Ressortforschungsberichte zur kerntechnischen Sicherheit und zum Strahlenschutz

Untersuchungen zum Zusammenwirken umweltbedingter Risikofaktoren mit genetischen und weiteren endogenen Faktoren bei der Entstehung von Leukämie im Kindesalter Teilvorhaben 4: Pilotstudie zum Vergleich der Inzidenz von Leukämie im Kindesalter in verschiedenen Ländern - Vorhaben 3611S70028

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Das Vorhaben wurde mit Mitteln des Bundesministeriums für Umwelt, Naturschutz, Bau und Reaktorsicherheit (BMUB) und im Auftrag des Bundesamtes für Strahlenschutz (BfS) durchgeführt.

Bundesamt für Strahlenschutz

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Salzgitter, November 2016

International Agency for Research on Cancer

World Health Organization

Pilot to develop a main study protocol for a multinational study of childhood leukemia investigating the potential aetiological roles of genetic pre-disposition, biomarkers of infectious exposure, and selected environmental factors

Final report

Tracy Lightfoot, Laila Starr, Friederike Erdmann, Joachim Schüz

Lyon, May 2013

Executive summary:

This pilot project arose following a meeting initiated by the German Federal Office for Radiation Protection (BfS) in July 2010 to devise a long-term strategic research agenda for childhood leukemia. It was recognised at this meeting that in order to increase our knowledge of disease aetiology and outcome more needed to be known about the descriptive epidemiology of leukemia (both acute lymphoblastic leukemia and acute myeloid leukemia) at a global level. Although it is well documented, for example, that acute lymphoblastic leukaemia (ALL) is the most commonly diagnosed cancer in children under the age of 15 in economically developed countries there is a paucity of reliable data relating to the incidence and mortality of the disease in less economically developed regions of the world. With a view to providing insight into this area, we designed a pilot study and identified the following aims and objectives as being key to taking this initiative forward.

1. To establish an international network for a multi-disciplinary study of childhood ALL
2. To hold a meeting of representatives from the international network to discuss and identify priorities for future research investigations
3. To draft a study protocol based on conclusions from the network meeting of country representatives.

The project which started in May 2012 was carried out at the International Agency for Research on Cancer (IARC) under the direction of the Head of the Environment and Radiation Section, Dr Joachim Schüz, and coordinated on a day to day basis by Laila Starr who was funded as a doctoral fellow at IARC by the project. In addition, the research was supported by Dr Tracy Lightfoot (Senior Lecturer University of York/Senior Visiting Scientist, IARC) as the scientific supervisor (Appendix I), and a steering group comprising clinicians, biologists and epidemiologists from Germany and the UK.

During this pilot, we successfully identified 24 countries, and 38 centers within these countries, to which a preliminary questionnaire was sent in order to obtain basic information about the available facilities and the number of cases diagnosed/treated within each center. From this, 16 representatives (predominantly paediatric oncologists/ haematologists) were selected from 15 countries and invited to attend a two-day meeting at IARC in February 2013. During the meeting representatives described in detail the health care infrastructure of their country and center, what catchment population their center covered, how the children were treated and

followed up, how care was financed, what challenges they faced and what they thought the key questions were that needed to be addressed.

Following on from these discussions, and in consultation with the steering group, a protocol was developed to provide the basis for future global investigations of childhood leukaemia. This protocol comprises a series of distinct but inter-related work-packages which we hope will lead to improved knowledge about global variation in childhood leukaemia incidence and the geographical distribution of leukemia subtypes as well as providing the infra-structure and support for the development of refined treatment protocols targeted directly at the specific needs and constraints of each country.

In summary, the original aims and objectives of the pilot project have clearly been achieved and we have established a very enthusiastic and dedicated network of partners that can now progress this research further with a view to providing answers to some of the key questions mentioned above. Critical to the success of this project, and also going forward, has been the bringing together, probably for the first time with respect to childhood leukemia, clinicians, epidemiologists and biologists from across over the world.

Project report

The following report summarises the main activities and outcomes of childhood leukaemia pilot project from May 2012 –May 2013.

1. Establishment of project steering group

The first objective was to establish a steering group to oversee and direct the research carried out within the project. A multi-disciplinary team with clinical, epidemiological and biological expertise was assembled in spring 2012, and the group convened for a two-day meeting in July 2012 to develop the strategic agenda for the project, agree on the participating countries and to identify the key questions to ask the participating centers. The agenda and minutes from this meeting are provided in Appendix I.

The steering group included the following members:

IARC – Epidemiology (Section of Environment and Radiation)

- Dr. Joachim Schüz (Chair)
- Dr Tracy Lightfoot
- Laila Starr
- Friederike Erdmann

Paediatric Oncology

- Professor Sally Kinsey, Department of Paediatric Haematology and Oncology, Leeds General Infirmary, Leeds, UK
- Dr Claudia Rössig, Klinik für Kinderheilkunde der Abt. Hämatologie u. Onkologie, Münster, Germany
- Dr Kjeld Schmiegelow, Department of Pediatrics, Rigshospitalet, Copenhagen, Denmark
- Dr Martin Schrappe, Universitätskinderklinik Kiel, Klinik für Allgemenine Pädiatrie, Kiel, Germany
- Dr Martin Stanulla, Department of General Pediatrics, University Medical Centre Schleswig-Holstein, Kiel, Germany

Epidemiology / Biology

- Professor Eve Roman, Epidemiology & Cancer Statistics Group, University of York, UK
- Dr Hans Lehrach[1], Max Planck Institute for Molecular Genetics, Berlin, Germany

[1] Dr Lehrach was represented by Dr Marc Sultan at both the steering group and network meetings held at IARC.

