Pancare Childhood and Adolescent Cancer Survivor Care and Follow-up Studies

PanCareSurFup

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Dear Friends,

Since the last Bulletin in December 2013, the project has been busy with the second 18-month report to the European Commission. All Work Package Leaders have produced a Scientific Report and all partners have been asked to fill out their Financial Reports (Form C) and (where needed) their Certificate of Financial Statement. The Scientific Report and the Financial reports where uploaded to the Commission and sent by courier where necessary by Friday March 28. The response from the Commission is eagerly awaited. The web conferences for all Data Providers have been on-going as planned and all relevant queries in relation to each set of data is being addressed where appropriate. The work on the Guidelines together with the International Guidelines Harmonization Group is progressing well and several sub-groups within both WP 6 and WP 7 have been formed to address queries related to the implementation of the Guidelines. Several meetings for the purpose of dissemination are in the pipe-line and plans toward a final event for PanCareSurFup are beginning to be drawn.

So it is with great confidence for the future that the PanCareSurFup project continues its fourth year. This is the year when much of the data to be gathered in the project will be collected and we will all certainly be very busy.

I wish you all good reading and a warm and relaxing spring!

Lars Hjorth
Project Coordinator

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Production and editing: SIOP Europe

Latest developments in PanCareSurFup

Work Package 1

To date, data on more than 90,000 individual patients have been provided to Work Package (WP) 1. For all data providers that delivered data, comprehensive plausibility checks and clarification of open questions have been undertaken, recently relating in particular to the usage to ICD-O and ICD in the cohort on second primaries. Data quality has been therefore improved. Whole cohort data on second primary tumours were sent from WP1 in Mainz to WP4 in Birmingham (resulting in additional questions to be clarified), first data on cardiac toxicity were sent to WP3 in Amsterdam, and data on late mortality will be soon sent to WP5 in Lund. Improved follow-up data are announced from some data providers and will be incorporated into the databases.

A survey of practices among the European population-based cancer registries was developed jointly with the ENCCA Network of Excellence in IARC, Lyon. The questionnaire was distributed to over 200 cancer registries in Europe, with the aim to map the follow-up data items that are already routinely collected. Preliminary results indicate that virtually all registries collect information on multiple primary tumours and about two thirds have access to death certificates, but almost none of them collects data on other late effects. Data collection and validation is still on-going. Simultaneously, a database of almost 370,000 records of children and adolescents with cancer was built in collaboration with population-based cancer registries. Data validation and preliminary analyses are under way.

Work Package 5

Work Package 5 on 'late mortality' prepared the deliverable report D5.2 'Description of existing information in Europe on late mortality of childhood cancer survivors' in collaboration with WP1. Up to now 10 cohorts were provided to Mainz, a total of almost 57,000 five-year survivors of cancer in childhood and adolescence, among those 7,155 events of death occurred at the latest follow-up. The cause of death was known for 92.5% of the deceased. Unfortunately, three cohorts could not yet be delivered by the data providers: for this reason, three milestones directly dependent on the late mortality database could not be achieved. This delay will hopefully not affect the work program in the future.

Work Package 6

WP6 continues to make good progress on guidelines' development. The guideline on 'Transition of Survivors' is making steady progress, but the complexity of the topic implies that still much work needs to be done before it is completed. Currently, WP6 is collaborating with the International Guideline Harmonisation Group as concerns three other guideline topics. The 'Female Gonadotoxicity' guideline is at an advanced stage of writing, whilst the 'Male Gonadotoxicity' guideline is close to completion, including a final recommendation. The 'Thyroid Cancer' guideline group is finalising the clinical questions which will inform the literature searches for this topic. The 'Methodology, Implementation and Feasibility' and 'PLAIN Information' sub-groups have each held their first web-conference during January/February. Each of these groups is clarifying its aims and scheduling their next meetings.

PanCareSurFup Partners

The project's dissemination team this month interviews the leader of Work Package 3 'Cardiac disease: cohort and nested case control study', Prof. Leontien Kremer from the Emma Children's Hospital in Amsterdam (The Netherlands).

