Childhood cancer survivors: cardiac disease & social outcomes
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Late cardiac event after childhood cancer: methodological aspects of the pan-European study PanCareSurFup

Elizabeth Feijen on behalf of PanCareSurFup

Manuscript in preparation
Abstract

Background and aim

Childhood cancer survivors (CCS) are at high risk of long-term effects of cancer and its treatment, including cardiac adverse events. The pan-European PanCareSurFup (PCSF) study will determine the incidence and risk factors for cardiac disease among CCS. We describe the methodology of the cardiac cohort and nested case-control study within PCSF.

Methods

Seven countries in Europe participating in PCSF have been identifying and validating symptomatic cardiac events in their cohorts of CCS. Data on symptomatic heart failure, ischemia, pericarditis, valvular disease and arrhythmia will be collected and graded according to the Criteria for Adverse Events. In the cardiac cohort and case control studies we will determine the incidence and risk factors for symptomatic cardiac disease among CCS. Detailed treatment data, data on potential confounders, lifestyle related risk factors and general health problems will be collected.

Results

The PCSF cohort consists of 57,514 5-year CCS with malignancies diagnosed between 1940 and 2008 and classified according to the International Classification of Childhood Cancer 3. Different strategies have been used to identify CEs such as linkage to population/hospital or regional based databases, and patient and GP based questionnaires.

Discussion

The cardiac part of the European collaborative research project PCSF will provide the largest cohort of 5-year CCS with systematically ascertained and validated data on symptomatic cardiac events. This will provide a structure to minimize the burden of cardiac events in CCS by tailoring the follow-up for CCS at higher risk of cardiac adverse events, transferring this knowledge into evidence-based clinical practice guidelines and providing a platform for future research studies in CCS.
Introduction

Treatment for children with cancer has improved considerably over the last decades, resulting in better survival\(^1\). Unfortunately, due to this improved prognosis, there is great concern about the long-term effects of cancer and its treatment. Approximately 75\% of childhood cancer survivors (CCS) will have at least one chronic health condition (such as cardiac, endocrine, neurologic or psychosocial effects) induced by the cancer treatment.\(^2\)\(^-\)\(^4\) Symptomatic cardiac adverse events (CEs) such as heart failure, cardiac ischemia, arrhythmia, pericarditis and valvular disease are well-known long-term side effects of treatment for childhood cancer. CEs can lead to long-term morbidity and early mortality among CCS.\(^5\)\(^-\)\(^9\) Previous studies in CCS have identified treatment-related risk factors for CEs, especially in heart failure, cardiac ischemia and valvular disease. These include anthracyclines and radiation therapy where the heart was in the field.\(^5\)\(^,\)\(^6\)\(^,\)\(^10\)\(^-\)\(^13\) Other suggested risk factors are gender, age at cancer diagnosis,\(^5\)\(^,\)\(^14\) modifiable risk factors (like smoking habits, hypertension or diabetes mellitus)\(^15\) and genetic factors.\(^16\)\(^,\)\(^17\) The evidence concerning these non-treatment related risk factors for CEs is sparse and sometimes conflicting. Current studies on the evaluation of risk factors for different types of CEs have limitations including small study samples, self-reported outcomes, or outcomes based on record linkage without validation. Furthermore detailed treatment information and information on other contributing risk factors, such as lifestyle, is often lacking. Knowledge of the incidence and risk factors for specific CEs is essential, as it contributes to optimal follow-up care for CCS and to recommendations for less toxic treatments for future childhood cancer patients. PanCareSurFup (PanCare Childhood and Adolescent Cancer Survivor care and Follow-up studies (PCSF); EU-Grant agreement number 257505) is a collaboration of European cancer registries and clinical centers, that have agreed to pool their cohorts.\(^18\) The objective of this article is to describe the methodology of the cardiac work package within the PCSF study.
Methods
PanCareSurFup is a 5-year study that started in 2011 and it was developed to determine the incidence and risk factors of second cancers, late mortality and CEs, and to develop evidence-based clinical practice guidelines for models of long-term follow-up, transition to adult care and health promotion for CCS. The cardiac part of the PCSF study consists of a cohort study and a nested case-control study including seven European cohorts provided by eight data providers (DPs): France, Hungary, Italy (two cohorts), the Netherlands, Slovenia, Switzerland and the United Kingdom. The medical ethics committees of each country approved this study.

PCSF cardiac cohort study

Objective cardiac cohort study
The main objective is to determine the incidence and absolute risk for symptomatic CEs in European CCS. Furthermore, we will determine the cumulative incidence of symptomatic CEs per childhood cancer type, different treatment modalities, age at treatment and calendar period of treatment.