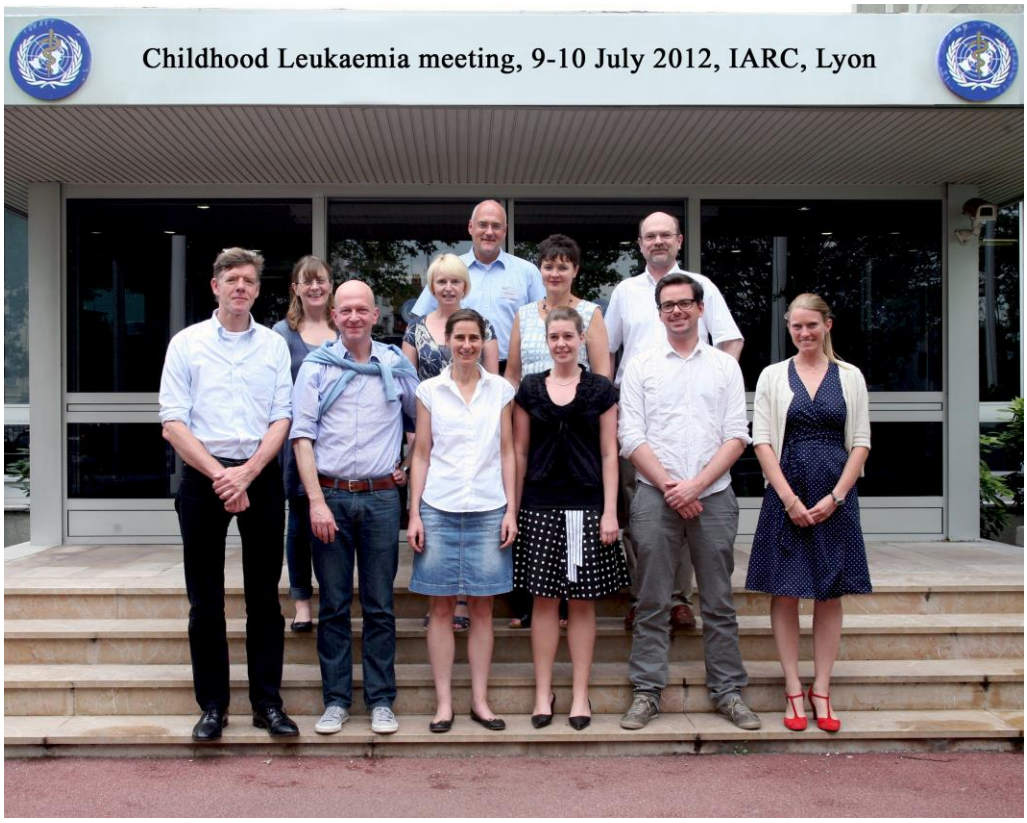


Photo: Steering Group Meeting, 9-10th July 2012, IARC, Lyon, France

2. Identification of potential partner countries/centers

One of the primary objectives of the project was to establish an international network of collaborators to provide a platform for future investigations of childhood leukaemia pathogenesis. A novel approach to choosing the international partners was adopted, with the plan to link directly with clinicians and hospitals (wherever possible) as opposed to the conventional route of linking exclusively to cancer registries and/or epidemiological partners.

Potential target countries/partners were initially identified either through previous contacts with members of the steering group, links with IARC and/or literature searches of published studies. It was also important to ensure that the selected countries provided adequate global coverage and were sufficiently diverse with respect to economic development (low, middle and high income) and ethnicity.

The countries identified were:
Argentina, Australia, Brazil, China, Denmark, Egypt, Germany, India, Japan, Jordan, Kenya, Republic of Korea, Mexico, Nepal, Russia, Rwanda, South Africa, Thailand, Turkey, Uganda, the UK, USA, Vietnam, Yemen.

3. Pilot Questionnaire Development

In order to obtain additional information about the potential partners identified, a pilot questionnaire was developed and sent to all centers and institutions listed above details of which can be found in Appendix II. In summary information was requested in relation to the following:

- Number of cases of leukaemia and leukaemia subtypes diagnosed each year
- Demographics of cases (age, sex)
- Description of the catchment area (population size, distance to travel etc)
- Funding for treatment
- Treatment protocol and follow-up care
- Clinical facilities available
- Medical record availability
- Biospecimen collection and storage

In addition, recipients of the questionnaire were also asked if they would be interested in participating in future research collaborations and to confirm if they were most appropriate person to be involved and if not to provide alternative suggestions.

Overall a very good response was received from those contacted. In a few cases, questions were left blank or answers were unclear and these were followed up by further emails or by phone. The results from the pilot questionnaire were very interesting and there was clear diversity between centers with respect to many of the variables.
A brief summary of the results is provided below.

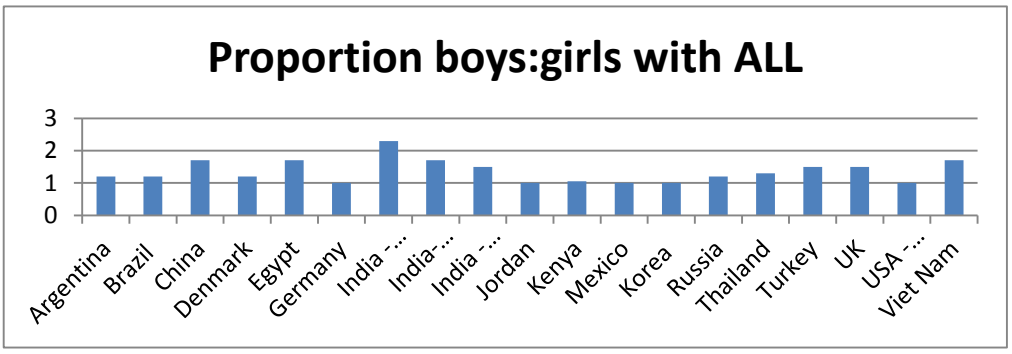
Age range of children treated in the center
Whilst the majority of centers focused on children diagnosed with cancer up to the ages of 15-18, some institutions had a cut-off at 14 years of age whilst others treated teenagers and young adolescents up to the age of 30.

