Reviewer's report

Title: The prevention, detection and management of cancer treatment-induced cardiotoxicity: A meta-review

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Reviewer: Steven Lipshultz

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Conway et al. sought to appraise and synthesize evidence from systematic reviews with and without meta-analyses on the prevention, detection or management of treatment-induced cardiotoxicity in patients who have been diagnosed with cancer. Studies such as these help identify areas that require more evidence before implementing certain clinical practices that might otherwise cause more harm than good or be cost prohibitive. However, there are some concerns about the interpretations and use of the data in this study as outlined below.

Major Compulsory Revisions

Abstract - Results

1. The first result that the authors state, “One systematic review concluded that cardiac biomarkers do not detect cardiotoxicity”, is simply not correct. Please see comment on page 15 regarding the inaccurate interpretation of this result.

2. Regarding the strategies that can reduce the risk of cardiotoxicity, some might be age-specific, and even so, the results are only merely suggestive. For example, continuous administration might be beneficial for adults, but it is still questionable in children.

Background

3. Line 11: “This adverse effect of cancer treatment is associated with a higher mortality rate than the cancer itself.” Perhaps the author cited the wrong study here, as ref 7 is a review on the incidence of cardiovascular complications from cancer treatments. Nowhere in that study do they mention mortality rates from adverse effects being higher than from the cancer itself. Furthermore, as it relates to cardiotoxicity, cardiovascular-related death is among the leading cause of death after recurrence and malignancy. Cancer-related mortality is currently higher than cardiovascular.

4. The above is then followed with “… subacute cardiotoxicity associated with the administration of anthracycline-based chemotherapy is associated with a 60% mortality rate.” The article cited here is dated (2007), and that 60% stated in that review was had no reference to support the data and was part of the background and not from the conclusions of the review itself. Besides, a mortality rate of 60% for subacute cardiotoxicity seems high, and without putting it in the context of a
time period can seem arbitrary.

Discussion

5. Lines 10-11 on page 15: “First, cardiac biomarkers, are probably not sensitive enough to detect cardiotoxicity.” This interpretation is not accurate, as also noted in the abstract. The review by Bryant et al. 2007 “found that evidence on the use of cardiac markers for quantifying cardiac damage is limited in quantity and quality making conclusions problematic”, not that they were not sensitive enough to detect cardiotoxicity.

6. Line 12: Regarding the conclusions drawn from the systematic reviews, the authors should be more cautious to not overstate them. Some are more age-specific (adult vs. children), such as the continuous vs. bolus administration of doxorubicin. Cardioprotection from continuous administration might be true for adults, but it is still questionable for children, as there is not enough evidence to determine.

7. Also, this is a review of other reviews, which is a limitation on its own. Assuming the initial reviews have no major flaws in their design and their interpretations of the original study are accurate, they still have to account variability among the studies and the fact that many of their findings cannot be generalized. For this study, the authors must not only be aware of the limitations inherent in the reviews they are analyzing, but they must also take into account the additional variability that comes with analyzing a group of reviews.

Table 2

8. For Bryant 2007, for the finding on dexrazoxane, it is not clear why it says “No benefit in mortality (83% in both groups)”. The aim of this study to test whether use of dexrazoxane reduced the risk of cardiotoxicity, not whether it improved mortality. Mortality was not one of the primary outcomes. This study demonstrated cardioprotective effects in patients who received dexrazoxane without impacting overall survival the risk of mortality any more or less than using doxorubicin alone.

9. For Ferguson 2007, this study should be removed as it did not specifically look at cardiotoxicity. Their primary objectives were overall and disease free survival. General toxicity was a secondary objective.

Minor Essential Revisions

10. It would be helpful and more informative if the authors performed a current-day meta-analysis from 2006 forward to account for new evidence on monitoring for cardiotoxicity that has come about since then.

11. In Table 2 it seems the findings for some of the reviews that have no meta-analysis have references, but others do not. Unless those that have references are discussed in detail in the text, I would suggest removing the references from the table for consistency.
12. For Table 2, it would be helpful to have a column that gave the range of years of the data that were included in a particular review. Also, for the findings, it would help if a follow-up period was given. For example, a lower rate of clinical heart failure after how many years of diagnosis or since end of treatment.

13. Table 2: For Viani 2007, which treatment regimen was associated with cardiotoxicity? There are multiple comparisons that were compared.

14. Table 2: For Lord 2008, which type of treatment does the OR for cardiotoxicity pertain to? Again, there are multiple comparisons.

Discretionary Revisions: None

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests.