Childhood cancer survivors: cardiac disease & social outcomes
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Summary and discussion
The general aims of **part 1** were to create optimal conditions for the evaluation of chronic cardiac health conditions or cardiac events (CEs) in 5-year childhood cancer survivors (CCS), to apply this research in an evaluation of the long term risk of CEs in Dutch CCS, and to uncover the associated risk factors.

In **chapter 2** we presented a protocol for a Cochrane systematic review on clinical heart failure in children, adolescents and young adults treated with anthracyclines and/or radiation therapy involving the heart region. The aim of this systematic review will be to describe and summarize the incidence and associated risk factors that are currently mentioned in the literature. In the protocol the digital search strategy is described, also the criteria for the studies that will be included in the systematic review, method of risk of bias assessment as well as the proposed statistical analyses.

In **chapter 3** we studied the relative cardiotoxicity of daunorubicin versus doxorubicin in CCS. At this moment this ratio is assumed equal. Data from four CCS cohorts were used: Emma Children’s Hospital/Academic Medical Center, National Wilms Tumor Study, St. Jude Lifetime Cohort Study and, Childhood Cancer Survivor Study. To calculate the ratio between daunorubicin and doxorubicin, Cox regression was used to calculate the hazard ratio for clinical heart failure through age 40 years for daunorubicin and doxorubicin doses (per 100 mg/m² increments). Models were adjusted for gender, age at diagnosis, presence of other anthracycline agents, chest radiation and cohort. We also determined the ratio by modelling dose-response curves for each agent. The pooled study population consisted of 15,815 CCS with a median age at diagnosis of 6.7 years and a median follow-up time after cohort entry of 17.3 years. The ratio between the hazard ratios of daunorubicin and doxorubicin in groups of 100 mg/m² increments was 0.45 (95% Confidence Interval (CI) 0.23-0.73) on average. In the dose-response analysis we estimated a daunorubicin:doxorubicin ratio of 0.49 (95% CI 0.28-0.70) using a linear model. These results imply that daunorubicin appears to be associated with less cardiotoxicity compared with doxorubicin among CCS followed through age 40 years.
In chapter 4 we described a newly developed method, a combination of a data-extraction form and a set of flowcharts to grade CEs. We tested the validity and consistency of this method in a series of 40 patients. The Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 and 4.0 were used to define the CEs. Forty patients were randomly selected from a cohort of 72 patients with known symptomatic or asymptomatic CEs, these were graded by a physician for a previous study. A non-physician also graded the CEs by using the new method in order to establish whether the new method was valid for appropriate grading. To evaluate consistency of the grading, the same patients were graded again by two other non-physicians: one received a brief introduction and the other received an extensive training on the new method. We calculated weighted Kappa statistics to quantify inter-observer agreement. We compared the known outcome from the previous study with the outcome of the non-physicians. The inter-observer agreement for validity was 0.92 (95% CI 0.80-1.00), and 0.88 (95% CI 0.79-0.98) and 0.99 (95% CI 0.96-1.00) for consistency with the outcome assessors who had the brief introduction and the extensive training, respectively. We concluded that the newly developed standardized method to grade CEs shows excellent validity and consistency. Moreover, the method can be correctly applied by non-physician and the consistency will improve when they receive adequate training.

In chapter 5 we determined the incidence and associated risk factors of validated symptomatic CEs (heart failure, cardiac ischemia, pericarditis, valvular disease and arrhythmia) after childhood cancer treatment in a Dutch nationwide cohort. Our nationwide Dutch Childhood Oncology Group - Long term Effects after Childhood Cancer (Dutch acronym: DCOG LATER) cohort included 6,168 five-year CCS treated between 1/1/1963 and 12/31/2001 in one of the seven Dutch pediatric oncology/hematology centers before age 18 years. We identified CEs (defined as grade ≥3 according to the CTCAE) reported in patient/general practitioner questionnaires or in medical records with the aid of the newly developed method described in chapter 4. We calculated the cumulative incidence for the first CE and for all specific types of CEs. For the risk factor analysis we
used a Cox multivariable regression model for separate types of CEs. We collected cardiac information of 5,687 CCS (92.2% of the total cohort). The overall cumulative incidence of the first occurring CE 40 year post-diagnosis was 9.6% (95% CI 7.5-11.7). The cumulative incidence 40 year post-diagnosis survival for heart failure was 4.5% (95% CI 3.4-5.5), for cardiac ischemia 1.7% (95% CI 0.6-2.8), for pericarditis 1.1% (95% CI 0.1-2.2), for valvular disease 1.7% (95% CI 0.8-2.8) and for arrhythmia 2.3% (95% CI 1.3-3.4). In a multivariable model, treatment with anthracyclines, radiation therapy involving the heart region, mitoxantrone and cyclophosphamide significantly increased the risk of developing heart failure. Significant risk factors for ischemia were radiation therapy involving the heart region and older age at diagnosis. Whereas, for pericarditis the only significant risk factor was radiation therapy involving the heart region. For valvular disease treatment with radiation therapy involving the heart region and splenectomy increased the risk. When we considered only a specific arrhythmia; supraventricular tachycardia/ atrial fibrillation the following risk factors came out as significant risk factors: older age at diagnosis and radiation therapy involving the heart region. CCS are at high risk of developing CEs, even 40 years post-diagnosis. This study established new risk factors: mitoxantrone, cyclophosphamide and splenectomy. More research is needed to confirm these risk factors and to investigate their role in developing CE.