Number of children diagnosed each year

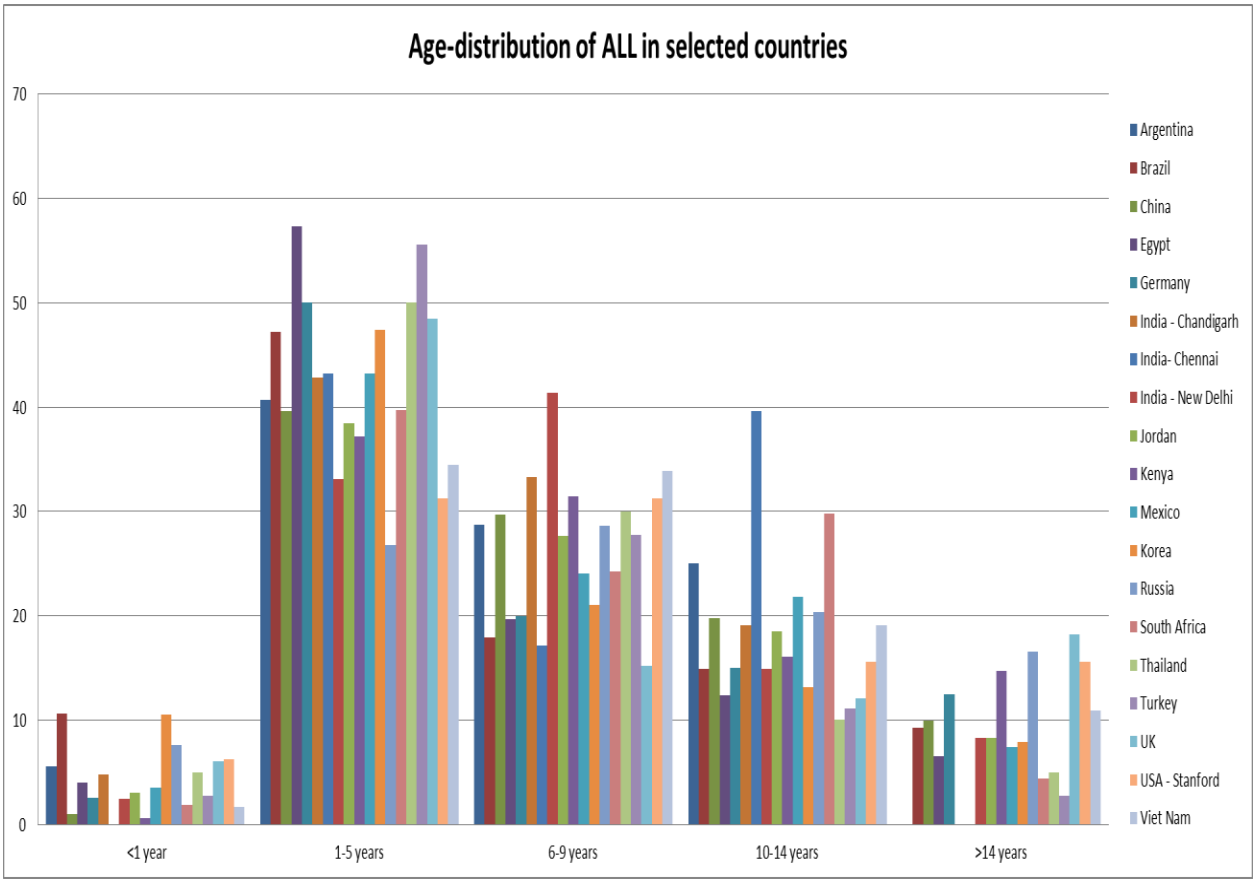
The number of children diagnosed at each of the centers ranged from around 25-30 (Turkey, USA and UK) up to 350 in Egypt and Russia. As expected, generally, the number of children diagnosed and the number of treated were comparable, but for some in India, (Chandigarh and Chennai), Kenya and Vietnam the numbers differed, with as low as 60 % treated.

Leukaemia diagnoses: age, sex and subtype

Acute lymphoblastic leukaemia was the most commonly diagnosed subtype of leukaemia in all centers ranging from 51% in Kenya to 90% in Chandigarh, India. As shown below there was variation in the number of boys being diagnosed compared to girls.



There were also differences with respect to the age distribution of the children being diagnosed in the centers, although as expected the majority of cases were diagnosed between 1 and 5 years of age. Interestingly, in some centers very few children under 1 were diagnosed whereas in others this age group represented more than 10% of their cases.



Other parameters which differed markedly between centers included the distance families had to travel for treatment, how the children were treated and followed-up, and the size of the facility both with respect to the number of available beds and the number of staff.

Medical records were available in all centers, with most having them available electronically. In addition, biological specimens were also generally collected and stored.

4. Selection of centers for inclusion in the network

Whilst ideally it would have been good to include all of the centers identified from the initial searching exercise, it was agreed by the steering group, from a practical point of view, to restrict the number of centers that would participate in the next phase of the project and attend a two-day workshop at IARC. The data collected from the pilot questionnaire were used to aid in the short-listing process to ensure that each center had a sufficient number of cases to contribute to any future investigations and that taken together the centers provided global representation, in particular with respect to economic status. Table 1 includes details of the institutions invited to join the network, along with the center representative.

