Cardioncology. What else?

Daniela Cardinale, MD, PhD, FESC

Director - Cardioncology Unit

European Institute of Oncology - Milan - Italy

Tampa, 27th September 2018
DAUNOMYCIN, AN ANTITUMOR ANTIBIOTIC, IN
THE TREATMENT OF NEOPLASTIC DISEASE
Clinical Evaluation with Special Reference to Childhood Leukemia

Charlotte Tan, MD, Hideko Tasaka, MD, Kou-Ping Yu, MD, M. Lois Murphy, MD, and
David A. Karnofsky, MD

Daunomycin is a new antibiotic in the anthracycline group obtained from
Streptomyces peucetius. It consists of a pigmented aglycone (daunomycinone) in
glycoside linkage with an amino sugar (daunosamine). Differences in the bi-
ological effects of daunomycin, which reacts with DNA, and actinomycin D
which complexes with DNA in a different manner to inhibit RNA production,
are discussed. The toxic effects of daunomycin are a severe local reaction if
the drug extravasates, bone marrow depression resulting in leucopenia, anemia,
thrombocytopenia and bleeding, fever, oral ulcers and alopecia. In patients
receiving maintenance doses of daunomycin the development of tachypnea,
tachycardia pulmonary insufficiency, heart failure and hypotension possibly is
associated with daunomycin but the evidence is unclear. Sixty per cent of chil-
deren with leukemia obtained brief complete or partial hematological remis-
ions from a single course of daunomycin. The remission could be prolonged
by maintenance therapy. Daunomycin is temporarily effective in some cases of
neuroblastoma, reticulum cell sarcoma and rhabdomyosarcoma.
Cardiac disease

Oncologic disease
Cardiologia. 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]

MeSH Terms, Substances
ITALY
CARDIOnCOLOGY UNITS
1996-2010
ITALIAN CARDIONCOLOGY UNITS 2018

- Ancona
- Aosta
- Aviano
- Bari
- Belluno
- Busto Arsizio
- Cagliari
- Como (2)
- Cosenza
- Empoli
- Firenze
- Genova
- Lecce
- Milano (3)
- Napoli
- Negrar
- Padova
- Padova
- Perugia
- Reggio Calabria
- Roma
- Rozzano
- Saronno
- Sassari
- Sondrio
- Trieste
- Varese
- Viareggio
CARDIONCOLOGY UNITS/CENTRES
NORTH AMERICA (2005)

- Ottawa
- Detroit
- Boston
- New York
- Philadelphia
- Washington
- Nashville
- Memphis
- Houston
Fig. 1. Landscape of cardio-oncology clinics in the United States based on Google term search in August 2016.
Before cardioncology...
Classification of AC-induced cardiotoxicity
## Classification of AC-induced cardiotoxicity

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Acute cardiotoxicity</th>
<th>Early-onset, chronic cardiotoxicity</th>
<th>Late-onset, chronic cardiotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>During or within 2 weeks after AC treatment</td>
<td>Within 1 year after the completion of AC treatment</td>
<td>&gt;1 year after the completion of AC treatment</td>
</tr>
<tr>
<td>Dose dependent</td>
<td>Unknown</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Clinical features</td>
<td>Depression of myocardial contractility</td>
<td>Dilated/Hypokinetic cardiomyopathy</td>
<td>Dilated/Hypokinetic cardiomyopathy</td>
</tr>
<tr>
<td>Course</td>
<td>Usually reversible</td>
<td>Usually irreversible.</td>
<td>Usually irreversible.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Refractory to traditional HF therapy</td>
<td>Refractory to traditional HF therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poor prognosis</td>
<td>Poor prognosis</td>
</tr>
</tbody>
</table>

