Strahlenschutzkommission

Geschäftsstelle der
Strahlenschutzkommission
Postfach 12 06 29
D-53048 Bonn

http://www.ssk.de

Research of the causes of leukaemia in children and adolescents

Recommendation by the German Commission on Radiological Protection

Adopted at the 288th meeting of the German Commission on Radiological Protection on 19 and 20 June 2017

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Ursachenforschung zu Leukämien bei Kindern und Jugendlichen

Empfehlung der Strahlenschutzkommission

CONTENTS

1 Introduction

In Germany, every year, approximately 650 children and adolescents under the age of 18 develop leukaemia and related diseases[1]. Leukaemia and related diseases account for 31 % of all cases of cancer in children and adolescents under the age of 18 in Germany (approx. 650 out of approx. 2 100 cases per year). 75 % (nearly 500 per year) of these are lymphatic leukaemia, LL, (to date, also often referred to as acute lymphatic leukaemia (ALL) as the non-acute LL forms are extremely rare in children and adolescents) with the most common sub-form being precursor cell lymphoblastic leukaemia (pre-B cell, 73 % (approx. 450 per year) of all cases of leukaemia in children and adolescents), also referred to as c-ALL (common ALL), the most common oncological single diagnosis in children and adolescents. The peak age for LL is between one and four years of age. Another 14 % (nearly 100 per year) are attributed to acute myeloic leukaemia (AML) where the peak age is in the first two years of life. The remaining 11 % are divided up among myelodysplastic syndrome (MDS, approx. 50 per year), a disease that also occurs in adults; chronic myeloproliferative leukaemia, which is extremely rare in children (approx. 10 per year) and is the leading malignant hematological disease among adults and other rare malignant forms (under 10 per year). To date, causal research in children has focused on LL or, in a narrower sense, on precursor cell leukaemia (Kaatsch and Spix 2014).

With respect to non-ionising radiation (low-frequency magnetic fields), there is evidence of an increased risk of leukaemia in children with measured or projected exposures of 0.4 µT or higher, which, however, occur very seldom (Ahlbom et al. 2000). In the pooled analysis of 9 large-scale studies, considerably less than 1 % of the test subjects had been introduced to such high exposure.

It is considered proven that ionising radiation can in principle cause leukaemia in children. According to the present level of knowledge, an absolute risk coefficient for leukaemia of no more than 0.03 %/10 mSv is assumed for children under the age of 15 (SSK 2011). In its assessment of the epidemiological study on cancer in children in areas around nuclear power plants (KiKK study), the German Commission on Radiological Protection (SSK) came to the following conclusion: "The additional radiation exposure attributed to the nuclear power plants is well over 1 000 times lower than the amount of radiation exposure capable of giving rise to the risks reported on in the KiKK study." (SSK 2008). It determined that "further, interdisciplinary research of the causes and mechanisms leading to the development of childhood leukaemia is necessary".

Until 2016, the Federal Office for Radiation Protection (BfS) carried out five international workshops with the goal of developing a strategic research plan to further clarify the aetiology of childhood leukaemia (Matthes and Ziegelberger 2008, Ziegelberger et al. 2011a, b, Laurier et al. 2014). Based on the second workshop, the BfS initiated five preliminary studies whose goal was to investigate whether the respective recommended approach effectively contributes to clarifying the complex causes of leukaemia in children and adolescents and whether a recommendation for conducting future studies can be derived from it. In a letter dated 30 March 2015, the Federal Ministry for the Environment, Nature Conservation, Building and Nuclear Safety (BMUB) asked the SSK for a recommendation "as to whether continuation of these or

[1] In paediatric oncology, diseases are classified according to the International Classification for Childhood Cancer (ICCC) (Steliarova-Foucher et al. 2005). Lymphatic leukaemia, acute myeloic leukaemia, chronic myeloproliferative diseases, myelodysplastic syndrome and other malignant forms of leukaemia belong to the category I of "Leukaemias, myeloproliferative and myelodysplastic diseases" referred to here.

similar studies is necessary and conducive to clarifying the causes of cancer and whether further or other approaches should be taken in this respect."

On 16 June 2015, the BfS presented the individual preliminary studies to the "Radiation Risk" committee of the SSK. The studies will be briefly evaluated and their outlook described below followed by a recommendation as to the further course of action.

2 Evaluation and further outlook of the individual preliminary studies

2.1 National birth cohorts

Summary:

In the preliminary study, the feasibility of a birth cohort including an analysis of the umbilical cord blood with prenatal recruitment in Germany is to be investigated. The design of the planned birth cohort was, on one hand, to be set up on the basis of the design already developed for a German birth cohort (Schmidt et al. 2012) and, on the other hand, to be reconciled with the basis design of the cohort studies of the "International Childhood Cancer Cohort Consortium (I4C)" to the extent possible (Brown et al. 2007). It was possible to determine basic feasibility. Recommendations were issued as to how the response of 24 % can be improved and how women with a migrant background or from low-status social groups can be reached.

