International Late Effects of Childhood Cancer Guideline Harmonization Group
Williamsburg Lodge, Virginia
June 7, 2012

Participants: Saro H. Armenian, Greg Armstrong, Smita Bhatia, Ming Hui Chen, Eric Chow, Richard Cohn, Louis S. Constine, Andrica de Vries, Mary Dwyer, Junichiro Fujimoto, Satomi Funaki, Dan Green, Riccardo Haupt, Tara Henderson, Lars Hjorth, Melissa M. Hudson, Hiroyuki Ishiguro, Leontien Kremer, Claudia Kuehni, Chikako Kiyotani, Wendy Landier, Gill Levitt, Miho Maeda, Gisela Michel, Renee Mulder, Paul Nathan, Kevin C. Oeffinger, Cecile Ronckers, Michael Schaapveld, Sadhna Shankar, Jane Skeen, Roderick Skinner, Charles Sklar, Elvira van Dalen, Helena van der Pal, Flora van Leeuwen

1. Melissa Hudson welcomed the attendees and provided an overview of the harmonization process and progress [see attached slide file labeled: Hudson_Overview & Introduction_Williamsburg_06-07-2012]. Highlights are noted below:
   - A core leadership and official name (International Late Effects of Childhood Cancer Guideline Harmonization Group) of the harmonization effort has been established.
   - Policies and procedures have been developed to assure that a standard methodology is used in the research undertaken to evaluate and grade the evidence related to discordant recommendations.
   - Three previous meetings have been convened that resulted in the successful harmonization of breast cancer surveillance recommendations.
   - A manuscript summarizing the harmonization methodology is under review at the *Eur J Cancer*. A manuscript summarizing the breast cancer surveillance harmonization has been developed and will be submitted to the *J Clin Oncol* in the near future.
   - Criteria for authorship in harmonization manuscripts include participation in an expert panel or working group preparing the evidence summaries and drafting the manuscript, or significant intellectual contribution through manuscript review or editing.
   - The work of the core leadership group, expert panels and working groups should be acknowledged in presentations featuring harmonization efforts. A preferred acknowledgement slide format will be made available in the near future.
   - Meeting attendance will be by invitation only to assure that group deliberations remain manageable and that conference facilities are suitable. However, representation across diverse disciplines and countries is desired. Melissa Hudson or Leontien Kremer should be advised about individuals interested in participating in harmonization efforts (there is plenty of work to be done!) or those interested in attending the meeting as observers (they are welcome as long as space is available in the conference venue).

2. Saro Armenian presented an overview of the cardiomyopathy surveillance harmonization methods. Evidence summaries were developed by 4 working groups for the clinical questions derived from the discordant recommendations among the DCOG, and SIGN UKCCLG, USCOG. The evidence was graded according to AHA/ACC criteria. A core group (Saro Armenian, Melissa Hudson, Gill Levitt, Leontien Kremer, Renee Mulder) supervised the literature review and evidence grading performed by 4 working groups [see attached

slide file labeled: Armenian_Cardiomyopathy Surveillance_Overview_Williamsburg_06-07-2012].

3. The 4 working group leaders presented a summary of the evidence related to the following research questions formulated according to the areas of discordance [Slide files will distributed after completion of the harmonization process.]

   WG 1: Who needs cardiomyopathy surveillance?
   Saro Armenian, Sadhna Shankar, Hamish Wallace, Sandy Constine
   WG 2: What surveillance modality should be used?
   Elvira van Dalen, Gill Levitt, Ming Hui Chen, Julia Steinberger, Berthe Aleman, Elske Sieswerda
   WG 3: At what frequency should cardiomyopathy surveillance be performed?
   Paul Nathan, Ming Hui Chen, Wim Tissing, Melissa Hudson
   WG 4: What should be done when abnormalities are found?
   Helena van der Pal, Elske Sieswerda, Mary Dwyer, Rod Skinner

4. Melissa Hudson moderated the discussion to harmonize recommendations for cardiomyopathy surveillance [Slide file will be distributed after completion of the harmonization process]. Key issues raised include:

   Nomenclature:
   - Per radiation oncologist, term "radiation with potential impact to the heart" is not optimal as this could refer to any radiation delivered to any location. Change to "radiation fields including cardiac structures" suggested, although more terse term would be preferred. The radiation oncologists were asked to consider this issue and propose alternative nomenclature.
   - Should term "cardiomyopathy surveillance" be changed to "Evaluation of LV systolic function"?

