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