Do we have to change our anti-cancer strategy in case of cardiac toxicity?

Point of view of the oncologist

Guy Jerusalem, MD, PhD

CHU Sart Tilman Liège
Anticancer therapy: cardiac toxicity

- New anticancer therapies have led to long life expectancy for many patients
- Treatment related co morbidities have become an issue for cancer survivors
- Cardiac toxicity vary from mild ECG changes to serious arrhythmias, myocarditis, pericarditis, MI & heart failure
Cardiac disease does matter in early stage breast cancer

Patients (age at least 50) with early stage breast cancer are 4x more likely to die of non-cancer conditions (up to 45% are cardiac in nature)

Anticancer therapy and cardiac toxicity: the drug

- Reversible (at least partially)? Monitoring
- Cumulative dose-dependent? Adapt regimen
- Major risk factors well known? Patient selection
Anticancer therapy and cardiotoxicity: specific oncological situations

• Childhood tumors:
  - curative treatment, not adjuvant
  - low incidence
  - anthracyclines frequently used

• Very long life expectancy

• Risk factors? How to adapt treatment?
Anticancer therapy and cardiotoxicity: specific oncological situations

Adjuvant treatment of common cancers, such as breast cancer

Avoid or reduce exposure to cardiotoxic drugs such as anthracyclines:

Anthracycline free adjuvant regimens or sequential therapy with taxanes, reducing cumulative toxicity
Anticancer therapy and cardiotoxicity: specific oncological situations

Challenges:

- Long term follow-up if late occurrence of cardiotoxicity

- Outcome in the real world setting??? (highly selected, exclusion of patients with high risk of cardiotoxicity, younger patients in clinical trials)

Patient selection is a key factor (oncological and cardiotoxicity risk?)
Breast Cancer Subsets

- All Breast Cancer
- ER+: 65% to 75%
- HER2+: 20% to 25%
- Triple Negative: 15% to 20%
Intrinsic molecular subtypes of breast cancer

Therapeutic Strategies

- Monoclonal antibodies can block the RTK signal from the outside
- Small molecules can block the RTK signal at the source

Monoclonal antibodies (Trastuzumab)

Small Molecule (Lapatinib)

MAPK Pathway  PI3K Pathway

No Growth- No Proliferation – No Survival
Adjuvant Trastuzumab Trials
MAJOR IMPROVEMENTS IN DFS

Hazard Ratio for Disease Free Survival

HERA | NSABP & NCCTG | BCIRG 006 | FinHER

Adjuvant Trastuzumab: Time to First Distant Recurrence

AC→PT

AC→P

AC, cyclophosphamide + doxorubicin; P, paclitaxel; T, trastuzumab.

Cardiac toxicity: trastuzumab
(HERA study)

Anticancer therapy: HER2 positive breast cancer

- Use of anthracyclines?
- Use of trastuzumab?
- Combined treatment or sequential treatment?
Trastuzumab: Changes in left ventricular ejection fraction

Trastuzumab: cardiac monitoring

Martin M et al., The Oncologist 14: 1-11, 2009
Adjuvant trastuzumab cardiotoxicity

BCIRG 006: Risk of relapse

Risk of relapse

AC-T = Anthracycline + Cyclophosphamide + Taxotère®
TCH = Taxotère® + Carboplatine + Herceptin®
AC-TH = AC-T + Herceptin®

- AC-T: 33%
- TCH: 39%
- AC-TH: 6%

No statistically significant difference.
### BCIRG 006: Cardiotoxicity

<table>
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<th>AC-T N = 1050</th>
<th>AC-TH N = 1068</th>
<th>TCH N = 1056</th>
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<tr>
<td>CHF NYHA grade III IV</td>
<td>4</td>
<td>20</td>
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- Trastuzumab used without prior anthracycline is largely more safe
- Benefit: difference between AC-TH and TCH isn’t statistically significant
- Why not using Herceptin as first agent?
Cardiac toxicity: trastuzumab

Factors associated with risk of developing a cardiac event:

- Use of hypertensive medications
- Age >49
- Baseline LVEF <54

Risk Score = 100 x \(7.4 \times (0.03 \times \text{Age}) - (0.10 + \text{baseline LVEF}) + (0.68 \times C)\)

\(4.82\)

C = HTN medication status: none = 0; yes = 1

Example:
62 yo woman on antihypertensive medication
Baseline LVEF = 60%

Cardiac Risk Score = 82

3-year predicted incidence of symptomatic heart failure/cardiac death ≅ 10%
Future Directions

PREVENTION?

• Pre-emptive use of *ACE inhibitors* or *beta-blockers* in may prevent cardiotoxicity

EARLY DETECTION

• Cardiac biomarkers may help identify high risk patients

CLOSE COLLABORATION !!!