In chapter 6 we described the methodology of a large pan-European cardiac cohort and case-control study (PanCare Childhood and Adolescent Cancer Survivor care and Follow-up studies (PCSF)). Seven countries in Europe are identifying or identified, and validate symptomatic CEs in their cohort of CCS. The data of these countries will be pooled. The CEs that will be collected are heart failure, ischemia, pericarditis, valvular disease and arrhythmia. The CEs will be graded according to the CTCAE and only symptomatic CEs (grade ≥3) will be included in the study. Both a cohort and a nested case-control study will be conducted. For the cohort study an analyses of the cumulative incidence of symptomatic CEs will be done. Also we will perform a Cox multivariable regression analysis that includes general patient and treatment related risk factors. In the subsequent
nested case-control study, detailed treatment data (chemotherapy and radiotherapy) but also data on confounding, lifestyle risk factors (e.g. smoking habits) and comorbidities will be collected for all the cardiac cases and controls. Therefore we will be able to evaluate patient or treatment related risk factors in the case-control study. We will perform a conditional logistic regression analysis for matched-pairs data. These studies will be the largest of their kind which allows us to study multiple clinical questions with data collected by this pan-European collaboration.

The general aims of **part 2** were to evaluate healthcare consumption and social outcomes among 5-year CCS.

In **chapter 7** we researched whether CCS are at increased risk for health problems, leading to increased hospitalization rates. We aimed to examine the hospitalization rate over time for diseases of the circulatory system, endocrine/nutritional/metabolic diseases, neoplasms and diseases of the eye in CCS compared with the general population. We also compared the type and number of involved medical specialties of CCS and the general population. We linked a complete cohort of 1564 five-year CCS treated (EKZ/AMC cohort) in the Emma Children’s Hospital between 1966-1999 and who survived until January 1995, with the Hospital Discharge Register. We retrieved anonymous hospitalization characteristics from the CCS cohort between 1995-2005 and compared them to a random sample of the general Dutch population matched on age and gender. We used a Poisson regression model for longitudinal data to compare the hospitalization rate over time of CCS and the general population for four main health problems in CCS and to compare which medical specialties were involved in the hospitalizations. Within CCS, we examined the associated demographic-, cancer- and treatment-related risk factors. After medical record linkage, 1,382 CCS and 26,583 reference persons had available hospitalization data. We observed that five-year CCS had an increased hospitalization rate over time for all four types of health problems up to 30 years after primary cancer diagnosis as compared to the general population. Moreover, more different medical specialties were involved in these hospitalizations. Within CCS, we found that specific types of cancer treatment were associated with
higher hospitalization rates for the four health problems. For instance, hospitalization rates for neoplasms were increased after radiotherapy treatment and hospitalization rates for diseases of the circulatory system were increased after treatment with anthracyclines and radiotherapy to thorax and/or abdomen.

In chapter 8 we determined the likelihood of adverse social outcomes in adult CCS and compared this to the general population. We performed medical record linkage between a single-center cohort of 1,768 five-year CCS treated (EKZ/AMC cohort) treated in the Emma Children’s Hospital between 1966-2002, who were 18 years old during the 1999-2009, and who survived until January 1999 and two national registries (the Municipal Personal Records Database (Dutch acronym: GBA) and the Social Economic Categories register (Dutch acronym: SECMBUS)). We obtained a random sample of the general population matched on gender and year of birth (sampling rate 1:20 at maximum). We used multivariable logistic regression to calculate the odds of not being married (or having a registered partnership), not living independently and using social benefits (receiving social benefits for employment, disability or welfare benefits). We compared this to the general population and analyzed risk factors for the adverse social outcomes within the CCS population. We retrieved social outcome data from 1,283 unique CCS and 25,082 reference persons. CCS had higher odds (odds ratio; 95% CI) of not being married (1.2; 1.07-1.42), not living independently (1.7; 1.41-2.00) and using social benefits (2.3; 1.98-2.69) compared to the general population. Within the CCS group, we observed that radiotherapy to head and/or neck and a central nervous system tumor as primary diagnosis negatively influenced marital status, living situation and use of social benefits among CCS. Surgery negatively influenced the likelihood of getting married. CCS are more likely to have adverse social outcomes compared to the general population in all outcomes examined.
**Overall conclusions**

