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Cardio-Oncology in Lymphoma: How and Why

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No Disclosures
Disclosures

• None
Case

63 yo F with HTN, DM, prior MI, DLBCL

Treatment plan:
  • R-CHOP

How might a cardiologist be relevant in her care?
Anthracycline Cardiotoxicity in Lymphoma Pts without CVD
n=2440

Baech J et al BJH; 2018: 183, 717–726
How do we risk assess?

• There are some individuals who are unexpectedly sensitive
• Identifying these pts who may be at highest risk is important
• Data is sparse
• Consensus Statements:
  • ASCO: Armenian SH et al, JCO 2016;35:893-911
  • ESC: Zamarano JL. Lancelotti P et al, Eur Heart J 2016; 37:2768-2801
  • ASE: Plana JC et al, JASE 2014; 27; 911-939
  • AHA: Mehta L, et al, Circulation 2018;137:e2-e37
Why so little known about cardiotoxicity in lymphoma pts?

• Studies that established benefit of R-CHOP and ABVD regimens were mainly focused on efficacy

• Toxicity mainly defined as change in EF
  • Hard to compare studies since definition of toxicity and methodology for EF detection variable

• No large scale studies examining subclinical cardiotoxicity in adults during treatment
Cardio-Oncology Risk Assessment:

1. Risk Prediction
2. Early Detection
3. Management of Cardiotoxicity
4. Surveillance After Treatment

Healthy Lifestyle
Risk Prediction

Treatment-Related Risk Factors

Patient-Related Risk Factors
Risk Prediction:

Treatment Related Risk Factors:
- \( \geq 250 \text{mg/m}^2 \) Doxorubicin
- \( \geq 600 \text{mg/m}^2 \) Epirubicin
- XRT \( \geq 30 \) Gy when heart is in field
- Lower dose anthracycline + lower dose RT where the heart is in the field
- Sequential lower dose anthracycline then Trastuzumab

Patient Related Risk Factors:
Any of the following + Anthracycline or XRT:
- Older age at treatment \( \geq 60 \) yrs
- CVD
  - MI, moderate valve disease, low normal EF (50-55%) before or during Rx
- \( \geq 2 \) CRFs during or after treatment
  - HTN, DM, HL, Tob, Obesity

Armenian, S et al, JCO 2016; 35: 893-911
Risk Prediction:

Treatment Related Risk Factors:
- ≥250mg/m² Doxorubicin
- ≥600mg/m² Epirubicin
- XRT ≥30 Gy when heart is in field
- Lower dose anthracycline + lower dose RT where the heart is in the field
- Sequential lower dose anthracycline then Trastuzumab

Patient Related Risk Factors:
Any of the following + Anthracycline or XRT:
- Older age at treatment ≥ 60 yrs
- CVD
  - MI, moderate valve disease, low normal EF (50-55%) before or during Rx
- ≥2 CRFs during or after treatment
  - HTN, DM, HL, Tob, Obesity

Armenian, S et al, JCO 2016; 35: 893-911
Baseline Risk Assessment Checklist

- CRF assessment and optimization
- Baseline echo
- Mitigation of treatment related risk factors
- Outline a plan for f/u

Wang L, et al, Am J Cardiol 2015;116:442e446
Early Detection

Strain (GLS)

Biomarkers (Troponin)
Speckle Tracking

Myocardial Strain

\[
\text{Strain} = \frac{L_B - L_A}{L_A} = \frac{\Delta L}{L_A}
\]
Strain

- GLS is the most predictive index of choice for subclinical LVD
- Change in strain precedes and predicts decline in LVEF
- Training effect; QA needed
- Vendor/software dependent
- Varies with loading conditions
- Predictive of long term events?
Early Detection using GLS

If GLS abnormal, repeat in 2-3 weeks after initial abnormal study

Note loading conditions
Timing relative to infusion

* The data supporting the initiation of cardioprotection for the treatment of subclinical LV dysfunction is limited.