Final report: Zeeb et al. (2016). A publication of results can also be found in Ernst et al. (2015).

Evaluation:

A birth cohort including the analysis of umbilical cord blood in Germany is feasible. Measures to achieve a high level of participation, particularly among less educated groups of the population, must be defined. If a birth cohort is established in Germany (Schmidt et al. 2012), it generally makes sense to include questions regarding childhood cancer because this could be achieved with limited effort. Within Germany, cases of leukaemia can be identified in cooperation with the German Paediatric Cancer Registry. Due to the considerable financial and logistical effort, an extended pilot phase should be provided for where all instruments are tested in advance and international experiences with setting up birth cohorts is processed specifically for Germany. There are specific experiences from successful (Japan, JECS[2]) and unsuccessful (Switzerland, USA) large-scale birth cohort projects (Kawamoto et al. 2014, SNF 2009, NRC and IOM 2013).

[2] Japan environment and children's study (JECS)

2.2 Pediatric-oncological network

Summary:

The incidence rate for childhood leukaemia is significantly lower in less developed countries than in western industrialised countries (Parkin et al. 1998). It is unclear what portion thereof is attributable to living conditions on one hand or insufficient diagnosis and underreporting on the other hand. In the preliminary study, contact was established with centres from less developed countries and information from said centres was compiled. Overall, the customary practice suggests that insufficient diagnosis and underreporting of ALL frequently occurs in developing countries. However, it is difficult to assess the extent to which actual ALL incidence is underestimated. Generally speaking, the network would allow for a comparison of western cases with cases involving significantly different living conditions.

Final report: Lightfoot et al. (2016)

Assessment:

The newly established international network can provide for new research approaches that cannot be carried out at a national level. As a result, it is e.g. to be expected that the sub-type distribution in various countries will allow for conclusions regarding genetic and environmental risk factors.

The questions prepared for this focus appear to be spread too widely or are in part redundant. The simple documentation of incidence rates worldwide is institutionalised around the world. Soon, the International Agency for Research on Cancer (IARC) in Lyon will publish, for die World Health Organization (WHO), the overview IICC3 (International Incidence of Childhood Cancer, 3rd edition), a comprehensive collection of incidence data on cancer in children and adolescents worldwide. At least the question regarding different age distributions can therefore be considered without the need for specific large-scale project. Improving the clinical infrastructure and establishing a network of paediatric oncologists in low-income countries is in principle a goal worth pursuing, but would go well beyond the scope of the question (research of causes of childhood leukaemia). There is no mention of a cooperation with the International Society of Paediatric Oncology (SIOP).

An increase in the overall incidence and especially the peak age between one and four years of age with increasing affluence and a lower birth rate was described on multiple occasions, also between European countries or within countries with rather reliable documentation of cases such as e.g. in Great Britain or the Czech Republic (Coebergh et al. 2006, Hrušák et al. 2002, Kaatsch 2006, McNally et al. 2001). Figures from 1911 on are available in Great Britain (Shah und Coleman 2007). Particularly in Germany, the numbers for the territory of the former GDR before 1990 tend to be approx. 25 % below those in West Germany. Following reunification, the incidence rates within the territory of the former GDR from 1991 to approximately 1997 increased to the rate reported in former West Germany (Spix et al. 2008). One of the changes to the living conditions of children within the territory of the former GDR is the substantial and sudden decline in the birth rate after 1990 such that in the 1990s, children grew up much more often in one-child families compared to before 1990. This is consistent with the observations described on multiple occasions in case-control studies on childhood leukaemia that siblings, particularly older ones, can reduce a child's risk of developing leukaemia (Eden 2010, Rudant et al. 2015). Therefore, one can assume that the even lower incidence rates in developing countries are only partially due to underreporting and in part to the different living conditions of the children.

2.3 Sequencing of 10 cases of acute lymphoblastic leukaemia

Summary:

Specific translocations and aneuploidies are often the first step to developing leukaemia in children and adolescents, to which further genetic and/or epigenetic changes have to follow for the disease to break out. The genetic differences between two selected types of leukaemia with different translocations were described in each five cases each with next generation sequencing. The complex methods required would have to be developed further and their quality assured before widespread future application.