Study population
Specific inclusion criteria for the cardiac cohort were: 5-year survivors in which the age at cancer diagnosis ranges from 0 to 20 years.

Primary outcomes
The CEs included in this study are symptomatic heart failure, cardiac ischemia, pericarditis, valvular disease and arrhythmia graded according to the Criteria for Adverse Events (CTCAE)\textsuperscript{19} as grade 3 (severe), 4 (life-threatening) or 5 (death) (see Table 1). Any CE that does not meet these criteria was graded as ≤2. We will use an extraction and flowchart method previously described to grade the CEs.\textsuperscript{20} We will assess only symptomatic CEs because asymptomatic CEs are mostly identified by screening during follow-up care which can introduce selection bias since not all CCS underwent screening.
**Data collection for baseline characteristics**

Each DP collects the following data for each CCS included in the cohort analysis: gender, month and year of birth, month and year of first cancer diagnosis, morphology code, topography code, laterality and basis on which the first cancer diagnosis was made (histology, cytology, specific tumor markers or clinical investigation), and method of ascertainment of the first cancer diagnosis. In addition, the DP collects information on surgery (yes/no), chemotherapy (yes/no), radiotherapy (yes/no), and/or a bone marrow transplant (yes/no), and the month and year of the start of treatment.

**Statistical analyses**

The outcome of interest will be the occurrence of a symptomatic CE (grade 3, 4 or 5 according to the CTCAE v3.0 & 4.0). Time at risk starts 5 years after first primary cancer diagnosis. To determine the absolute risk of the first occurring symptomatic CE and for the separate type of events, we will divide the number of events by the number of CCS in the total population.

We will calculate the cause-specific cumulative incidence for the first occurring symptomatic CE and separately for each type of CE. The cause-specific cumulative incidence reflects the number of specific CEs in the CCS cohort and takes into account that some patients may die before ever developing a CE. When calculating the cause-specific cumulative incidence, individuals who die before developing a CE are not censored but remain in the risk set with a weight. This weight depends on the timing of the last known medical status for those who did not have a CE and did not die.

We will use Cox proportional hazards models, with attained age as the time scale, to investigate the influence of gender, age at treatment, type of childhood cancer, type of treatment modality, and calendar period of treatment for the first occurring symptomatic CE and for the separate type of events. Two sided P values will be reported and those of less than 0.05 will be considered significant. R (version 3.1.1, R Foundation) and SPPS (version 20, IBM SPSS Statistics) will be used for analyses.
Nested case-control study within the PCSF cardiac cohort

Objective of the nested case-control study
The main objective is to determine the treatment-related risk factors for developing symptomatic CEs in CCS; both to confirm earlier identified risk factors and, to identify new treatment, patient, lifestyle and co-morbidities related risk factors for CEs.

<table>
<thead>
<tr>
<th>Table 1. Definitions of cardiac events (using CTCAE v3.0 and CTCAE v4.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 3</strong></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Cardiac ischemia</strong></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Pericarditis</strong></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Valvular disease</strong></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Arrhythmia</strong></td>
</tr>
</tbody>
</table>

*as reported in the Criteria for Adverse Events (CTCAE)v4.0
CHF = congestive heart failure
EF = ejection fraction
SF = shortening fraction
ICD = implantable cardioverter defibrillator
CRT = cardiac resynchronisation therapy
**Study population**

For each CCS with a validated CE identified in the cardiac cohort study described above (i.e. a case), a matched control will be randomly selected from individuals in the underlying survivors’ cohort who have not developed a CE. Cases and controls will be matched on DP, gender, age at first primary cancer diagnosis, calendar year of first primary cancer diagnosis and length of follow-up after first primary cancer diagnosis. This procedure for sampling risk sets (i.e. density sampling) requires controls to be still at risk at the time when the case developed the event. This implies that the length of follow-up (starting at first cancer diagnosis) in the control should be at least that of the corresponding case. STATA (version 13, StataCorp) will be used for control selection.