Table 1: Centers identified for invitation to a two-day workshop at IARC

Country	Institution/Center/Hospital	Contact/Representative
Argentina[2]	Institute Nacional del Cancer, Buenos Aires, Argentina	Florencia Moreno
Australia[2]	Molecular Epidemiology Group, Children's Cancer Institute, Sydney, Australia	Leslie Ashton
Brazil	Institute de Cancer (INCA), Rio de Janeiro, Brazil	Maria Pombo-de-Oliveira
China	Capital Institute of Pediatrics, Beijing 100020, China	Xiadong Shi
Denmark	University Hospital Rigshospitalet, Copenhagen, Denmark	Kjeld Schmiegelow
Egypt	Children's Cancer Hospital, Cairo, Egypt	Sameera Ezzat
Germany	University Children´s Hospital Muenster, Münster, Germany	Claudia Rössig
India	Cancer Institute (WIA), Chennai, India	Rajaraman Swaminathan
India	Dr. B.R.A. Institute Rotary Cancer Hospital, New Delhi, India	Sameer Bakhshi
Japan	Tokyo Women's Medical University, Tokyo, Japan	Naohito Yamaguchi
Jordan	Department of Pediatrics, King Hussein Cancer Center, Amman, Jordan	Faris Madanat
Kenya	Kenyatta National Hospital, Nairobi, Kenya	Walter Otieno
Republic of Korea	Seoul National University Children's Hospital	Hee Young Shin
Russia	Federal Scientific Clinical Centre of Pediatric Hematology Oncology Immunology, Moscow, Russia	Kachanov Denis Yurievich

[2] Unfortunately were unable to attend the meeting but remain part of the network

South Africa[2]	Charlotte Maxeke Johannesburg Academic Hospital and University of the Witwatersrand, Johannesburg, South Africa	Janet Poole
South Africa	Department of Pediatrics & Child Health, University of the Free State, Bloemfontein, South Africa	Karlien Rautenbach
Turkey	Pediatric Hematology Division, Hacettepe University, Ankara, Turkey	Selin Aytac
UK	Department of Pediatric Hematology & Oncology, Leeds General Infirmary, Leeds, UK	Sally Kinsey
USA	Department of Pediatrics and Masonic Cancer Center, Minneapolis, USA	Logan Spector

5. International Childhood Leukaemia Meeting, IARC February 21-22nd 2013

In addition, to establishing an international network for a multi-disciplinary study of childhood ALL, a major objective of this project was hold a meeting/workshop with representatives from the network. As such, a two day meeting on February 21/22nd 2013 was held at IARC (Lyon, France) to discuss and develop new strategies for future epidemiological investigations to further our knowledge and understanding of the causes and outcomes of childhood leukaemia. Prior to the meeting representatives from each of the selected centers were asked to provide a presentation containing more detailed information about their center, building on what was already collected as part of the pilot questionnaire. The template for this presentation can be found in Appendix III.

The list of participants that attended the meeting includes all those in Table 1 (unless otherwise stated), in addition, to members of the steering group and individuals listed below. The agenda, minutes of the meeting and a full list of participants are provided in Appendix IV.

- Alice Kang, University of California, Berkeley, USA: Representing the Childhood Leukaemia International Consortium (CLIC https://ccls.berkeley.edu/clic/)
- Dr Terry Dwyer, Senior Visiting Scientist, IARC: representing the International Childhood Cancer Cohort Consortium (I4C - https://communities.nci.nih.gov/i4c/default.aspx)
- Dr Gunde Ziegelberger, Bundesamt für Strahlenschutz, Germany
- Dr Helen Bailey, Section of Environment & Radiation, IARC
- Dr Rachel Denholm, Section of Environment & Radiation, IARC
- Dr Eva Steliarova-Foucher, Section of Cancer Information, IARC

Photo: Childhood leukaemia meeting, 21st-22nd February 2013, IARC, Lyon, France

6. Development of a study protocol

The final objective of the project was to develop a study protocol based on the conclusions of the network meeting in order to provide new strategies for future investigations of childhood leukaemia. One of the main aims of the protocol was not only to provide ways in which to further our knowledge and understanding of the disease but importantly establish a framework in countries where resources are limited by which to provide help in dealing with the burden of the disease. In order to achieve these goals a series of distinct, yet complementary work-packages (WP's) each with its own aims and objectives and timescales for completion have been put together. The delivery of such a programme of work requires intrinsic knowledge and hands on experience of the challenges that childhood leukaemia poses in different parts of the world. As such WP1 (see document 2 – proposed study protocol) aims to extend further the achievements of this pilot project by formalizing the network and by reviewing its composition to ensure that it does provide the level of global representation required to undertake WPs 2-4. Key to this is creation of a members website and a follow-up meeting scheduled for 2014. WP's 2&3 are very much targeted towards trying to more accurately determine the incidence and outcome of childhood leukaemia by conducting detailed investigations at specific centers with reliable demographic data, and by using on-line data entry programs to facilitate global data collection and real time data capture from participating centers over a 2 year period. Additional features of these WP's are to look at leukaemia subtypes, as well as patterns in relation to age and sex and collect detailed information throughout the patient pathway as well as biospecimens wherever possible. WP4 is focused on disease outcome and the development of new protocols for use in low-income countries. This will also involve establishing twinning arrangements between centers for diagnosis and treatment and providing educational support and resources for centers and families.

The study protocol was developed as separate deliverable to this final report.

Appendix I Additional project information

During the period of this project (01.03.13-31.05.2013) Dr Tracy Lightfoot, University of York, York, United Kingdom, held a Senior Visiting Scientist position at IARC. She provided scientific direction for the projects and visited IARC on the following dates:

- 29.02.2012- 02.03.2012
- 07.05.2012 - 18.05.2012
- 11.06.2012 – 22.06.2012
- 02.07.2012 - 13.07.2012
- 27.08.2012 – 31.08.2012
- 15.10.2012 - 19.10.2012
- 14.01.2013 - 17.01.2013
- 03.02.2013-07.02.2013
- 18.02.2013-27.02.2013
- 24.03.2013-28.03.2013
- 12.05.2013-16.05.2013

Childhood Leukemia Meeting

9-10 July 2012

IARC, Lyon, France
Calum Muir Lounge

AGENDA

Monday 9 July 2012

14:30-14:45	Welcome and introduction of participants, J. Schüz
14:45-15:30	Outline of the project, J. Schüz
15:30-16:00	**Coffee break**
16:00-16:30	Hypotheses to be addressed and discussion, T. Lightfoot
16:30-18:00	Continue discussion of hypotheses (All)
20:00	**Dinner**

