-L1 is expressed in human and murine cardiomyocytes. Its expression can increase during myocardial injury.
• Myocarditis appears early (median presentation of just >30 days after starting ICIs, and 81% presenting within 3 months of initiation).
• Immune-mediated myocarditis is characterized by fulminant progression.
• Cardiovascular testing before ICIs was normal in the majority of patients,
  • → cardiovascular testing screening have limited impact.
• Serum troponin = useful test for surveillance also in the setting of ICI administration (abnormal in 94%)
• EF with myocarditis was normal in one-half of the cases.
CENTRAL ILLUSTRATION: Algorithm for Work-Up and Management of Immune-Mediated Myocarditis

Patient on immune checkpoint inhibitors (ICI) or prior ICI use

Patient presenting with new cardiovascular (CV) symptoms

Patient with acute CV symptoms

Electrocardiogram (ECG) and troponin test

Normal results

New ventricular arrhythmia or conduction system disease?

Outpatient echo and NT-proBNP testing

Elevated results

Elevated troponin/abnormal EKG

If indeterminate troponin, retest to eliminate false result

Possible myocarditis: Admit patient
Stop ICI therapy; Urgent Cardiology/Cardio-Oncology consult; Determine whether patient is stable or unstable to dictate treatment

Cardiac toxicity

- When a myocarditis is suspected, admit the patient and immediately start high-dose (methyl)prednisone (1–2 mg/kg). In the case of deterioration, consider adding another immunosuppressive drug (MMF or tacrolimus) [V, B].
Checkpoint inhibitors SAE induced

“Supportive care makes excellent cancer care care possible”

Dorothy M.K. Keefe, past-President of MASCC