Daniela Cardinale, MD, PhD, FESC

Director

European Institute of Oncology - Milan - Italy

Paris, 26th November 2016
European Institute of Oncology

Scientific Director
Prof. Umberto Veronesi

The first to introduce and to develop the conservative treatment of breast cancer
210 ordinary beds
32 day-hospital beds
30 day-surgery beds
14 operating rooms
European Institute of Oncology

STAFF

1600 PEOPLE

- MD 390
- Post Doctoral Fellows 217
- Nurses 454
- Technicians 158
- Administrative personnel 395
European Institute of Oncology

2015 Activity

- Admissions 37,000
- Surgical Interventions 15,250
  - DH Surgery 4,553
- Chemotherapy courses 21,350
- Radiation Treatment 150,000 + IntraOperative RT 900
- Radiodiagnostic Examinations 120,000
- Nuclear Medicine Examinations 10,000
  - Endoscopic Procedures 15,000
    - Outpatient visits 151,500
- Hystological Examinations 30,000
  - Laboratory Tests 123,000
IF: 2006 - 2016

Cardioncology Unit

IEO
Istituto Europeo di Oncologia
Cardiology Division
Director: Carlo M. Cipolla, MD

STAFF:
6 cardiologists
1 pneumologist
6 nurses
1 fellow
1 sonographer
1 secretary
Clinical activities:

Pre and post-operative cardiovascular assessment
Cardiovascular monitoring during and after CT
Respiratory evaluations
General internal medical consultations
Antismoking activities
Management of all the emergencies
Check-up activities for oncologic and cardiovascular prevention
Cardioncology Unit
Director: Daniela Cardinale

STAFF:
1 cardiologist full time
2 cardiologists 30%
1 fellow full time
1 sonographer 50%
1 secretary 50%
Cardiology. 1996 Sep;41(9):887-91.

[A new frontier: cardio-oncology]

[Article in Italian]

Cardinale D.

Servizio di Cardiologia, Istituto Europeo di Oncologia, IRCCS, Milano.

PMID: 8983846 [PubMed - indexed for MEDLINE]
Exam room + cycloergometer
Main exam room + videoscopy
Exam room + Holter

Doctors Private Office
My Private Office
Urgent care Room
Waiting Room

ECHO
Exam room + Holter

Doctors Private Office
Patients developing CV problems are sent to the Cardioncology Unit.
Cardiovascular problems in cancer patients
The two main aims of the cardioncologist are:
- to avoid the possibility that cancer therapy could induce cardiac disease
- to avoid the possibility that pre-existent cardiac disease be a barrier and lead to a reduction of therapeutic opportunities for the patient.
Patients sent to Cardioncology Unit

- LVEF reduction = 70%
- High CV risk for CT = 30%
- Troponin I increase = 45%
- High CV risk for CT = 30%
- CV events during CT = 25%:
  - Hypertension
  - Arrhythmias
  - Pericardial effusion
  - LVEF reduction
FOUR KEY POINTS

RISK STRATIFICATION

EARLY DIAGNOSIS

PREVENTION

TREATMENT
Figure 3. Stages in the development of HF and recommended therapy by stage.

**At Risk for Heart Failure**

**STAGE A**
At high risk for HF but without structural heart disease or symptoms of HF
- e.g., Patients with
  - HTN

**STAGE B**
Structural heart disease but without signs or symptoms of HF
- Drugs
  - ACEI or ARB as appropriate
  - Beta blockers as appropriate
  - In selected patients
    - ICD
    - Revascularization or valvular surgery as appropriate

**STAGE C**
Structural heart disease with prior or current symptoms of HF

**Heart Failure**

**STAGE D**
Refractory HF

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- Prevent vascular, coronary disease
- Prevent LV structural abnormalities
- ACEI or ARB in appropriate patients for vascular disease or DM
- Statins as appropriate

- Prevent further cardiac remodeling
- ACEI or ARB as appropriate
- Beta blockers as appropriate
- ICD
- Revascularization or valvular surgery as appropriate

- Improve NOG LLC
- Prevent hospitalization
- Prevent mortality

- Diuretics for fluid retention
- ACEI or ARB
- Beta blockers
- Aldosterone antagonists

- Drugs for use in selected patients
  - Hydralazine/isosorbide dinitrate
  - ACEI and ARB
  - Digoxin
  - In selected patients
    - CRT
    - ICD
    - Revascularization or valvular surgery as appropriate

- Reduce hospital readmissions
- Establish patient’s end-of-life goals

- Advanced care measures
- Heart transplant
- Chronic inotropes
- Temporary or permanent MCS
- Experimental surgery or drugs
- Palliative care and hospice
- ICD deactivation
Patients at standard cardiac risk

According to the American College of Cardiology and American Heart Association (ACC/AHA) guidelines, patients receiving chemotherapy may be considered a Stage A HF group, defined as those with increased risk of developing cardiac dysfunction.