Final report: Stanulla et al. (2015)

Evaluation:

New advancements in technology and information with respect to the collection and analysis of data from genomic deep sequencing have made it possible for the study group to specify, with a high degree of accuracy, genomic changes of cases of acute pre-b cell lymphoblastic leukaemia occurring in childhood. The decision to use five cases with the translocation t(17:19) and five cases with the translocation t(1:19) addresses the urgent need of clinical medicine to understand the inherent differences between individual patients. The preliminary study constitutes certainly a significant advancement in this area. Multiple interesting genetic markers have been identified, which could be used to select possible therapies in the future, such as is already the case with gene translocations in the treatment of adult leukaemia.

The study used a series of analytical techniques (genome and exome sequencing, analysis of the mRNA transcriptome, miRNA transcriptome and epigenome) in order to provide the most comprehensive input for bioinformatic analyses. The results of the analyses on the genome, exome, mRNA transcriptome, miRNA transcriptome and epigenome are presented and discussed in the final report (Stanulla et al. 2015). The results have not yet been integrated at the system level. This requires substantial methodological effort, which could not be provided for in this preliminary study with respect to time. Overall, the anticipated evidence for differences between the two selected ALL-subtypes was provided and as yet unknown stem cell-like properties were identified that account for the substantial differences between the two leukaemia subtypes. It was possible to improve the understanding of the subtypes in a molecular and genetic sense. As part of therapeutic process, sequencing is now increasingly performed for all cases as standard procedure (Braggio et al. 2013). The method employed in the evaluated project does not, however, offer any direct starting point for improving the understanding of the aetiology of childhood leukaemia with respect to environmental factors.

2.4 Genomic Inverse PCR for Exploration of Ligated Breakpoints (GIPFEL)

Summary:

The controversy surrounding the incidence of preleukaemic clones has already existed for some time in the research of the causes of childhood leukaemia. Mori et al. (2002) described that the detection of known leukaemia fusion genes such as *TEL-AML1* or *AML1-ETO*, in umbilical cord blood occurs 100 times more often than the risk of developing the corresponding leukaemia. However, these findings could not be confirmed by Lausten-Thomsen et al. (2011). The reliable identification of preleukaemic changes in newborns would have a far-reaching influence on further research on the causes of childhood leukaemia. Therefore, in the

preliminary study an innovative PCR[3] method (GIPFEL, genomic inverse PCR for exploration of ligated breakpoints) based on stable genomic DNA had to be developed in order to detect the most common leukaemia-specific translocations in clinical specimens such as umbilical cord blood without knowing the exact breakpoint.

The findings show a range of fluctuation with respect to sensitivity depending on the translocation type and complexity of the breakpoints; a high sensitivity was only reached for one of five fusion genes. The 100-percent specificity found is based on only few negative tests (ratio 1:1).

Final report: Borkhardt and Slany (2016). The project findings were also published in Fueller et al. (2014).

Evaluation:

The described genomic inverse PCR for exploration of ligated breakpoints (GIPFEL) is generally suitable for detecting translocations. The "stable" and relatively limited starting material (1 µg genomic DNA) can also be viewed as an advantage. However, unlike other techniques, only known partner genes can be identified, which was done successfully in the preliminary study for the five selected translocations. In a blinded proof-of-principle study of 144 children with B-cell ALL, the newly developed method was 100 % specific. The fact that the 100-percent specificity found is based on only a few negative controls (ratio 1:1) is to be viewed critically and it is imperative that it be confirmed through the inclusion of further negative controls (ratio 1:5 to 1:10). It is also critical that the required high level of sensitivity was only achieved for one of five fusion genes (MLL-AF4, 83 %) so that the sensitivity of the method has to be increased and further possible error sources have to be explored. The use of GIPFEL in a screening programme could only be recommended if its validity can be proven; for this, the 100-percent specificity must be proven by means of adequate control experiments and, at the same time, the sensitivity for other fusion genes must be increased.

For this, a follow-up project has been underway since the end of 2014; the findings are not yet known. If the sensitivity of the method is shown to be adequate, a robust and relatively low-input method is available for prospective study approaches.

[3] PCR: polymerase chain reaction

2.5 Literature study of animal models

Summary:

Background and objective: A suitable animal model can significantly contribute to investigating the mechanisms leading to initiation of leukaemia, the role of further 'hits', their kinetics and age dependency. In this project, an overview of existing animal models was to be prepared as a literature study. All models and forms of leukaemia were to be considered in general; the main focus was, however, on mouse models and ALL. Furthermore, an evaluation of the models had to be performed and any further developments as well as aspects and possibilities lacking to date had to be outlined.