## Treatment of AC-induced CMP

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study</th>
<th>N. pts</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lefrak</td>
<td>1973</td>
<td>CR</td>
<td>2</td>
<td>Digitalis + Diuretics</td>
</tr>
<tr>
<td>Haq</td>
<td>1985</td>
<td>R</td>
<td>43</td>
<td>Digitalis + Diuretics</td>
</tr>
<tr>
<td>Saini</td>
<td>1987</td>
<td>CR</td>
<td>3</td>
<td>ACEI</td>
</tr>
<tr>
<td>Jensen</td>
<td>1996</td>
<td>P</td>
<td>8</td>
<td>ACEI</td>
</tr>
<tr>
<td>Fazio</td>
<td>1998</td>
<td>CR</td>
<td>1</td>
<td>Beta-blockers (BB)</td>
</tr>
<tr>
<td>Noori</td>
<td>2000</td>
<td>R</td>
<td>10</td>
<td>ACEI + BB</td>
</tr>
<tr>
<td>Jensen</td>
<td>2002</td>
<td>P</td>
<td>10</td>
<td>ACEI</td>
</tr>
<tr>
<td>Mukai</td>
<td>2004</td>
<td>CR</td>
<td>5</td>
<td>BB</td>
</tr>
<tr>
<td>Tallaj</td>
<td>2005</td>
<td>R</td>
<td>25</td>
<td>ACEI / ACEI + BB</td>
</tr>
<tr>
<td>Tabet</td>
<td>2006</td>
<td>CR</td>
<td>1</td>
<td>ACEI + BB</td>
</tr>
</tbody>
</table>

Total pts = n.108
201 pts with AC-induced CMP
- Treatment: ACEI + BB
- Mean follow-up: 36±27 months

- ↑ LVEF 50%: 42% = Responders
- ↑ ≥10 abs.points: 13% = Partial Responders
- ↑ ≤10 abs.points: 45% = No Responders

Inverse relationship between Time-to-heart-failure therapy and LVEF increase
The more time passes, the less recovery possibility we have.

JACC 2010

- 201 pts with AC-induced CMP
- treatment: ACEI + BB
- mean follow-up: 36±27 months
- pts treated within 6 months: = ↑ LVEF 50%: 71%

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.
Early Detection of Anthracycline Cardiotoxicity and Improvement With Heart Failure Therapy

Daniela Cardinale, MD, PhD, FESC; Alessandro Colombo, MD; Giulia Bacchiani, MD; Ines Tedeschi, MSc; Carlo A. Meroni, MD; Fabrizio Veglia, PhD; Maurizio Civelli, MD; Giuseppina Lamantia, MD; Nicola Colombo, MD; Giuseppe Curigliano, MD, PhD; Cesare Fiorentini, MD; Carlo M. Cipolla, MD

- **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.
Recovery

226/2625 pts with CTX (9%)

ACEI and BB in 90% pts

Recovery = final LVEF ≥50% in 185 (82%) pts

Mean time to LVEF normalization = 8±5 months
AC-induced CMP prognosis
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. CLEMETSON, DAVID L. HOWARD, KENNETH L. BAUGHMAN, M.D., AND EDWARD K. KASPER, M.D.
<table>
<thead>
<tr>
<th>Enalapril + β-blocker, n (%)</th>
<th>Full Recovery (n=25)</th>
<th>Partial Recovery (n=160)</th>
<th>No Recovery (n=41)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25 (100)</td>
<td>145 (91)</td>
<td>31 (75)</td>
<td>0.004</td>
</tr>
<tr>
<td>Cumulative events, n (%)</td>
<td>2 (8)</td>
<td>27 (17)</td>
<td>19 (46)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Sudden death</td>
<td>0 (0)</td>
<td>1 (0.5)</td>
<td>0 (1)</td>
<td></td>
</tr>
<tr>
<td>Cardiac death</td>
<td>0 (0)</td>
<td>2 (1)</td>
<td>4 (10)</td>
<td></td>
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<tr>
<td>Acute pulmonary edema</td>
<td>0 (0)</td>
<td>2 (1)</td>
<td>3 (7)</td>
<td></td>
</tr>
<tr>
<td>HF requiring hospitalization</td>
<td>0 (0)</td>
<td>1 (0.5)</td>
<td>3 (7)</td>
<td></td>
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<tr>
<td>Acute coronary syndrome</td>
<td>0 (0)</td>
<td>4 (2.5)</td>
<td>2 (5)</td>
<td></td>
</tr>
<tr>
<td>Life-threatening arrhythmias</td>
<td>2 (3)</td>
<td>14 (8)</td>
<td>5 (12)</td>
<td></td>
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<tr>
<td>ICD implantation</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Conduction disturbances requiring pacemaker implantation</td>
<td>0 (0)</td>
<td>3 (2)</td>
<td>2 (5)</td>
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</table>
Does late onset cardiotoxicity really exist?
Cardiac Toxicity 4 to 20 Years After Completing Anthracycline Therapy