Patients at increased cardiac risk

- Age < 18 or > 70 yrs
- Previous diagnosis of:
  - coronary artery disease
  - dilated/hypokinetic cardiomyopathy
  - diabetes mellitus
  - LVEF < 55% from any case
  - previous LVEF drop during or after CT
  - arrhythmias requiring treatment
  - valve disease - degree > moderate
- Previous or scheduled AC therapy > 300 mg/mq
- Previous mediastinum RT
FOUR KEY POINTS

RISK STRATIFICATION

EARLY DIAGNOSIS

PREVENTION

TREATMENT
Myocardial cell injury leads to myocardial deformation, which can result in asymptomatic cardiotoxicity. Over time, this can progress to overt cardiotoxicity. The timeline shows that changes in troponin, GLS, and LVEF can indicate the onset and progression of cardiotoxicity. HF symptoms can also develop.

Source: Cardinale et al. Curr Cardiol Rep 2016
Left Ventricular Dysfunction Predicted by Early Troponin I Release After High-Dose Chemotherapy

Daniela Cardinale, MD, Maria Teresa Sandri, MD,† Alessandro Martinoni, MD, Alessio Tricca, LabTech,† Maurizio Civelli, MD, Giuseppina Lamantia, MD, Saverio Cinieri, MD,* Giovanni Martinelli, MD,* Carlo M. Cipolla, MD, Cesare Fiorentini, MD
Milan, Italy

- 204 pts
- High-dose chemotherapy
- TnI 0,12,24,48,72 h after CT
- N. 65 (32%) TnI +
- N. 139 (68%) TnI -

Figure 2. Left ventricular ejection fraction (LVEF) at baseline and during the seven months of follow-up of troponin I positive (cTnI+; solid circle) and negative (cTnI−; solid square) patients. *p < 0.001 vs. baseline (month 0); $p < 0.001 vs. cTnI− group. Data are shown as mean ± 95% confidence interval.
Patients undergoing Adriamicin and Cyclophosphamide x 4

✔ Troponin I assessment:
  - immediately before
  - immediately after each AC cycle

✔ LVEF assessment:
  - at baseline
  - at the end of AC therapy
  - in case of Troponin increase

<table>
<thead>
<tr>
<th></th>
<th>Tnl before</th>
<th>Tnl after</th>
<th>LVEF%</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC 1°</td>
<td>0.02</td>
<td>0.01</td>
<td>n.v.&lt;0.08</td>
</tr>
<tr>
<td>AC 2°</td>
<td>0.02</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>AC 3°</td>
<td>0.06</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>AC 4°</td>
<td>0.10</td>
<td>0.11</td>
<td></td>
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after 2 months: 45
TnI+ = 36/251 pts (14%)

At multivariate analysis:
TnI+ was the only independent predictor of:

- **CARDIAC DYSFUNCTION**
  (HR, 17.6; CI 8.85-35.0, P<0.001)

- **LACK OF LVEF RECOVERY**
  (HR, 2.88; CI 1.78-4.65; P<0.001)
FOUR KEY POINTS

RISK STRATIFICATION

EARLY DIAGNOSIS

PREVENTION

TREATMENT
Detection of pre-clinical cardiotoxicity and prevention of LVD

Primary prevention

Detection of pre-clinical cardiotoxicity and prevention of LVD

Treatment of asymptomatic LVD

Treatment of symptomatic HF

Cardinale et al. Curr Cardiol Rep 2016
Prevention of High-Dose Chemotherapy–Induced Cardiotoxicity in High-Risk Patients by Angiotensin-Converting Enzyme Inhibition