Tuesday 10 July 2012

09:30-10:30	Discussion of international network, L. Starr
10:30-11:00	**Coffee break**
11:00-13:00	Outline of possible study protocol (All)
13:00-14:00	**Lunch**
14:00-16:30	Further steps, next meeting (All)
16:30	Adjourn

Childhood Leukaemia Steering Group Meeting Summary
9-10 July 2012
IARC, Lyon, France

Participants:
Friederike Erdmann, Sally Kinsey, Tracy Lightfoot, Eve Roman, Claudia Rössig, Kjeld Schmiegelow, Martin Schrappe (MSc), Joachim Schüz, Martin Stanulla (MSt), Laila Starr, Marc Sultan (MSu)

Chair
Joachim Schüz

Rapporteurs
Friederike Erdmann, Laila Starr

Welcome and introduction of participants + Outline of the project
JS welcomed everyone to the meeting and gave a brief outline of the project's origin following the BfS workshop in Munich (August 2011) alongside the main aims and objectives. In summary, the primary aims of the pilot project are to establish an international network of clinical collaborators and develop a study protocol with a view to furthering our understanding of the pathogenesis of childhood leukaemia. JS emphasised that it was important firstly to ensure that we include countries across the spectrum of ethnic backgrounds and economic development, and secondly to design the study protocol to reflect what research should be carried out irrespective of the cost implications. With respect to the latter, if the study proposal is put together in a work package format then the BfS have the option to create their own "menu" of research.

Issues were raised in relation to other on-going research initiatives and possible duplication of efforts, what are the new questions that we want to ask and the timescale for delivery of such a project. It was agreed that we needed to look at leukaemia subtypes independently, as these are likely to have different underpinning biological mechanisms, different critical windows of exposure and, possibly different exposure risks (assuming there is an environmental impact). In addition it was agreed that a new protocol should be as comprehensive as possible with respect to environmental and genetic factors and the interaction between them. Further, it was agreed that projects would include all childhood leukaemis and not be restricted to lymphatic types.

Hypotheses to be addressed and discussion

TL gave a presentation "Childhood Leukaemia – what do we know & what do we want to know" (See Appendix 1 for slides). A summary of the known risk factors (age, sex, trisomy 21) was given, alongside details of existing collaborations in this field (CLIC, ACCIS etc) and the main areas to address (descriptive epidemiology, role of infectious exposure and the incidence of leukaemia associated chromosomal translocations at birth in newborns).

Areas of discussion included:

- The segregation of subtypes by age and the sex ratio (1.2:1, M:F) and MSt outlined on-going work he is involved in looking at specific genetic lesions and differences in frequency in relation to sex.

- Increasing incidence in economically developed countries – is this real, or is it because it is such a rare disease that errors in either the numerator or denominator could quite easily lead to a 1% increase being observed. Interestingly in the Nordic countries where there are excellent data-linkage systems no increase has been observed. It was acknowledged that determining if the incidence is increasing is difficult but nevertheless very important, and that patterns in relation to the specific subtypes should also be looked at wherever possible.
    - MSt suggested that he could address this question using German data from 2000 and calculating time trends.

- The patterns of incidence in economically developing countries, does the peak between 2-5 years exist? How do we capture this information - cancer registries are only as good as the information they have with respect to the actual number of cases that are registered and also the total population that the registry covers. It needs to be determined in the variations in incidence are real or mainly problems with reporting mechanisms. Also if geographical differences really exist, how does this relate to the different subtypes?
    - ER proposed that we could make predictions of the number of cases of ALL in developing countries by extrapolating data from developed countries.

- The role of infectious exposure in relation to ALL initiation and progression. Several hypotheses exist and whilst in essence they are all different, they could all act in parallel – ultimately however, they all pinpoint an important role for the immune system.

- What is the true frequency of chromosomal translocations at birth? Original research suggests that 1% of newborns have a ETV6-RUNX1 translocation at birth, however this has recently been disputed by a paper from Denmark that analysed over 1500 cord blood samples.
    - It was agreed that the screening of different ethnic groups as well as screening of larger populations (tens of thousands) needs to be carried out but that robust methodologies need to be established for doing so across different laboratories, and for validation studies to be incorporated.

- Other questions which need to be addressed
    - Why do some children not respond to therapy?
    - Should we also be looking at AML and lymphomas?
    - The role of epigenetics?

Discussion of an International Network

LS gave a presentation on the "potential international network partners and preliminary questionnaire results".

Countries were initially identified to display geographical and economical spread and within these categories based on having a member of the team having a previous contact, links with IARC or identified from the literature as having some data. In addition, wherever possible clinical collaborators were identified as opposed to cancer registries for the reasons outlined earlier.

Particular noteworthy points in relation to the specific countries are as follows:

- Argentina – there is an option to look at population based data, and the denominator is fairly accurate.
- Brazil – the contact identified only has access to one particular region.
- India – CR also recommended contacting Bharti Agarwal. SK has also sent the questionnaire to 3 of her contacts. There is clearly variation in India and the question is do we have more than one contact in India to try and build up the bigger picture?
- Jordan – there is only one treatment centre and therefore probably as close as we can get to a national registry.
- Kenya – the contact here represents the largest of the three centres.
- Oman – given the size of the population (2.77 million) it was decided that whilst it's clearly a country of interest it is probably too small.

It was agreed to select a minimum of 8 countries in which to pursue further investigations.

Outline of a possible study protocol

In terms of study design the following points were identified as important for consideration in the next steps of the project:

- Introduction of a family questionnaire/interview – this would include questions on lifestyle, symptoms of the child prior to diagnosis and would hopefully aid in our understanding of the natural history of the disease in each country.
- Introduction of surrogate questions in order to assess the reliability of the data
- Access to biological specimens
- Subtyping of leukaemias - would this be carried out locally or would a central reference laboratory be set up? If it was possible to set this up locally and an establish an infrastructure for doing so within a country then this could be an attractive proposition for countries to be involved. However, this would clearly have bigger resource implications.