Laurel J. Steinherz, MD; Peter G. Steinherz, MD; Charlotte T. C. Tan, MD; Glenn Heller, PhD; M. Lois Murphy, MD

Patients, %

Time, yrs

N=14/58
24%

N=12/87
14%

N=21/56
38%

0 4-6 7-9 ≥10

Patients With Abnormal Cardiac Function at LTFU, %

Mild, FS 25-28%

Moderate, FS 21-24%

Severe, FS 25-28%

Follow-up yrs

JAMA 1991
Late Onset Cardiotoxicity

- Data obtained from retrospective studies and only from survivors of childhood cancers
- Lack of studies with prospective serial LVEF monitoring for more than 1 year
- Diagnosis based on symptoms or on occasional LVEF evaluation for cancer relapse
Cumulative incidence of cardiotoxicity

n. 226/2625 = 9%
n. 221 (98%) within 12 months
## Classification of AC-induced cardiotoxicity

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Diagnosis of cardiotoxicity
Trastuzumab-associated cardiac events in the Persephone trial

Helena M Earl, Anne-Laure Vallier, Janet Dunn, Shrushma Loi, Emma Ogburn, Karen McAdam, Luke Hughes-Davies, Adrian Harnett, Jean Abraham, Andrew Wardley, David A Cameron, David Miles, Ioannis Gounaris, Chris Plummer and Louise Hiller

Background: We report cardiac events in the Persephone trial which compares 6–12 months of adjuvant trastuzumab in women with confirmed HER2-positive, early-stage breast cancer.

Methods: Clinical cardiac events were defined as any of the following: symptoms and/or signs of congestive heart failure (CHF) and new or altered CHF medication. In addition, left ventricular ejection fraction (LVEF) was measured at baseline and then 3 monthly for 12 months.

Results: A total of 2500 patients, aged 22–82, were included: 1251 randomised to 12 months and 1249 to 6 months of trastuzumab treatment. A total of 93% (2335/2500) received anthracyclines, 49% of these (1136/2335) with taxanes. Cardiotoxicity delayed treatment in 6% of 12-month and 4% of 6-month patients (P=0.01), and stopped treatment early in 8% (96/1214) of 12-month and 4% (45/1216) of 6-month patients (P<0.0001). Between 7 and 12 months, more 12-month than 6-month patients had LVEFs<50% (8% vs 5%; P=0.004). LVEFs showed quadratic change over time, and 6-month patients had a more rapid recovery (P=0.02). In a landmark analysis twice as many 12-month patients, free of cardiac events at 6 months, had cardioprotectin in months 7–12 (6% (66/1046) vs 3% (29/1035) of 6-month patients (P=0.0002)). Lower baseline LVEF predicted more cardiac dysfunction in both arms (reference ≥65%: 55 to <65% OR 1.61 (95% CI 1.26–2.04); <55% OR 5.22 (3.42–7.95)) as did increasing age (reference <50: 50–59 OR 1.58 (1.17–2.12), 60–69 OR 1.91 (1.42–2.57)) 70+ OR 2.72 (1.82–4.08) and prior use of cardiac medication (OR 8.46 (4.69–15.25)). >3 cycles of anthracycline was associated with higher risk of cardiac events only for 12-month patients (OR 1.41 (1.04–1.90)), and not for 6-month patients (OR 1.28 (0.91–1.79)).