Daniela Cardinale, MD; Alessandro Colombo, MD; Maria T. Sandri, MD; Giuseppina Lamantia, MD; Nicola Colombo, MD; Maurizio Civelli, MD; Giovanni Martinelli, MD; Fabrizio Veglia, PhD; Cesare Fiorentini, MD; Carlo M. Cipolla, MD

N = 403
HD CT

TnI + = 114

Enalapril
n = 56
1 month after CT
Continued for 1 year

Controls
n = 58

Circulation 2006
Enalapril prevents cardiac dysfunction and cardiac events in TNI+ patients

**LV DYSFUNCTION**

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=58)</th>
<th>ACEI group (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td>43%</td>
<td>0%</td>
</tr>
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**CARDIAC EVENTS**

<table>
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<tr>
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<th>Controls (n=58)</th>
<th>ACEI group (n=56)</th>
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<tbody>
<tr>
<td>Cardiac events (%)</td>
<td>52%</td>
<td>2%</td>
</tr>
</tbody>
</table>

- Sudden death
- Cardiac death
- Acute pulmonary edema
- Heart failure
- Acute coronary syndrome
- Life-threatening arrhythmias
- PM implantation

Modified from Cardinale et al. Circulation 2006
CARDIOLOGICAL MONITORING IN PATIENTS UNDERGOING CANCER THERAPY

Patients undergoing Adriamicin and Cyclophosphamide x 4

- Troponin I assessment:
  - immediately before
  - immediately after each AC cycle

- LVEF assessment:
  - at baseline
  - at the end of AC therapy
  - in case of Troponin increase

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</tr>
<tr>
<td>AC 2°</td>
<td>0.02</td>
<td>0.03</td>
<td>62</td>
</tr>
<tr>
<td>AC 3°</td>
<td>0.07</td>
<td>0.11</td>
<td>66</td>
</tr>
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</table>
Baseline cardiologic evaluation, ECHO

Anthracycline-therapy

TnI evaluation at each cycle

TnI positivity

Enalapril for 1 year

ECHO end AC, 3, 6, 9 months

ECHO 12 months

ECHO every 6 months for 5 years

TnI negativity

ECHO 12 months

ECHO every year

3841 post-study pts

Negative cardiovascular history

Different kinds of tumor

Cardiotoxic oncologic treatments

TnI before and after every CT cycle

TnI+ = n. 653 (17%)

Enalapril in TnI+ pts

Serial LVEF measurements

10-year FU

NO significant LVEF reduction from baseline

FOUR KEY POINTS

RISK STRATIFICATION

EARLY DIAGNOSIS

PREVENTION

TREATMENT
UNDERLYING CAUSES AND LONG-TERM SURVIVAL IN PATIENTS WITH INITIALLY UNEXPLAINED CARDIOMYOPATHY

G. Michael Felker, M.D., Richard E. Thompson, Ph.D., Joshua M. Hare, M.D., Ralph H. Hruban, M.D., Diedre E. Clementson, David L. Howard, Kenneth L. Baughman, M.D., and Edward K. Kasper, M.D.
Inverse relationship between 
Time-to-heart-failure therapy 
and LVEF increase

JACC 2010
The more time passes, the less recovery possibility we have.

- 201 pts with AC-induced CMP
- treatment: ACEI + BB
- mean follow-up: 36±27 months

- pts treated within 6 months: 
  = ↑ LVEF 50%: 71%

**Figure 1**

Percentage of patients with complete cardiac function recovery according to time elapsed from AC administration and start of HF therapy.

AC = anthracyclines; HF = heart failure.
Baseline cardiologic evaluation, ECHO

Anthracycline-therapy

TnI evaluation at each cycle

TnI positivity
- Enalapril for 1 year
- ECHO end AC, 3, 6, 9 months
- ECHO 12 months
- ECHO every 6 months for 5 years

TnI negativity
- ECHO 12 months
- ECHO every year

TnI not evaluated during AC

ECHO at end AC
- ECHO 3 months
- ECHO 6 months
- ECHO 9 months
- ECHO 12 months
- ECHO every year

LVD

Clinical Follow-up
- ACEI + BB

**Inclusion criteria:**
- AC-chemotherapy (CT-naïve pts.)

**Prospective LVEF monitoring:** at baseline, end-CT, every 3 months during the first year, every 6 months during the first 5 years, every 12 months thereafter, or whenever required by the clinical situation.