It was also agreed to communicate with SIOP to make them aware of the project and to aid in identification of any key contacts.

Further steps

It was agreed that we want to establish a network of heterogeneous countries to investigate the global distribution of leukaemia subtypes.

How do we progress forward from here?

- Hold a bigger meeting and invite collaborators/contacts from selected countries early in 2013
- Develop a new questionnaire to collect additional information from contacts, in particular in relation to biospecimens, and other co-morbidities and competing causes of death (e.g HIV, malaria).
- Design a questionnaire for the parents to complete
- KS to prepare a paragraph about the main leukaemia subtypes we want to investigate (also include AML and NHL?).
- Prepare a review article on the global incidence of childhood leukaemia
- Prepare a hypothesis paper to summarising our views on the direction of future childhood leukaemia research
- Finalise countries to be included (this will partially depend on those who completed the preliminary questionnaire – at present includes Argentina, Germany, Jordan, India, Kenya, South Africa, South Korea, Taiwan & Turkey)
- Draft study proposal
    - Clarify what biological we want to bank for the future

Appendix III Pilot Questionnaire

Childhood Leukemia Questionnaire

1. Disease specific information and demographic information

What is the upper age limit of children diagnosed/treated in your facility? years

Overall what is the estimated number of total childhood leukemia cancer cases diagnosed/treated per year in your facility?

Of those childhood leukemias, what is the estimated proportion of lymphocytic leukemia (ALL)? %

What is the estimated proportion of boys: girls with ALL? % boys

In terms of the age distribution: How many cases are diagnosed each year (approximate numbers are sufficient)?

< 1 year

1 - 5 years

6 - 9 years

10 -14 years

>14 years

2. Treatment coverage

Please describe the coverage area of your facility (population coverage, completeness of coverage, etc):

What is the maximum distance that a child with leukemia has to travel to reach your facility? km

What are the other treatment facilities available in your coverage area?

What is the estimated childhood population in the area?

Who pays for the treatment?

3. Treatment protocol & follow-up

Please describe the normal treatment for ALL (which drugs are given, what is the clinical care, etc):

Are you normally in touch with the patient after treatment? Yes ☐
No ☐

What happens after the treatment?

4. Facilities (please fill in with approximate numbers if exact numbers are not readily available)

How many pediatric beds are there in your facility?

How many pediatric oncologists are there in your facility?

How many pediatric oncology centers are there in your country?

5. Potential future collaboration and studies

Would you be interested in participating in future studies? Yes ☐ No ☐

If yes, which phone number can we reach you on?

Would it be you personally ☐ yes or a colleague we should contact?

Please provide name and e-mail of colleague:

Do you have any medical record data from the past 5 years? Yes ☐ No ☐

If so, are they available in electronic form? Yes ☐ No ☐

Do you have any biospecimens stored? Yes ☐ No ☐

If so, what kind?

Do you or have you collected neo-natal blood spots? Yes ☐ No ☐

Appendix IV Powerpoint template for completion by centers prior to IARC February 2013 meeting

Childhood Leukemia in (country)

(name of presenter)

International Agency for Research on Cancer
Lyon, France

Country presentation

- Provide an overview of the health care system in your country related to paediatric haematology/oncology
  - Describe the differences between the private versus public sector
  - Who pays for diagnosis/treatment?

International Agency for Research on Cancer
World Health Organization

Catchment area

- Please give your impression of the catchment area of your hospital compared to the background population or the entire country e.g
  - age
  - sex
  - socio-economic status
  - urban/rural status
  - ethnicity
  - religious

International Agency for Research on Cancer
World Health Organization

Hospital or Network Description

- Describe your facility, e.g.:
  - How many pediatric oncology beds are there?
  - How many physicians look after children with cancer?
  - etc.

International Agency for Research on Cancer
World Health Organization

Diagnosis and referral (1)

- What is the process for how children with leukaemia get referred to the hospital?
- How far do they have to travel to get to the hospital both with respect to time and distance?
- What are the available means of transport and how much does it cost?
- What methods are used for diagnosing the leukaemia?

International Agency for Research on Cancer
World Health Organization

Diagnosis and referral (2)

- Is it your impression that your hospital sees all cases?
- If not, are there differences between those who do get referred and those that don't, e.g. in respect to age, sex, social economic status, where they live, ethnicity, religion, etc.
- Who decides which hospital the children with leukaemia are treated at?
- Are there other hospitals in the catchment area, either private or public that see childhood leukaemia cases?
- If so what proportion are referred elsehwhere?

International Agency for Research on Cancer
World Health Organization

Treatment (1)

- Describe how children with leukaemia are treated?
- Is there a specific protocol that is followed?
- Are all the children treated with the same protocol?
- Are there any children who do not get treated and if so what are the reasons for this?

Treatment (2)

- How much contact do you have with the family during treatment?
- Once the treatment is finished how much contact do you have with the family?
- Which means of communication do you use to keep in touch with the family?
- How long do you continue the follow-up?
- Are there any who do not get treatment? What is the main reasons herefore?

Number of patients

- Approximately, how many patients with leukaemia do you see per year?
- Is it possible to also obtain information on subtype? If so how many ALL, AML?
- What is your impression of the age and sex distribution of children with ALL?

Research infrastructure

- Do you have:
  - Patient records (electronic or paper) that can be accessed?
    - If so, for how many years?
  - Information on leukemia subtypes?
  - Contact information for the families with leukemia patients?
    - If so would it be possible to contact any of them?
  - Any biospecimens available?
  - Any other information you think could be of interest?
- Future:
  - What are the ethical requirements in your country for contacting families or accessing patient data or biospecimens?
  - Would it be possible to build up a database and/or biobank? Do you have storage facilities for biospecimen? Which testing facilities are available? Would you be able to ship biospecimen to abroad partners?

Future

- What are your hopes and expectations for attending this meeting and joining this network?