Prof. Leontien Kremer

Can you describe how you got involved in PanCareSurFup?

I think the first start of our collaboration was in 2007 at the farewell scientific meeting for Stanislaw Garwicz. Lars Hjorth and his colleagues invited me to give a presentation about cardiac disease in childhood cancer survivors. It was a very inspiring meeting and I remember the warm welcome of Lars and his team. At that meeting we discussed working together more extensively. One year later Lars and Stan invited a few people to discuss future collaborations more in details. They asked me to present future perspectives in research on chronic disease in childhood cancer survivors. I was surprised by this invitation("what do I now about this…"), but it is one of those moments in your life when you are stimulated to think about really relevant issues. My statement was that our research has to focus on patient relevant outcomes. During this meeting we started the PanCare European collaboration. Nearly 6 years later, it is exciting to realise what we achieved in our collaboration. I am happy to contribute to PanCareSurFup (PCSF) as a WP leader for cardiac disease, as a data-provider and as an expert in guideline development. Many people from the Netherlands contribute to PCSF at this moment, and three of them have a coordinating role. Lieke Feijen, a PhD student in our hospital, is involved in WP3 coordination and planning, and also coordinates data-providing for the Netherlands for the different Work Packages together with Cecile Ronckers, a senior investigator in our group. Renee Mulder is involved in guidelines' development. I would like to take the opportunity to thank the Lund group for their initiative years ago, as well as all the collaborators in Europe for the inspiring time we always have together. It is so stimulating to work with people who have the same focus; improving the quality of life of survivors of childhood cancer by improving the quality of research and care.

Could you please explain what is the scientific methodology used in a 'cohort and nested case control study'?

A cohort study can evaluate the incidence of cardiac disease in the whole cohort of childhood cancer survivors. We will get insight in the long-term risk of cardiac diseases in childhood cancer survivors, years after the start of the treatment. Data on cardiac diseases will be collected in Switzerland, France, United Kingdom, Italy, Slovenia, The Netherlands and Hungary. On the other hand, through a nested case-control study we will evaluate risk factors in childhood cancer survivors with a cardiac disease compared to survivors who did not develop such a disease. Within this case control study we will be able to provide more precise information about specific risk factors such as chemotherapy, radiation dose, and the joint role of treatment and more classic risk factors for cardiac disease.

Which kind of cardiac risks may childhood cancer survivors face in their life?

Survivors can develop heart diseases, especially after treatment with anthracyclines and radiation therapy. Some of these survivors will have no symptoms and we can only see abnormalities in heart function when we perform an echocardiography. A small percentage of the survivors may develop heart failure, ischemia, valvular disease, pericarditis and arrhythmia after childhood cancer treatment. Overall, the mortality due to cardiac disease in long-term survivors of childhood cancers is 5 to 7 times higher than expected compared to the general population.

Are radiotherapy and chemotherapy the main responsible for cardiac long term effects?

Anthracyclines and cardiac irradiation are the two main known treatment-related risk factors for cardiac diseases. Anthracyclines, e.g., doxorubicin, daunorubicin and epirubicin, are known risk factors of long-term cardiotoxicity, which can become manifest as either asymptomatic or symptomatic clinical heart failure. Radiotherapy involving parts of, or the entire heart, is also associated with cardiac disease, including atherosclerosis, pericarditis, myocardial infarction and valvular defects. The frequency of radiation-induced clinical cardiac diseases after childhood cancer increases with higher dose.

Lieke Feijen, Phd student helping Prof Kremer in WP3

Are there or do you foresee any ways to prevent cardiotoxicity due to chemo- or radiotherapy in childhood cancer patients?