**Study end-point:** occurrence of cardiotoxicity, defined as an absolute decrease >10 percent points in rest LVEF, associated with a decline below the normal limit value (50%).

**HF therapy:** ACE-inhibitors (ACEI) + beta-blockers (BB) up-titrated to maximal tolerated dose.
Study population

- 2625 pts (1949 women; 74%) enrolled
- mean age: 50±13 yrs (range 18 to 82)
- mean baseline LVEF: 63±4% (range 50 to 78%)
- mean AC cumulative dose: 252±86 mg/mq (range 30-900)
- mean follow-up: 5.2 yrs (IQ range 2.6-8.0)
  (range 4 months -19 yrs)
RESULTS:

- CTX: 226/2625 pts (9%)
- NYHA I-II: 283 (81%)
- Mean time from end CT to CTX: 3.5 months (IQ 3-6)

CTX = cardiotoxicity
Cumulative incidence of cardiotoxicity

n. 226/2625 = 9%
n. 221 (98%) within 12 months
Recovery

- 226 pts with CTX
- ACEI and BB in 90% pts
- Recovery = final LVEF ≥50% in 185 (82%) pts
- Mean time to LVEF normalization = 8±5 months
Recovery

- **Full recovery:** Final EF = baseline
  - n=25/226 (11%)

- **Partial recovery:** Final EF ≥50%
  - n=160/226 (71%)

- LVEF (%) vs. months:

  - Before CT
  - End CT
  - HF therapy

  - Months: 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54
Baseline cardiologic evaluation, ECHO

Baseline cardiologic evaluation, ECHO

Anthraclycline-therapy

TnI evaluation at each cycle

TnI positivity

Enalapril for 1 year

ECHO end AC, 3, 6, 9 months

ECHO 12 months

ECHO every 6 months for 5 years

TnI negativity

ECHO 12 months

ECHO every year

TnI not evaluated during AC

ECHO at end AC

ECHO 3 months

ECHO 6 months

ECHO 9 months

ECHO 12 months

ECHO every year

LVD

ACEI + BB

Clinical Follow-up

PREVENTION

EARLY DIAGNOSIS AND TREATMENT
Cardioncology: curing cancer saving the heart

Cancer treatments whether new or traditional, can damage the heart. The occurrence of cardiac toxicity often necessitates the suspension of cancer treatment with negative consequences from the oncological and cardiological point of view.

For this reason, patients treated here at the IEO undergo a careful and constant monitoring of the health of their heart. Our Cardioncology Unity, a separate and dedicated unit, has developed an innovative approach based on the evaluation of cardiac biomarkers, combined with targeted preventive treatment, which has proven extremely effective in preventing cardiotoxicity in more than 3800 patients receiving potentially toxic cancer treatments for the heart at our institution.

Insight into the topic of anthracycline cardiotoxicity

Anthracycline cardiotoxicity is a serious complication of cancer treatment that could weigh negatively on cancer patient prognosis independently of the underlying problems the tumor itself presents. Cardiotoxicity is still considered to be irreversible due to its lack of responsiveness to cardiological therapy. A prospective study of 2,625 patients conducted at IEO calls into question this outdated belief and demonstrates that if cardiotoxicity is diagnosed early and cardiological treatment is initiated promptly, a complete recovery of cardiac function is possible.

Read the article published by Circulation "Early Detection of anthracycline cardiotoxicity and Improvement With Heart Failure Therapy".

Read Dr. Cardinale’s interview on OpenHeart.
Cardioncology Unit

Director
DANIELA MARIA CARDINALE

HIGHLIGHT

Cardioncology is a novel, interdisciplinary, rapidly evolving area of growing interest, based on a comprehensive approach for the management of cardiovascular problems of cancer patients, pre-existent or induced by anticancer therapy.

Cardioncology Unit of the IEO is the first created in Italy to deal with this need.

Our Activities

The main clinical and research areas of the Unit are early diagnosis of cardiotoxicity, cardiac risk stratification, prevention, treatment and monitoring of cardiotoxicity during anticancer therapy, including both traditional and new biologic agents. As the current standard diagnostic methods allow to detect cardiotoxicity only when a function impairment has already occurred, precluding any chance of prevent its development, the Cardioncology Unit of the IEO has created specific internal procedures, based on our almost twenty-year-long clinical and research experience.