**Detailed treatment data collection from medical records**

In addition to the baseline data collected in the cohort study, detailed treatment data from all the cases and controls will be collected. Data will be collected from the medical records using an extraction form designed especially for PCSF. The method is explained in detail in an extensive manual (see appendix). We will collect data on the type of chemotherapy, cumulative dose (in mg/m² or equivalent) and method of administration of each chemotherapeutic agent. For anthracyclines/anthraquinones (doxorubicin, daunorubicin, epirubicin, idarubicin and mitoxantrone) we will also collect data on infusion duration, dose per week and whether a cardio-protectant (like dexrazoxane) was given concurrently. For all cardiac cases and controls who received radiotherapy dosimetry will be done for the whole body including seven points in the heart as described previously.²²

**Collection of detailed data by chart abstract and questionnaire**

We will also be able to collect data on congenital heart disorders (e.g. atrial/ventricular septum defect, bicuspid aortic valve), hypercholesterolemia treated with medication, hypertension treated with medication, diabetes mellitus treated with medication or diet, clotting disease (protein S or C deficiency), thyroid disease treated with medication, pregnancies, lung transplant, kidney transplant, height, weight, waist circumference, hip circumference, family history of cardiac disease, physical activity, type of occupation, smoking and medication use. The collection of these possible confounding factors will be mainly done by (telephone)
questionnaires to patients or their families. DPs will enter the data in a secure online database.

Collection of biomaterial

For future use, DNA data is collected from the cardiac cases and cardiac controls that are alive and it will be stored in the country of the DPs. Blood samples will be requested from CCS who will visit an outpatient clinic, and saliva/oral epithelial cells will be requested by mail for those CCS who do not visit an outpatient clinic or for those who have received an allogeneic stem cell transplant.

Statistical analyses

For the separate types of CEs we will assess the following covariates: gender, age at primary childhood cancer diagnosis and different aspects of childhood cancer treatment (chemotherapy and radiotherapy). Since not all the different CEs have the same risk factors, each model will have different covariates based on the literature and clinical knowledge of each CE. We will investigate the role of anthracyclines, mitoxantrone, cisplatin and alkylating agents (as cyclophosphamide equivalence dose (CED) and separate types of alkylating agents such as cyclophosphamide) as risk factors for CEs. We will also investigate the role of radiation therapy where the heart was part of the field and the role of radiation therapy to the head. The covariates and confounding factors will be considered in a conditional multivariate linear logistic model, to control for analysis of nested case-control studies with pairwise matching.

Two sided P values will be reported and those less than 0.05 are considered significant. R (version 3.1.1, R Foundation) and SPPS (version 20, IBM SPSS Statistics) will be used for analyses.

Results

Study population

In Table 2 the different cohorts are described. The PCSF cohort consists of 57,514 5-year CCS with malignancies diagnosed between 1940 and 2008. Diagnosis are classified according to the International Classification of Childhood Cancer 3.
<table>
<thead>
<tr>
<th>Country</th>
<th>Type of cohort</th>
<th>Identification of survivors</th>
<th>Number in cohort of childhood cancer survivors</th>
<th>Age at primary cancer diagnosis</th>
<th>Type of malignancy</th>
<th>Period of primary cancer diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>5 pediatric oncology centers</td>
<td>Hospital data, clinical trials, and cancer registry (ongoing)</td>
<td>3,097</td>
<td>0-&lt;15 year</td>
<td>Solid tumors</td>
<td>1940-1986</td>
</tr>
<tr>
<td>Hungary</td>
<td>Nationwide cancer registry</td>
<td>Hospital data, clinical trials, and cancer registry (ongoing)</td>
<td>5,162</td>
<td>0-&lt;18 year</td>
<td>All, including benign CNS tumors</td>
<td>1971-2008</td>
</tr>
<tr>
<td>Italy hospital based</td>
<td>Nationwide cancer registry</td>
<td>Nationwide cancer registry</td>
<td>3,004</td>
<td>0-&lt;15 year</td>
<td>All</td>
<td>1960-2008</td>
</tr>
<tr>
<td>Italy population based</td>
<td>Nationwide cancer registry</td>
<td>CCRP (Childhood Cancer Registry of Piedmont) and AIRTUM (Italian Association of Cancer Registries)</td>
<td>15,124</td>
<td>0-&lt;18 year</td>
<td>All</td>
<td>1967-2009</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Nationwide cancer registry</td>
<td>DCOG LATER registry based on nationwide hospital based cohorts</td>
<td>6,087</td>
<td>0-&lt;18 year</td>
<td>All</td>
<td>1964-2001</td>
</tr>
<tr>
<td>Slovenia</td>
<td>Nationwide cancer registry</td>
<td>Slovenian cancer registry, follow-up clinic</td>
<td>2,341</td>
<td>0-&lt;16 year</td>
<td>All</td>
<td>1961-2002</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Nationwide cancer registry</td>
<td>Swiss Childhood Cancer Registry</td>
<td>4,718</td>
<td>0-&lt;21 year</td>
<td>All, and LCH</td>
<td>1964-2005</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Nationwide cancer registry</td>
<td>National cancer registration</td>
<td>17,981</td>
<td>0-&lt;15 year</td>
<td>All</td>
<td>1940-1991</td>
</tr>
</tbody>
</table>