Findings**:** The most important models and the resulting findings in leukaemia research were summarised in an overview and published as a review article for the international scientific community in a respected professional journal (Hauer et al. 2014). The literature study explains the development and use of different animal models, which are employed in leukaemia research and provides an overview of this subject area with over 220 citations. First, different forms of leukaemia are explained, then the findings and animals models are presented. The focus is then on mouse models, the arguments for this are discussed in detail. The weaknesses with respect to existing animal models were explained and the "ideal" animal model was developed theoretically as a logical consequence.

Final report: Borkhardt et al. (2015)

Evaluation:

A good overview of this narrow field of knowledge is provided. The problems with respect to transferring findings from mouse studies to people are described: A lack of comparability of conditions under which experimental animals are kept with the living conditions of people, high sporadic incidence rates as well as the difficulty of determining the chronology of genetic changes leading to the initiation of cancer.

Overall, the main problem associated with researching the causes of childhood leukaemia with animal models is attributed to the absence of a mouse version that has high similarity to childhood ALL in all developmental stages.

The Sca1-TEL-AML1 mouse model (ARIMMORA 2015, Schüz et al. 2016), which has recently been developed, was not yet available at the time of the final report for the preliminary study and therefore could not be considered in this evaluation.

3 Summarising assessment

The preliminary studies have provided valuable findings, which, however, due to the complexity of the material and the relatively small number of persons affected at this point in time, do not allow for a clear recommendation for a larger study exclusively researching the causes of leukaemia in children and adolescents. The research evaluated here reflects the status as of 2015. Since then, further developments have taken place in some of the fields.

3.1 Key findings from the preliminary studies

– It is possible to integrate the collection and storage of umbilical cord blood into a future birth cohort in Germany.

- The cooperation with paediatric oncologists from other, in particular developing countries, can provide findings that cannot be obtained on a national level.
- The genetic analysis used can clearly differentiate subgroups and identify essential differences in the activated or deactivated signalling pathways in the tumour cells.
- The "GIPFEL" protocol provides new approaches for identifying preleukaemic clones. The method requires substantial further development and validation. If sufficient sensitivity and specificity of the method can be demonstrated, for the first time a robust and relatively low-input method will be available for prospective study approaches.
- A comprehensive mouse model for ALL is not yet available.

3.2 Evaluation with respect to the main question

The preliminary studies on the birth cohort and on the international cooperation offer potential frameworks for study designs aimed at further investigating the question. So far, the lack of a suitable method for the reliable detection of rare preleukemic clones has been a significant obstacle for such studies (Ziegelberger et al. 2011a). GIPFEL could provide such a method after further development and validation. A large number of newborns would have to be examined for this. Deep sequencing is of substantial importance with respect to the further development of individualised therapies; its importance with respect to aetiological research is currently unclear. It is conceivable that the analyses reveal correlations with external risk factors in future. In general, suitable animal models could serve as a starting point for first studies exploring the role of environmental factors, such as e.g. electromagnetic fields, in ALL genesis.

The studies performed are not suitable on their own for achieving a breakthrough in etiological research. No preliminary study dealt with the role of the immune system, which many view as central with respect to the aetiology of ALL (Rudant et al. 2015, Wiemels 2012, Ziegelberger et al. 2011b). Possible synergies between the projects have not been used to date. One possibility would be to integrate an interdisciplinary approach of molecular studies into the further framework of a birth cohort that does not only include newborns, but also pregnant women. In connection with such projects, corresponding exposure measurements and/or an assessment of potential risk factors must be ensured. Another possibility would be initiating additional pilot projects on this topic.

3.3 Recommendation of the SSK

In order to detect relevant risk factors for rare diseases like childhood leukaemia, in general a sufficiently large number of participants as well as the broadest possible range of the most important risk factors must be determined, which presumably could only be achieved in a European or global association or in cooperation with an existing association. One such existing research association currently is the International Childhood Cancer Cohort Consortium (I4C). For scientific reasons (greater range of lifestyle factors), it is recommended that less developed countries be included.

With future pilot projects, it is advisable to tackle the role of the immune system and the open question of potential viral genesis (Eden 2010, Kinlen 2012, McNally und Eden 2004, Murray et al. 2002, Martin-Lorenzo et al. 2015, Rudant et al. 2015). Furthermore, it would make sense to network different individual projects to take advantage of synergies, as is customary in competence clusters.

When planning research activities, transparency should be observed when selecting topics and during the evaluation procedure (Krimsky 2010).

The SSK therefore recommends:

- continuing research efforts in this field in order to clarify the causes of leukaemia,
- observing transparency with respect to the selection of topics and assessment,
- engaging an independent, international expert panel for the selection of topics and evaluation, ,
- cooperating with international associations in case of projects for which data on the topic of causal research for leukaemia in children and adolescents is generated ,
- exploring the role of the immune system and open questions with respect to possible genesis due to infection and
- networking different individual projects in order to take advantage of synergies.

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