Conclusions: We demonstrate significantly fewer cardiac events from 6 months of adjuvant trastuzumab compared with that from 12 months. This cardiac signal adds importance to the question of the optimum duration of adjuvant trastuzumab treatment. If 6 months is proven to have non-inferior outcomes to 12 months treatment, these data would support 6 months as the standard of care.
myocardial cell injury

myocardial deformation

asymptomatic cardiotoxicity

overt cardiotoxicity

start of chemotherapy

hours/days/weeks

months

years

increase in troponin

decrease in GLS

decrease in LVEF

HF symptoms

Diagnosis of Cardiotoxicity
European Institute Of Oncology Path

- TNI predicts cardiac dysfunction (JACC 2000)
- TNI allows for cardiac risk stratification (Circulation 2004)
- Enalapril prevents cardiotoxicity in TNI+pts (Circulation 2006)
- TNI+ predicts LV dysfunction after trastuzumab (JCO 2010)
- Prevention of High-Dose Chemotherapy-Induced Cardiotoxicity in High-Risk Patients by Angiotensin-Converting Enzyme Inhibition
- Prognostic Value of Troponin I in Cardiac Risk Stratification of Cancer Patients Undergoing High-Dose Chemotherapy
- Left Ventricular Dysfunction Predicted by Early Troponin I Release After High-Dose Chemotherapy
Baseline cardiologic evaluation, ECHO

Anthracycline-CT

Tnl evaluation at each cycle

Tnl POS

Enalapril for 1 year

ECHO at end CT, 3, 6, 9 months

ECHO 12 m

Tnl NEG

WE DON’T STOP CHEMOTHERAPY

CARDIOLOGICAL MONITORING IN PATIENTS UNDERGOING CANCER THERAPY

Adriamicin + Cyclophosphamide x 4

<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>0.002</td>
<td>0.001</td>
<td>n.v.&lt;0.040</td>
</tr>
<tr>
<td>AC 2°</td>
<td>0.002</td>
<td>0.003</td>
<td>66</td>
</tr>
<tr>
<td>AC 3°</td>
<td>0.007</td>
<td>0.080</td>
<td>66</td>
</tr>
<tr>
<td>AC 4°</td>
<td>0.006</td>
<td>0.005</td>
<td>64</td>
</tr>
</tbody>
</table>

after 2 months

after 1 year

Enalapril for 1 year
Fig. 1. Algorithm for the management of cardiotoxicity in patients receiving anthracyclines. CT = chemotherapy; ECHO = echocardiogram; Tnl = Troponin I.

D. Cardinale, M.T. Sandri / Progress in Pediatric Cardiology 39 (2015) 77–84
Can troponin + enalapril approach work in other clinical realities?

Primary vs. secondary prevention
What is better??
Original Research

Anthracycline-induced cardiotoxicity: A multicenter randomised trial comparing two strategies for guiding prevention with enalapril: The International CardioOncology Society-one trial

Daniela Cardinale a, Fabio Ciceri b, Roberto Latini c,*, Maria Grazia Franzosi c, Maria Teresa Sandri d, Maurizio Civelli e, GianFranco Cucchi f, Elisabetta Menatti g, Maurizio Mangiavacchi h, Raffaele Cavina i, Enrico Barbieri j, Stefania Gori k, Alessandro Colombo a, Giuseppe Curigliano l, Michela Salvatici d, Antonio Rizzo m, Francesco Ghisoni n, Alessandra Bianchi o, Cristina Falci p, Michele Aquilina q, Andrea Rocca r, Anna Monopoli s, Carlo Milandri t, Giuseppe Rossetti u, Marco Bregni v, Marco Sicuro w, Alessandra Malossi x, Daniele Nassiacos y, Claudio Verusio z, Monica Giordano aa, Lidia Staszewsky c, Simona Barlera c, Enrico B. Nicolis c, Michela Magnoli c, Serge Masson c, Carlo M. Cipolla e on behalf of the ICOS-ONE Study Investigators
Prevention of anthracycline-induced cardiotoxicity

*a multicentre randomized trial comparing two preventive strategies*

Anthracycline-containing chemotherapy is well known to cause dose-dependent, progressive cardiac damage in particular left ventricular dysfunction evolving to heart failure. The development of cardiac dysfunction, even asymptomatic, leads to the exclusion of cancer patients from effective chemotherapy, with a possible negative impact on their oncologic prognosis.