International Agency for Research on Cancer

World Health Organization

Summary report from the Childhood Leukemia meeting

21st to 22nd of February 2013

International Agency for Research on Cancer

Lyon, France

Host: Section of Environment and Radiation

Table of Contents

List of participants

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International Agency for Research on Cancer

World Health Organization

Childhood Leukaemia Meeting

21 to 22 February 2013

IARC, Lyon, France

AGENDA

Thursday 21st February

09:00-09:30	**Welcome**	Christopher Wild & Joachim Schüz
09:30-10:00	**Introduction of participants**	
10:00-10:30	*Coffee break*	
10:30-10:45	**Characteristics of participating countries**	Laila Kærgaard Starr
10.45-13.00	**Country specific presentations** Country presentations Catchment area	All participants
13:00-14:00	*Lunch break*	
14:00-15:00	**Country specific presentations** Hospital/network description, patients, and Diagnosis & referral	All participants
15:00-15:30	*Coffee*	
15:30-16:00	**Country specific presentations** Hospital/network description, patients, and Diagnosis & referral (cont.)	
16:00-18:00	**Group sessions "Identifying Research Priorities"**	
16:00-16:15	Introduction to group sessions	Joachim Schüz
16:15-18:00	Group sessions "Identifying Research Priorities"	All participants

Friday 22nd February

09:00-10:00	**Country specific presentations** Treatment	All participants
10:00-10:30	*Coffee*	
10:30-11.30	**Country specific presentations** Treatment (cont.)	All participants
11:30-12:00	**Siblings and leukemia**	Kjeld Schmiegelow
12:00-12.30	**Summary of group work and discussion**	Moderator: Tracy Lightfoot

12:30-13:15	**Country specific presentations** Research infrastructure	All participants
13:15-14:15	*Lunch*	
14:15-16:00	**Next steps and future directions**	Moderator: Joachim Schüz
16:00	**Meeting close**	

Minutes

Welcome

The meeting was opened by Joachim Schuz (JS), Head, Radiation & Environment Section, IARC, and Christopher Wild (CW), Director, IARC. The Director emphasized the importance of establishing global networks to undertake research of this kind, and how this project complements IARC's strategy by including counties from across the world at all levels of economic development. JS outlined the background to the project, alongside the plan for the 2-day meeting. Participants were encouraged to actively participate in discussion and ask questions, with the aim to create a more informal meeting to allow ideas and experience to be shared openly. The aims and objectives of the meeting were to create networks for future investigations, establish clinical links between centers, and develop a study protocol for future investigations.

Characteristics of participating countries

Laila Kærgaard Starr (LKS) described how the participating partners had been selected, and gave an overview of the demography and estimated childhood leukemia incidence of their respective country. It was emphasized that incidence data were only estimates as cancer registries do not have global coverage and therefore not all cancer cases will be registered, in addition not all cancer cases will make it to the clinical setting.

The heterogeneity of childhood leukemia was discussed and it was agreed that there was a need, wherever possible, to have immunophenotype data to see if there are differences with respect to the incidence of the different subtypes. It was put forward that even within a country there may be differences with respect to the immunophenotype which is important both with respect to looking for risk factors but also for treatment.

Country Specific Presentations:

Prior to the meeting each participant had been asked to prepare a presentation to include information on the following: healthcare systems, catchment area covered by their center, a description of the clinical facilities available, how children were referred to their center, diagnosed and treated, and what infrastructure was in place for future investigations (e.g. biospecimens, clinical data etc). In order to compare and contrast between the centers/countries, and facilitate discussion, each of these aspects was considered separately

with each participant presenting their own data/information. More details are available on the slides which will be made available via the web.

Healthcare systems

It was evident from the participants presentations that there was a great deal of heterogeneity between countries in terms of their population size, healthcare system set-up, including how many patients have to pay to be treated, what the percentage of private care in each country is, how many patients per center are diagnosed/treated, and how many other centers there are nearby. In summary, in some countries, it was clear that trying to find sufficient funds for treatment was very difficult and dependent on family help.

Catchment area

Each participant described the catchment area covered by their centres and there was clear variation with respect to many of the features described including age, sex, religion, socio-economic profile, urban/rural status etc.

Hospital network description, Patients, and Diagnosis & referral processes

Each of the participants described their hospital or network in terms of size (number of pediatric beds, number of physicians/pediatric oncologists, etc.), how many patients with leukemia they see per year, and how these differ with respect to age, sex and subtype, assuming subtype information is available. It was apparent that some centers treated only a small number of cases each year, whilst others had a very high throughput. Facilities also varied between centers with respect to the number of beds, family houses, as well as the number of clinical staff and treatment availability. Participants also outlined how children were referred to their center, and what methods were used to diagnose the leukemia. In some centers, availability of free beds dictated whether or not children were referred elsewhere, with families also allowed to choose which center they go to. There were large differences in the distance and time it takes families to travel to the center ranging from 30 minutes to over a day, with different methods of transport used - walking, car, plane, train and even helicopter - and variable financial support provided. In addition, some of the centers also received patients from neighboring countries. Differences were apparent between centers with respect to the age and sex distributions of the cases diagnosed, as well as the leukemia subtype.

Treatment

Each of the participants described how the children were treated, what protocol (if any) was used as a basis for treatment and if children weren't treated what were the reasons for this. In addition, they outlined the extent and nature of contact and communication with the family, both during treatment and follow-up and how long the families were followed up for.

In countries where clinical trials exist, generally more than 90% of children were entered on to them. The protocols used included those from St Jude's, IBFM and COG, with some centers developing their own in collaboration with others (e.g. the common Nordic protocol, the Moscow-Berlin protocol). Generally when children are not treated this is due to financial

reasons, and the economic constraints of the family e.g. having to miss work. Follow-up occurred in most centers for varying amounts of time and with varying levels of success. In some cases maintaining contact was very difficult, especially in light of the vast distances that some families had to travel for treatment.

There was discussion about developing a protocol for less economically developed countries which would provide a means by which to treat the children with medications that are more readily available and accessible, in particular with respect to cost.