   Methods:
   - In considering those who need cardiomyopathy surveillance, need to define that search focused on studies evaluating outcomes of children treated with cancer before 21 years and was not comprehensive for 21-30 years.
   - Should we consider expanding scope of search so our finding will be pertinent to young adult population? Have we likely missed papers relevant to this group?
   - Need to define the parameters used in evaluation of literature for cardiomyopathy (i.e., based on EF < 50% and SF < 28%; other parameters of cardiac dysfunction used in non-invasive studies were not considered in this harmonization effort).
   - Need to qualify that recommendations apply to those with normal function. Does not apply to those with abnormal LV systolic function as defined by EF/SF parameter.
   - Need to qualify that screening for other complications (beyond LV systolic dysfunction) related to these exposures (e.g., heart valve or conduction disorders) were not considered in this harmonization process.
   - Need to establish policy regarding used of unpublished data/studies and updating of recommendations.

Definitions of risk groups

- Group needs to achieve consensus about definition of risk categories if harmonized recommendations assign different frequency of screening for low, moderate, and high risk based on treatment exposures.
- Need to define age threshold for increased toxicity and if/how age will be considered in risk group designation.
- Need to define what constitutes a "decline in function" and if/how this factor will be considered in risk group designation.

Anthracycline dose

- Pertinent literature review has focused on relative risk identified in well-designed studies using non-exposed (anthracycline) group as referent. Further discussion of absolute risk and # needed to screen is needed.
- Threshold anthracycline dose for exponential increase in cardiomyopathy risk suggested to be 250-300 mg/m^2 based on results reported by Blanco et al., JCO, 2012 and van der Pal et al, JCO 2012. Suggestion made to use raw data from these studies to determine more exact threshold. Concern expressed that this approach is not appropriate considering one is case control study with prevalent cases and other is retrospective cohort study. Will exercise even be clinically useful if thresholds are now informed by protocol treatment thresholds?

Radiation fields including cardiac structures

- Need to discuss issue of TBI dose threshold.
- Need to qualify that RT volume and fraction not considered in risk groups defined by radiation dose.
- Is there no effect OR no evidence of effect in regards to risk from TBI or RT<15 Gy? Should recommendation remain red?

Risk Designation – Combined modality therapy

- Need to better define magnitude of increased risk observed in studies evaluating combined modality therapy (additive/super-additive or multiplicative/super multiplicative?). Need to consider how combination of risk factors (e.g., cumulative dose + age) impacts surveillance frequency. Will moderate anthracycline + moderate radiation exposure equal to high risk exposure?

Decline in LV systolic function

- History of decline of LV systolic function mentioned as high risk factor for development of cardiomyopathy, but not specifically discussed in presentation of results of evidence summaries.
- Do we have evidence for relation between risk and decline in function during and/or after treatment?
- Review of literature addressing this issue is needed if this factor will inform more frequent screening.

Cardioprotection measures

- Need to qualify that methods to prevent cardiotoxicity (e.g, use of cardioprotectants, continuous infusion) are not considered differently in risk designation based on dose.

- Evidence for risk groups about cardioprotection/ infusion duration/ long-term/short-term should be added.
- Need to address lack of long-term evidence for benefit of cardioprotective measures.

Exercise

- Need to add more definitive statement that there is no (or only poor/anecdotal) evidence to support deterioration of LV systolic function with exercise.
- What is the evidence for decompensation of LV systolic function related to weightlifting?

5. Renee Mulder presented the list of priority harmonization identified by the modified Delphi survey. Gonadal dysfunction is the next topic for harmonization. The remaining topics proposed (in order of priority) include: coronary artery disease, subsequent CNS neoplasms, growth hormone deficiency, neurocognitive deficits, metabolic syndrome, thyroid cancer, osteoporosis, CNS vasculopathy, thyroid dysfunction.

6. Leontien Kremer discussed immediate and future plans:

   - Based on the issues discussed today, further work is needed to harmonize cardiomyopathy surveillance recommendations. The expert panel will organize a conference call to outline the remaining research to be undertaken by the working groups and develop a new timeline.
   - Expert panel groups will be organized to evaluate the evidence related to discordant recommendations for ovarian and testicular dysfunction. Individuals interested in participating in this harmonization effort should contact Melissa Hudson or Leontien Kremer.
   - The possibility of convening a harmonization progress meeting in concert with the London SIOP meeting will be explored.
   - The development of an interactive website to include the harmonized guidelines, working group evidence summaries and other resources is planned.