Two different strategies could be implemented in order to reduce cardiotoxicity:

1. *use of enalapril in all cancer patients undergoing CT, in the attempt to prevent or blunt the rise of cTnI.*
2. *use of enalapril only in selected cancer patients showing an increase of cTnI above the threshold after CT.*

These strategies alone and in comparison will be tested for the first time in the multicentre randomized trial ICOS-ONE.

**OBJECTIVES OF THE STUDY**

**Primary Objective**

To assess whether enalapril started concomitantly to AC-containing treatments can prevent cardiac toxicity more effectively than when enalapril is prescribed to selected patients showing laboratory evidences of injury after chemotherapy, during follow-up visits.

**Secondary Objectives**

to reduce
- admissions to hospital for cardiovascular causes
- deaths for cardiovascular causes
- new occurrence of hypo- or hyperkinetic arrhythmias
to find differences in
- cardiac structural and functional variables by echocardiography
- magnetic resonance imaging
- biomarkers such as NT-pro-BNP and PTX-3

**ClinicalTrials.gov Identifier:**
NCT01968200

**Randomization**

- **n=273**

**GROUP 1**

- **n=136**

Start *enalapril* at the 1st cycle of CT

**GROUP 2**

- **n=137**

Start *enalapril* only after elevation of cTnI/T

**Follow-up:** clinical visit, echo and blood sampling for cTnI/T and circulating biomarkers before and 1, 3, 6, 12 months after the end of chemotherapy.

Plasma cTnI/T before and at the end of each cycle of chemotherapy

Cardinale et al. Eur J Cancer 2018
Table 1
Patient's baseline and clinical characteristics.

<table>
<thead>
<tr>
<th>Patients' characteristics</th>
<th>Total (n = 273)</th>
<th>Prevention (n = 136)</th>
<th>Troponin-triggered (n = 137)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women (%)</td>
<td>241 (88.3)</td>
<td>120 (88.2)</td>
<td>121 (88.3)</td>
<td>0.98</td>
</tr>
<tr>
<td>Age (year, mean ± SD)</td>
<td>51.3 ± 11.92</td>
<td>50.8 ± 11.8</td>
<td>51.8 ± 12.04</td>
<td>0.48</td>
</tr>
<tr>
<td>≤40 years (No. %)</td>
<td>44 (16.1)</td>
<td>20 (14.7)</td>
<td>24 (17.5)</td>
<td>0.53</td>
</tr>
<tr>
<td>BMI (kg/m², mean ± SD)</td>
<td>24.53 ± 5.6</td>
<td>24.52 ± 5.7</td>
<td>24.54 ± 5.6</td>
<td></td>
</tr>
<tr>
<td>Heart Rate (bpm, mean ± SD)</td>
<td>75.58 ± 11.2</td>
<td>75.62 ± 11.2</td>
<td>75.55 ± 11.2</td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg, mean ± SD)</td>
<td>122.5 ± 14.7</td>
<td>122.2 ± 14.7</td>
<td>122.6 ± 14.7</td>
<td></td>
</tr>
<tr>
<td>DBP (mmHg, mean ± SD)</td>
<td>75.53 ± 11.2</td>
<td>75.56 ± 11.2</td>
<td>75.51 ± 11.2</td>
<td></td>
</tr>
<tr>
<td>LVEF (%), mean ± SD</td>
<td>63.7 ± 8.2</td>
<td>63.6 ± 8.2</td>
<td>63.8 ± 8.2</td>
<td></td>
</tr>
<tr>
<td>Clinical history, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalisation in the last year</td>
<td>140 (51.0)</td>
<td>70 (51.5)</td>
<td>70 (51.0)</td>
<td>0.55</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (2.6)</td>
<td>3 (2.2)</td>
<td>4 (2.9)</td>
<td>0.72*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (2.6)</td>
<td>3 (2.2)</td>
<td>4 (2.9)</td>
<td>0.72*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (2.6)</td>
<td>3 (2.2)</td>
<td>4 (2.9)</td>
<td>0.72*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11 (4)</td>
<td>6 (4.4)</td>
<td>5 (3.7)</td>
<td>0.75</td>
</tr>
<tr>
<td>Current smoker</td>
<td>44 (16.2)</td>
<td>20 (14.7)</td>
<td>24 (17.7)</td>
<td>0.58</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>35 (12.9)</td>
<td>20 (14.7)</td>
<td>15 (11.0)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (0.7)</td>
<td>1 (0.7)</td>
<td>2 (1.5)</td>
<td>0.50*</td>
</tr>
<tr>
<td>Paroxysmal atrial fibrillation</td>
<td>2 (0.7)</td>
<td>2 (1.5)</td>
<td>1 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Type of cancer, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>207 (75.8)</td>
<td>103 (75.7)</td>
<td>104 (75.9)</td>
<td>0.17*</td>
</tr>
<tr>
<td>Acute leukaemia</td>
<td>29 (10.6)</td>
<td>14 (10.3)</td>
<td>15 (11.0)</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin's lymphoma</td>
<td>26 (9.5)</td>
<td>11 (8.1)</td>
<td>15 (11.0)</td>
<td></td>
</tr>
<tr>
<td>Hodgkin's lymphoma</td>
<td>8 (2.9)</td>
<td>7 (5.2)</td>
<td>1 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Lymphoma, unspecified type</td>
<td>1 (0.4)</td>
<td>0</td>
<td>1 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Sarcoma</td>
<td>1 (0.4)</td>
<td>1 (0.7)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.4)</td>
<td>0</td>
<td>1 (0.7)</td>
<td></td>
</tr>
</tbody>
</table>

The median number of cycles of anthracyclines was 4 [3-4], delivered over 65 [63-76] days. Epirubicin and doxorubicin were the most commonly prescribed anthracyclines, with a median cumulative dose of 360 [270-360] and 240 [240-240] mg/m², respectively. Dura-
**LVEF%**

<table>
<thead>
<tr>
<th></th>
<th>Enalapril at randomization</th>
<th>Enalapril after 1° cTn ↑</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>63 ± 6</td>
<td>64 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>1 month follow up</td>
<td>62 ± 6</td>
<td>64 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>3 months follow up</td>
<td>63 ± 6</td>
<td>63 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>6 months follow up</td>
<td>63 ± 5</td>
<td>63 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>12 months follow up</td>
<td>62 ± 6</td>
<td>63 ± 5</td>
<td>NS</td>
</tr>
</tbody>
</table>

**CARDIAC EVENTS**

<table>
<thead>
<tr>
<th></th>
<th>Enalapril at randomization</th>
<th>Enalapril after 1° cTn ↑</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Asymptomatic LVEF drop</td>
<td>2 (1.5%)</td>
<td>1 (0.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Arrhythmias requiring treatment</td>
<td>1 (0.7%)</td>
<td>3 (2.2%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Cardinale et al. Eur J Cancer 2018
Diagnosis of Cardiotoxicity
European Institute Of Oncology Path

TNI predicts cardiac dysfunction (Circulation 2000)

Left Ventricular Dysfunction Predicted by Early Troponin I Release After High-Dose Chemotherapy

Prognostic Value of Troponin I in Cardiac Risk Stratification of Cancer Patients Undergoing High-Dose Chemotherapy

TNI allows for cardiac risk stratification (Circulation 2004)

Enalapril prevents cardiotoxicity in TNI+ pts (Circulation 2006)

Prevention of High-Dose Chemotherapy-Induced Cardiotoxicity in High-Risk Patients by Angiotensin-Converting Enzyme Inhibition

Trastuzumab-Induced Cardiotoxicity: Clinical and Prognostic Implications of Troponin I Evaluation

TNI + predicts LV dysfunction after trastuzumab (JCO 2010)

Primary and secondary prevention with enalapril equally effective (Eur J Cancer 2018)

Anthracycline-induced cardiotoxicity: A multicenter randomised trial comparing two strategies for guiding prevention with enalapril: The International CardioOncology Society-one trial