Research infrastructure

In order to be able to identify possibilities for future investigations, participants described their research infrastructure. This included information about patient record accessibility, leukemia subtype, family contact details, availability of bio-specimens and their storage, as well as the ethical constraints governing access to both data and samples. Generally, patient records were available in many centers, some paper based and others electronic. Access to bio-specimens was more problematic with some centers not having the capacity to store them and access to them being heavily governed e.g. difficulties in shipping them outside their country. In addition, although for the most part data were fed through to cancer registries, in Kenya, for example, this did not occur as the links between the hospital and the cancer registry do not exist.

Group Sessions "Identifying Research Priorities"

Participants were divided into three groups to discuss the following questions. The suggestions and ideas that arose in the group sessions formed the basis of the study protocol which will be circulated to all participants for comment. It was emphasized that at this stage to not think about the financial implications but concentrate on what to do in an ideal world.
Potential research questions to be discussed during group sessions:

1. Appreciation of world view
2. Is the incidence the same?
3. Is there a gender difference?
4. Are the immunophenotyping features the same?
5. Are the genetic characteristics the same?
6. Is it possible to increase global access to treatment for children with leukemia?
7. Is it possible to recommend "reasonable" treatment and monitoring protocols?

	Group 1	Group 2	Group 3
Moderators	Joachim Schüz	Kjeld Schmiegelow	Claudia Rössig
	Martin Stanulla	Sally Kinsey	Eve Roman
	Sameer Bakhshi	Tracy Lightfoot	Walter Otieno
	Selin Aytac	Maria S. Pombo-de-	Faris Madanat
	Sameera Ezzat	Denis Kachanov	Xiaodong Shi
	Eva Steliarova	Karlien Rautenbach	Logan Spector
	Naohito Yamaguchi	Hee Young Shin	Rajaraman Swaminathan
	Terence Dwyer	Gunde Ziegelberger	Marc Sultan
	Friederike Erdmann	Helen Bailey	Alice Kang
		Rachel Denholm	Laila Kærgaard Starr

Summary from Group 1:

It was agreed that it is difficult to interpret the data shown by different hospitals and institutions, but that having good incidence data was important. However, there is still the issue that some cases may never even enter in the system through not turning up at clinic, and therefore the incidence will always be underreported. In order to investigate the variations in leukemia incidence, it might be a good starting point to look at immunophenotype, as this information is broadly available, and look at ratios between different types as it is possible that underreporting/underdiagnoses is non-differential. It was also suggested to focus on getting good incidence data for certain regions or cities (e.g Tokyo, Cairo, New Delhi) and compare with the observed hospital based data. Generally it was acknowledged, that trying to get this data may require using one or more different methods that needed to be adapted to that particular country/region. In addition, establishing and maintaining good links, between clinicians, epidemiologists and cancer registries is clearly important.

Summary from Group 2:

It was agreed that future investigations should focus on outcome as well as incidence. Concerns were raised about the true incidence as some cases were most likely missed, possible due to co-morbidities. It was suggested that expected rates could be calculated and cross checked with what countries/regions were seeing, or alternatively identify an index leukemia e.g. t(9;22) and compare the number of this subtype with others and look at the ratios. However, whilst in principle this seemed a good idea –it is dependent on collecting the correct data. It was also felt important to increase global awareness of cancer symptoms.

It was proposed to establish a global database with each center adding information about their cases; e.g. age, white cell count, treatment, T/B-cell disease, outcome, genetic abnormalities etc, which would allow us to ascertain if the disease is the same across different regions of the world. In addition, it was suggested that a protocol is developed for use where resources were

limited by identifying the keys drugs and timepoints – ideally this would be endorsed by IARC/WHO.

It was observed that there was an over-representation of high-income countries in the network and hence there is a need to ensure that enough low-income countries are included. Ideally each of these low-income countries would be visited to understand the issues faced with referral and diagnostic processes, sample collection, infrastructure etc. with one option being to set up partnerships between institutes to ensure transfer of knowledge and support mechanisms. The group felt that local centers needed to benefit from their involvement in such initiatives.

Summary from Group 3:

The group agreed that in order to answer these basic questions valuable data has to be collected and an obvious challenge is childhood leukemia registrations i.e. what are the absolute numbers and subtypes. However, it's not just about characterizing the number of cases of leukemia but also getting the denominator right. In addition, it was suggested to set up population based registries for childhood leukemia. It was agreed that some cancer registries at present may not be capturing all of the information required to answer some of the questions we are interested in. In addition, capturing cause of death can be difficult in some countries as well. Having a systematic way of collecting biological samples for future research was also thought to be important. Twinning programmes could also help in training staff, developing staff training programmes, and establishing new protocols and procedures. There was also discussion about screening tests for early detection but it wasn't clear how this would aid in preventing or treating the disease. It was agreed that having standardized immunophenotyping would also help in looking at differences.

The group was reminded that whatever activities are taken forward that they need to benefit the children and have to able to be implemented in a realistic way. It was agreed that if a study was set up, that it needs to include looking at treatment and outcome too. It was suggested to look at the prevalence of leukemia translocations in the cohorts, but it was unclear whether I4C was already doing similar studies.

Group Discussion

It was agreed that the questions posed are difficult to address, and that the existing information available maybe biased. It was recognised that help seeking behaviour of the families is very much tied with what is available to them and that this in turn impacts on health outcomes. It's important that any future initiatives are targeted towards helping the patients and families, and the consensus was that it would be difficult to do

Expectations

At the end of the meeting participants were invited to outline their expectations for the future of this network. There was an overwhelming consensus that the group had enjoyed the meeting and that it was a privilege hearing about other's experiences and the openness with which they

had shared these. It was felt that it had been a great learning experience and a fantastic opportunity to brainstorm. Finally everyone agreed that a good start had been made, and everyone was looking forward to developing collaborations and working together, and hoped that the meeting could become an annual event.

| Verantwortung für Mensch und Umwelt |

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