In **part 1** we created optimal conditions for the evaluation of CEs in 5-year CCS and we evaluated the long term risk and risk factors of CEs in a Dutch nationwide cohort of CCS. The following conclusions can be drawn:

- Compared with doxorubicin, daunorubicin is half as cardiotoxic among CCS. (chapter 3)
- The newly developed extraction-flowchart method to grade CEs using data from medical records has shown excellent validity and consistency. (chapter 4)
- 40 year post-diagnosis, 9.6% of all CCS will develop 1 or more symptomatic CE. 4.5% will develop heart failure, 1.7% will develop ischemia, 1.1% pericarditis, 1.7% valvular disease and 2.3% will develop an arrhythmia. (chapter 5)
- Risk factors (chapter 5):
  - We found that anthracyclines, radiation therapy involving the heart region, mitoxantrone and cyclophosphamide is associated with an increased the risk of heart failure
  - We found that older age at diagnosis, and radiation therapy involving the heart region is associated with an increased the risk of ischemia
  - We found that radiation therapy involving the heart region is associated with an increased the risk of pericarditis
  - We found that radiation therapy involving the heart region and splenectomy is associated with an increased the risk of valvular disease
  - We found that older age at primary malignancy diagnosis, and radiation therapy involving the heart region is associated with an increased the risk of supraventricular tachycardia/ atrial fibrillation
- When the PanCareSurFup cardiac cohort is finished it will be the largest cohort of CCS with validated symptomatic CEs. (chapter 6)
In **part 2** we evaluated healthcare consumption and social outcomes among 5-year CCS, the main conclusions are:

- CCS have an increased hospitalization rate over time for diseases of the circulatory system, endocrine/nutritional/metabolic diseases, neoplasms and diseases of the eye up to 30 years after primary cancer diagnosis as compared to the general population. (chapter 7)
- CCS are more likely of to have adverse social outcomes compared to the general population (chapter 8)

**Strengths and limitations of our studies**

*Chapter 3*

The pooled cohort data in which we evaluated the relative cardiotoxicity between daunorubicin and doxorubicin represents one of the largest CCS cohorts examining HF. This provides increased power to detect significant differences in HF risk between doxorubicin and daunorubicin. Although there is a risk of heterogeneity between the pooled cohorts, this seems unlikely. We investigated this by adding the origin of the cohort to the multivariable regression model. However, this appeared not to be a significant risk factor.

*Chapter 4-6*

The main strength of our nationwide study (chapter 5) is that there is a low risk of bias. The DCOG LATER cohort is an almost complete cohort of 5-yr CCSs. The inclusion list was cross linked with several different local and population based databases. Therefore we feel we have almost all CCS diagnosed since 1963, who meet all the inclusion criteria, thus the risk of selection bias is very low. In this study we only evaluated the symptomatic CEs. Asymptomatic CEs are generally discovered by screening which is usually performed in the long-term follow-up outpatient clinic. Because not all CCS attend the clinic, they do not have the same chance that an asymptomatic event is discovered. Even though the CEs events were partially self-reported, we validated the symptomatic CEs by checking the medical charts or contacting the treating physician. This has resulted very precise outcome assessment. As a result we limit possible detection bias. Moreover, the grading of CEs was performed by one person with the aid of the extraction form and flowchart method that we successfully have
developed (chapter 4). In addition, because the cardiac follow-up is almost complete, the risk of follow-up bias is very low. Within the PCSF project we will conduct a nested case-control study in which the numbers of the specific CEs will be sufficiently large for an extensive risk factor analysis (chapter 6).

Chapter 7 & 8
The overall quality of our hospital-based cohort/ linkage studies is good. The risk of selection bias of these studies is minimal; our cohort is complete, we were able to identify all CCS diagnosed since 1966. A strength of linkage is that the outcomes are totally independent of the treatment data. Also, because we performed a medical record linkage between our medical records and national registries, the follow-up is nearly complete. Additionally, because detailed treatment information was available for all CCS in our cohort, we could perform very accurate risk factor analyses. However, due to the small number in our cohort and due to regulations in the Netherlands, we could not perform a proper analyses in in some treatment/ outcome groups. Furthermore, for hospitalization study, less severe long-term morbidity is probably underestimated in our results as the health issue should be severe enough to merit a hospitalization.
**Recommendation for future research**

Based on the results of **part 1** of this thesis, continued follow-up studies of childhood cancer survivor cohorts are needed to address the following aims:

- Identify, whether the tumoricidal effects of doxorubicin and daunorubicin is equivalent or near equivalent for the different types of childhood cancer. This should first be done in cell/animal studies, before translating that to a prospective clinical trial.
- Identify the role and mechanisms behind mitoxantrone, cyclophosphamide and splenectomy related CE, this can be done in cell/animal studies. When the mechanisms are clear, identify protective/preventive interventions for the newly discovered risk factors (mitoxantrone, cyclophosphamide and splenectomy) that can be applied during childhood cancer treatment.
- Evaluate whether concomitant treatment of cyclophosphamide and anthracyclines poses a greater risk than treatment with anthracycline alone. This should first be done in cell/animal studies, before translating that to a prospective clinical trial and investigate whether changes in protocol influences the damage.

The PCSF nested case-control study offers sufficient opportunities to investigate the following research aims, owing to the larger study size:

- Validate the new risk factors, and identify additional risk factors for rare types of CEs, i.e., cardiac ischemia, pericarditis, valvular disease and arrhythmia.
- Identify equivalence ratio for mitoxantrone, epirubicin and idarubicin relative to doxorubicin.

Based on the results of **part 2** of this thesis, continued follow-up studies of childhood cancer survivor cohorts are needed to:

- Identify risk factors for adverse social outcomes in a larger group of CCS, in a retrospective linkage study with detailed treatment information.
- Identify what the impact of the adverse social outcomes is on the quality of life, in a questionnaire based study on a large retrospective cohort.
**Recommendation for clinical practice**

**Future childhood cancer treatments**

Based on the results of **part 1** of this thesis we could recommend the following for future childhood cancer treatment protocols:

- When the tumoricidal effects of doxorubicin and daunorubicin are equivalent, consider switching from doxorubicin to daunorubicin. This may allow a reduction in heart failure without compromising relapse-free survival.
- Consider taking into account the risk of mito xantrone, cyclophosphamide, splenectomy in developing new childhood cancer treatment protocols, to prevent heart failure and valvular disease.

**Future follow-up of childhood cancer survivors**

Based on the results of **part 1** of this thesis we could recommend the following for the follow-up of CCS:

- Regarding the long-term follow-up care, be aware that a significant number of CCS will develop severe, life threatening or fatal CE even 30 years post-treatment.
- Develop and implement a new long-term follow-up guideline for all types of CEs, with the incorporation of the established risk factors anthracyclines and radiation therapy involving the heart region but also the new identified risk factors mito xantrone, cyclophosphamide and splenectomy.
- Calculate the cumulative anthracycline dose the daunorubicin dose should be multiplied by 0.45 before adding it to the doxorubicin dose.
- If a CCS has not received any other cardiotoxic treatment and does not have an underlying predisposition for developing CEs (i.e another illness or genetic predisposition), a cumulative anthracycline dose of <100 mg/m² seems to be save.

Based on the results of **part 2** of this thesis we could recommend the following for the follow-up of CCS:

- Develop and implement new follow-up guidelines for psychosocial assessment of CCS, with incorporation of the new risk factors;
radiotherapy to the head and/or neck and CCS who had a central nervous system tumor as primary diagnosis.

- Develop and implement evidence-based support strategies for CCS, like development of psychosocial intervention programmes, not just for the CCS, but also for their families.

**Future perspectives**

Although the body of research in chronic health conditions in CCS is extensive, there are, however, still areas to explore:

- The incidence and risk factors of CEs could even be better established if investigated in large well-designed cohort studies. Because childhood cancer is rare, collaboration between research groups and countries is essential. A start is made by the pan-European study described in chapter 6. Prospective and harmonized treatment data collection, is also essential for collaborations. Moreover, collaboration between countries for the development of long-term follow-up guidelines is crucial. Especially multidisciplinary collaboration is imperative, to investigate the problems from different angles, e.g. a clinical point of view (e.g. pediatric oncology and adult cardiology) but also an epidemiological point of view.

- Prospective research to evaluate the effectiveness of long-term follow-up guidelines is important. For example, studies should evaluate whether early detection of CEs like heart failure, cardiac ischemia and valvular disease leads to a better quality of life and survival and whether treatment of a asymptomatic CEs results in better health outcomes. This is important to improve the care for CCS.

- To develop less toxic treatments or protective strategies for childhood cancer it is fundamental to research the mechanisms of the toxicities and to define why certain risk factors play an important role in developing CEs. Animal/ cell or mathematical modelling studies are herein necessary.

- The role of genes in the development of CEs. We should identify whether there are certain genes that may predict a predisposition for the development of a CEs. Also, can this knowledge then be applied in the development of targeted treatment of individual childhood cancer
patients. Collaboration is needed to obtain sufficient numbers. In the pan-European study described in chapter 6, DNA is being collected for future use.