2000  2004  2006  2010  2018
Pros & Cons

**Primary prevention with Enalapril (100%)**

- very low incidence LVD & MACE
- TNI assessment not required
- monitoring during up-titration in 100%
- all pts exposed to side effects
- FU monitoring required in all pts
- high cost-benefit ratio

**Enalapril in TNI+ patients (20%)**

- very low incidence of LVD & MACE
- repeated TNI assessment required
- monitoring during up-titration in ≈20% pts
- only pts at high-risk exposed to side effects
- FU monitoring not required in TNI neg pts (low risk)
- low cost-benefit ratio
Anthracycline-induced cardiotoxicity: A multicenter randomised trial comparing two strategies for guiding prevention with enalapril: The International CardioOncology Society-one trial
Who has to manage cardiotoxicity?

The cardiologist!
The patient developed a cardiac disease!

The oncolgist!
The patient has a cancer!
MV, 75-year-old man

- NSLC IIIA pN2
- CV risk factors:
  - ✔ smoking
  - ✔ hypertension
  - ✔ diabetes
- Hypokinetic CMP (post-MI)
- Pre-CT baseline ECHO: LVEF 23%

Guideline-recommended oncologic treatment = neoadjuvant CT with Carboplatin + Gemcitabine followed by lung surgery
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
Probably, we are the smallest cardioncology unit in the world!!!!
Cardiology Division
Director: Carlo M. Cipolla, MD
Cardiology Division
Director: Carlo M. Cipolla, MD

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 20%
1 sonographer 50%
1 secretary 50%
1 fellow full time
CATHETERIZATION LABORATORY

plumber

ELECTROPYSIOLOGY LABORATORY

electrician
CARDIOLOGY DIVISION
Routine monitoring during and after CT
• 30 visits and 24 ECHOs/week
• 1500 visits and 1200 ECHOs per year
Pts increasing troponin or developing CV problems

CARDIOLOGY DIVISION
Routine monitoring during and after CT
- 30 visits and 24 ECHOs/week
- 1500 visits and 1200 ECHOs per year

CARDIONCOLOGY UNIT
- 18 visits and 12 ECHOs/week
- 900 visits and 600 ECHOs per year

.....are sent to the Cardioncology Unit
Patients sent to the Cardioncology Unit

- Extra EIO Pts 30%
- EIO Pts 70%
- LVEF reduction = 60%
- Assessment of feasibility of CT in pts at high CV risk = 30%
- Arrhythmias = 10%
- CV events during CT = 25%:
  - Hypertension
  - Arrhythmias
  - Pericardial effusion
  - LVEF reduction
- Troponin I increase = 45%
- High CV risk for CT = 30%
Stakeholders in cardioncology service

- **ECHO**
  - To monitor LVEF during and after CT

- **LAB ANALYSIS**
  - To monitor cardiac biomarker during and after CT

- **EKG**
  - To check after evidence of Troponin increase

- **CARDIONCOLOGIC NURSE**
  - Patient’s reception and EKG execution

- **ONCOLOGIST**
  - Updates and sharing oncologic/cardioologic program
SP, 65-year-old man

- Hypo-pharyngeal cancer - cT2cN0M0
- Progressive dysphagia → PEG (percutaneous endoscopic gastrostomy) necessary
- CV risk factors:
  - Hypertension
  - Diabetes
- Hypokinetic CMP after silent MI
- Very recent PTCA + DES (IVA prox)
- Recent ICD implantation
- Baseline ECHO: LVEF 30%

Oncologic therapy options:
- Non conservative surgery rejected for the cardiac disease
- RT + cetixumab (EIO proposal)
Stakeholders in cardioncology service

To monitor LVEF during and after CT and RT

To monitor during and after each RT session (n=35)

To set PEG

To set PEG during bridging therapy with tirofiban

Updates and sharing oncologic cardiologic program

To monitor cardiac biomarker during CT and concomitant RT

To check ICD functions during and after RT
Cardiovascular problems in cancer patients
Cardioncology: a still mostly unexplored world