Evaluation of Drug Induced Cardiotoxicity: Logistical Issues

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Logistical Problems

- Monitoring cardiotoxicity by cardiac imaging is essential for cardiotoxic compound e.g. oncology studies
  - There is no clear consensus on the type of monitoring, frequency of monitor, and thresholds for concern and subsequent patient management
  - These differences potentially impair monitoring of patient safety
  - Comparison of the relative safety of compounds is difficult
- Use the discussion today as basis for addressing this issue

Ejection Fraction Thresholds for Action

- Differs based on Benefit/Risk
  - Life threatening condition, poor prognosis, no alternative treatments (or refractory to other treatments)
    - Risk tolerance high – much more likely to die from disease
  - Life threatening condition, poor prognosis, alternative treatments available
    - Risk tolerance not so high – more likely to die from disease
  - Non-Life threatening condition, better prognosis, alternative treatments may/may not be available
    - Low tolerance for risk – may die from disease under study, other diseases, or treatments

Ejection Fraction Values of Concern

- Do we discontinue, temporarily hold, dose modify for
  - Any asymptomatic ejection fraction drop (but EF still in normal range)
  - EF drop but only mild (>40%)
  - EF drop moderate to severe (<40%)
  - Most would agree that any symptomatic EF drop should result in holding/modifying/discontinuing dosing
- These criteria vary from compound to compound as well as professional societies
- Based on the concern of increasing risk of CV morbidity and mortality with decreasing EF – but this risk may be minor compared to underlying disease progression

Patients who have EF decrease

- Once drug is discontinued, can patient receive it again and if so, after how long?
- Does the patient have to return to baseline or return to normal range:
  - Example: Patient starts out at 60%, on therapy goes to 39%, off therapy returns to 51%. They have life threatening cancer?
- If rechallenged with drug, how frequently do they need to be monitored
  - May be an issue with nuclear scans due to radiation doses of frequent testing

- How do we treat these patients in an attempt to improve their ejection fractions?

Considerations

- Sick patients may have increased frequency of observed EF decreases
  - Unclear what percentage are due to underlying disease, comorbidity vs. drug therapy
- Other factors – prior CTX, chest XRT, underlying cardiovascular disease
- Unclear reversibility, unclear if patients can be treated with CHF meds to allow continuation of therapy
- What is the time course?

Considerations

- Is there an exposure-response?
- Long term monitoring for late cardiac effects?
- What about diagnosis and management of non-systolic cardiac dysfunction?
- Can these factors be determined early to modify future protocols and/or product labeling to improve patient safety?

Reducing Variability

- Central Core lab overreads
  - Either prospectively or retrospectively if an issue arises
- Point of care readings – but single reader at each site
- Using same technology
  - Not switching between Echo-MUGA
- Consistent frequency/type of monitoring within/across studies

Going Forward

- Formulate an expert working group/white paper on this topic
  - Describe what pros/cons of each methodology for various settings
  - Describe what has been used as reasonable cut-offs with established compounds and provide reasonable suggestions
  - Discuss potential inclusion/discontinuation/dose modification/ rechallenge criteria in the context of benefit/risk
  - Discuss the use of treatment for Cardiac Dysfunction