CNS= central nervous system, LCH= Langerhans Cell Histiocytosis
Primary outcome
The ascertainment of the cardiac outcome is described in Table 3. Different strategies have been used to identify CEs. These include linkage to population/hospital or regional based databases (hospitalizations, medication use, general practitioner (GP) visits) as well as patient and GP based questionnaires. Five of the 8 DPs used the flowchart to validate and grade the CEs. To obtain more information for this validation, 4 DPs retrieved information from the medical records and GP, and 3 DP used the medical records. With the available information, less than 20% CCS were considered lost to follow-up with respect to cardiac events, and more than 90% of the cardiac events were validated.

Discussion
PCSF is an ongoing EU-funded collaborative research project investigating late effect of 5-year CCS. We describe in detail the methodology of the cardiac part within the PCSF study and highlighted the unique features. This part of the study is investigating cardiac late effects in a large cohort and nested case-control study including data from 7 European countries. We believe, that the cohort size and the chosen methodology of this study will provide new evidence of risk factors of CEs in CCS. The PCSF study will add new knowledge to that gained from previously published studies. In the past CEs have been described in 3 types of studies. First, single-centre studies have assessed the incidence and risk factors of CEs in CCS. They often have a virtually complete follow-up and good outcome validation. However, due to their small sample sizes, these studies are not able to examine risk factors for all CE types. Second, multicentre studies with larger study populations have performed risk factor analysis per type of CE, but these have mainly analysed self-reported outcomes that could be at risk of outcome reporting bias. Finally, nationwide studies using medical record linkage have a large study population with complete follow-up and a diminished risk of selection and outcome report bias, but they usually lack detailed treatment information, thus preventing the possibility of carrying out an in-depth treatment related risk factor analysis. In contrast, PanCareSurFup will address the incidence and risk factors of symptomatic CEs in a design that
carries minimal risk of bias due to the method of ascertainment or extensive validation of CEs, and will also include detailed information on treatment.

Essential to the development of this project is the close collaboration between investigators from several European countries that will provide systematically ascertained and validated data on symptomatic CEs. A potential drawback is that the differences in inclusion criteria and method of identification of potential CEs might mean that the data will be too heterogeneous to pool. We will examine whether the differences in inclusion criteria and ascertainment influence the outcome, by conducting a sensitivity analyses in which we include “DP” as risk factors in the multivariate regression models. One of the main objectives of the cardiac component of PCSF is to adequately identify all potential risk factors for CE. This is especially important for less frequent CE for which we currently have only a small amount of data on risk factors. To adequately identify potential risk factors we need sufficient numbers for the separate types of CE. Studies have shown that the number of outcome events are accountable for the number of covariates (potential risk factors) in the Cox proportional hazard model.\(^{38}\) When there are less than 10 events per covariate the results of the Cox proportional hazard should be interpreted with caution. Although some studies showed that this “rule of ten” can be relaxed\(^{39}\) we have strived to ascertain as many events as possible so that we can analyze all potential risk factors. We assume that we will have around 750 cardiac cases in the case-control study. When we apply the division in types of CE of van der Pal 2012\(^6\), namely 54% heart failure, 12% cardiac ischemia, 4% pericarditis, 12% valvular disease and 18% arrhythmia, we can estimate the number of the different types of CE we will have in our case-control study (Table 4). Hence, a strength of our study is that the final number of the different types of CEs will be sufficient for adequate risk factor analyses and safe interpretation.