Timing of Strain Measurement in Lymphoma

Charbonnel, C, Eur Heart J – Cardiovascular Imaging (2017) 18, 392–401
Biomarkers

- Troponins appear to be more useful indicator of cardiotoxicity than BNP or NT proBNP
  - TNI better studied than TNT

- **Advantages:**
  - Cost
  - Easy to obtain
  - Reproducibility facilitates comparison

- **Disadvantages:**
  - How often, how many, timing relative to chemo
  - When can we stop checking?
Temporal trends in LVEF and HS-Trop T in CEpOP +/- R or CHOP +/- R

Xue K et al. Oncotarget 2015: 7, 32519-30
3 Distinct Patterns of TNI

- 495 TNI -/-
- 145 TNI +/-
- 63 TNI +/+ 

Correlation of early TNI with EF during f/u:

- \( r = 0.78 \) TNI +/-
- \( r = 0.92 \) TNI +/+ 

Figure 1. E-Tnl and L-Tnl values in 3 study groups. *P<0.05 versus E-Tnl; **P<0.001 versus E-Tnl; \#P<0.001 vs Tnl**; \#P<0.001 vs Tnl**. 

What Changes Are Considered Abnormal?

**EF:**
A decline from baseline of >10% to a value <53%

**Strain (GLS):**
\[ \Delta >15\% \text{ from baseline or abs value < -19\% if no baseline} \]

**us-Troponin I:**
Elevated from baseline, Persistently positive most concerning
Implications of Early Detection

- Dose limitation
- Schedule modification
- Alternative delivery
- Less toxic analogues
- Pharmacological protection
- ACEI/BB therapy
# Primary Prevention of Cardiotoxicity

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Prada</th>
<th>Overcome</th>
<th>Manticore</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=130 early breast cancer getting epirubicin, 22% also got Tzt</td>
<td>N=90 heme malignancies, getting high dose anthra</td>
<td>N=94 early stage breast cancer getting Tzt; 12-33% also got anthra</td>
<td></td>
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<tr>
<th>Design</th>
<th>Pre-chemo Candestartan vs. Metoprolol</th>
<th>Pre-chemo Enalapril + Carvedilol vs. normal care</th>
<th>1:1:1 Pre-chemo Perindopril vs Bisoprolol vs placebo</th>
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<tr>
<th>Outcomes</th>
<th>Change in EF by CMI at 10-64 weeks</th>
<th>Decline in EF by MRI and Echo at 6 mo</th>
<th>1º: change in LVEDVi by CMR at 1yr</th>
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| Findings | Candesartan blunted decline in EF by ~2-3%, metoprolol had no effect. No effect on GLS or Trop | Intervention group had no decline in EF compared to 3.1% by echo and 3.4% by CMR in the control group (6% in leukemias); p= sig | No change in remodeling EF declined by 3% in perindopril, 1% in bisoprolol group vs 5% in control group. P= sig |

Gulati G, EHJ 2016; 37: 1671–1680  
Bosch, X et al, JACC 2013; 61: 2355-2362  
Prognosis with Doxorubicin Cardiomyopathy

Cardiotoxicity: Relation b/t time to HF treatment initiation and response

Class I/II + TTT <6 months:
PPV for recovery 84%, NPV 87%

Timeline for LV Dysfunction During/After Chemo & Response to Therapy (n=2625)

Surveillance After Treatment

• Clinical assessment and management of CRFs
• Echo (MRI/MUGA) and/or biomarkers if symptomatic
• Echo between 6 & 12 mos post treatment reasonable in asymptomatic pt at increased risk
  • If LV dysfunction, refer to cardiologist

Armenian, S et al, JCO 2016; 35: 893-911
Cardio-Oncology Risk Assessment:

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Healthy Lifestyle
Summary

- Cardiac risk assessment in patients undergoing potentially cardiotoxic cancer treatment is a continuous process
- Be mindful of both treatment and patient related risk factors
- Baseline CRF optimization is important prior to initiation of therapy and should remain a focus of clinical care during and after treatment
- Imaging is an important component of surveillance during treatment
  - Biomarkers may also have a role
- Primary prevention studies have not been compelling thus far
- Early treatment of asymptomatic LVD increases chance of recovery
- Heart healthy lifestyle remains important in survivorship as CVD in survivors is associated with increased mortality
Thanks for your attention!