Yes there are ways to prevent cardiotoxicity. First of all, I think we should avoid this type of treatment as much of possible. This is a very strong statement, and I know it is not possible at this moment as anthracyclines are the cornerstones of the treatment for childhood cancer and, thanks to this treatment, the survival of children with cancer has improved spectacularly . However we should investigate which treatment is really effective to cure childhood cancer. For me it was embarrassing to conclude, in a Cochrane review, that there is a lack of evidence on the effect of this class of medications from randomised controlled clinical trials on survival. I do not advocate to stop the use of anthracyclines in the treatment of childhood cancer, but we should study the antitumour effect and possible adverse effects of anthracyclines. As a result we will be able to make a well-balanced choice between the benefits and harms of anthracyclines in the treatment of children with cancer.
Second, several preventive measures have been suggested to avoid cardiotoxicity during treatment, including liposomal anthracyclines and reduced cumulative and peak doses of anthracycline therapy. Despite these efforts, cardiotoxicity remains a problem. The use of the cardioprotective agent, dexrazoxane has been investigated intensively. The fact that dexrazoxane is not routinely used in clinical practice might be explained by the suspect of interference with antitumour efficacy and by the occurrence of secondary malignancies. However, in a previous Cochrane review we showed that dexrazoxane prevents heart damage and that there is no evidence for a difference in response rate to anthracyclines nor of a difference in tumour survival between the dexrazoxane and control groups. We concluded that if the risk of cardiac damage is expected to be high, it might be justified to use dexrazoxane in patients with cancer treated with anthracyclines.

Are there new alternative methods to treat and cure young patients?

Many new agents have been suggested for the treatment of childhood cancer. I think that we have to learn from the past. We should get evidence from well-designed randomised clinical trials to prove the effects of new agents on the survival and, more importantly, we have to collaborate in research on the possible adverse effects on the short and long term. It will be important to strengthen the collaboration between paediatric oncologists, radiation oncologists and late-effects experts to define clinically relevant outcomes for children who survive childhood cancer on the short and long term. I think the PanCare collaboration will play an important role here.

Are you already preparing the future DNA studies foreseen by your Work Package? What are their advantages?

Yes, we are preparing them, as knowledge in this field is developing very fast. Only a few years ago some genetic variants could be tested while, currently, genome wide association studies are performed. The strength of the cardiac study within PCSF is that all participants will try to collect DNA from the cases and controls. Within PCSF we use very strict definitions of cardiac diseases: such clear definitions are

important for genetic studies, because we would like to discover genetic markers for clinical relevant diseases and would like to avoid false positive results. It will be important to find additional funding for the analyses of the collected DNA. At this moment several studies on cardiac genetic markers have been done. A lot a variants have been suggested. A high quality study and replication of possible markers are needed to identify important genetic markers for cardiac diseases in childhood cancer survivors. Hopefully, this will help us in the future to predict with more precision who will be at risk for cardiac disease after treatment for childhood cancer.

Describe your typical working day / What do you love most about your job?

Ha-ha, that is a difficult question: I am doing a lot and I love many things about my job. PCSF is one of the projects that gives me a lot of energy: it focuses on some of the most important outcomes after for childhood cancer treatment, and this European collaboration is inspiring. I am learning every day how important it is to have such a collaboration. Communication is crucial, and the main challenge is to discuss common concepts and definitions. We can bring the knowledge to the next level, and this will improve the care for survivors.
My typical working day consists in many appointments, and my main focus is high-quality patient care based on high-quality research. I love to inspire, to collaborate and to teach people. We have a team of enthusiastic clinicians, scientists, research nurses and data-managers. I am working more and more together with patient representatives. These interactions support me to keep my focus on the main outcomes, which are relevant for patients. My projects are in the field of research (for example Dutch DCOG LATER study), systematic reviews (the Cochrane Childhood Cancer Group) and guidelines (for example within PCSF and the International Guideline Harmonization Group).
I love the weekends, when I have my own time with family and friends and I can reflect on all the work done in the previous week!

Describe one of your proudest moments/ an achievement you are particularly proud of.

I am proud that we were able to succeed in getting funding for 2 European projects and that we collaborate with many people who all have their special talents. I think that I am really inspired when I can contribute to a collaboration between many talented people, with the final goal to improve care based on high quality research. Examples of these collaborations are the DCOG LATER group, the Cochrane Childhood Cancer Group, PanCare and its associated groups and the International Guideline Harmonisation Group for surveillance of late effects after childhood cancer. I hope that I will be able to work together with these inspiring people for a long time.

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