Previous studies have suggested a possible association between genetic factors and CEs.\(^{16,17}\) Hence, the DNA that PCSF will collect from all the cardiac cases and cardiac controls in combination with the detailed information on the CCS will be a valuable source of information for future research.
<table>
<thead>
<tr>
<th>Method of identification of potential cardiac events</th>
<th>lost to follow-up cardiac events</th>
<th>Source of additional information to validate cardiac events</th>
<th>Completeness of validation cardiac events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Questionnaires to patients/medical records</td>
<td>20%</td>
<td>Questionnaire/Telephone</td>
<td>100%</td>
</tr>
<tr>
<td>Visit to follow up clinic/questionnaires to patients</td>
<td>Unknown at this moment</td>
<td>Medical records + GP</td>
<td>90%</td>
</tr>
<tr>
<td>Linkage: hospitalization database</td>
<td>Unknown at this moment</td>
<td>Medical records</td>
<td>Unknown at this moment</td>
</tr>
<tr>
<td>Hospital discharge database, medical records, questionnaire to patients</td>
<td>Unknown at this moment</td>
<td>Medical records</td>
<td>Unknown at this moment</td>
</tr>
<tr>
<td>Questionnaires to patients or GP/Visit to follow up clinic/medical records</td>
<td>&lt;15%</td>
<td>Medical records + GP</td>
<td>95%</td>
</tr>
<tr>
<td>Visit to follow up clinic/questionnaires to patients</td>
<td>6,5%</td>
<td>Medical records + GP</td>
<td>95%</td>
</tr>
<tr>
<td>Linkage with death registry</td>
<td>22%</td>
<td>Medical records + GP</td>
<td></td>
</tr>
<tr>
<td>Questionnaires to patients/linkage: different hospital episode databases (outpatient + in patient + emergency care + death registry)</td>
<td>Unknown at this moment</td>
<td>GP and medical record</td>
<td>Unknown at this moment</td>
</tr>
</tbody>
</table>

*GP* = general practitioner

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**Table 3. Cardiac outcome ascertainment per data provider**

France: Questionnaires to patients/medical records; 20% lost to follow-up; Questionnaire/Telephone 100%.

Hungary: Visit to follow up clinic/questionnaires to patients; Unknown at this moment; Medical records + GP 90%.

Italy hospital based: Linkage: hospitalization database; Unknown at this moment; Medical records; Unknown at this moment.

Italy population based: Hospital discharge database, medical records, questionnaire to patients; Unknown at this moment; Medical records; Unknown at this moment.

The Netherlands: Questionnaires to patients or GP/Visit to follow up clinic/medical records; <15%; Medical records + GP 95%.

Slovenia: Visit to follow up clinic/questionnaires to patients; 6.5%; Medical records + GP 95%.

Switzerland: Visit to follow up clinic/questionnaires to patients/Linkage with death registry; 22%; Medical records + GP.

The United Kingdom: Questionnaires to patients/linkage: different hospital episode databases (outpatient + in patient + emergency care + death registry); Unknown at this moment; GP and medical record; Unknown at this moment.

GP = general practitioner.
Furthermore, PCSF in collaboration with international guideline harmonization group\textsuperscript{40} focuses on developing evidence-based guidelines for long-term follow-up evidence-based guidelines to guide survivors and health care providers about, amongst others, the prevention, early detection and treatment of long-term effects of childhood cancer. The recently published clinical practice guideline on cardiomyopathy surveillance for CCS notes the existing gaps in knowledge to improve cardiovascular health of CCS.\textsuperscript{41} The authors highlighted the need for multidisciplinary and international collaboration with access to large population in order to filled in these current gaps in research.\textsuperscript{41} The successful identification of risk factors associated with the development of CEs can inform the further development of both less cardiotoxic treatment protocols of childhood cancer patients and new treatment strategies for high risk childhood cancer patients. Hence, the findings of the cardiac cohort and nested case-control study of PCSF will be an important source of evidence and will provide an information base for long-term cardiac follow-up guidelines of CCS.

**Conclusion**

In conclusion, the cardiac studies included within the PCSF project will allow us to benefit from the largest cohort of 5-year CCS with detailed treatment information and systematically ascertainment and validation of CEs. Risk factors for CE analyses in CCS studies are often limited by the small number of events. In order to achieve tailored follow-up for CCS at risk of CEs, the large number of individuals in PCSF will allow us to adequately identify risk factors for different types of symptomatic CEs and incorporate this knowledge into evidence-based clinical practice guidelines for long-term follow-up of CCS. Furthermore, the cardiac part of PCSF will serve as a source for future research including genetic evaluations of survivors at higher risk of symptomatic CEs.
**Table 4.** Estimated numbers of the separate types of CE based on the assumption of 750 cardiac cases.

<table>
<thead>
<tr>
<th>Estimated number of each type of cardiac adverse event</th>
<th></th>
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<tbody>
<tr>
<td>Heart failure*</td>
<td>405</td>
</tr>
<tr>
<td>Cardiac ischemia*</td>
<td>90</td>
</tr>
<tr>
<td>Pericarditis*</td>
<td>30</td>
</tr>
<tr>
<td>Valvular disease*</td>
<td>90</td>
</tr>
<tr>
<td>Arrhythmia*</td>
<td>135</td>
</tr>
</tbody>
</table>

*estimation based on van der Pal 2012
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