Søknadsinformasjon

Utlysning	Nordic Cancer Union Research Grant, 2015
Søknad	CLEAR: Individualized Central nervous system therapy of acute Lymphoblastic leukemia to increase Efficacy And Reduce toxicity
Søknadsid	176848
Innsendt av	Kjeld Schmiegelow

Oppgave: Progress report

Tilordnet	Kjeld Schmiegelow
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RAPPORT

Briefly describe the project in a language understandable to non-scientists

Many children with acute lymphoblastic leukemia (ALL) have involvement of the central nervous system (CNS) and accordingly all patients receive intensive CNS-directed therapy. However, many patients develop severe neurological toxicities due to this treatment. Thus, there is a need for i) better definitions of patients who need CNS-directed therapy and ii) identification of more efficacious and less toxic treatment strategies for such patients.
The CLEAR project consists of four studies that aim to facilitate and improve individualized CNS-directed therapy in ALL:
1. Exploring the frequency of CNS leukemia and the association with risk of relapse.
2. Identifying leukemic cell characteristics that are associated with risk of CNS leukemia at diagnosis.
3. Exploring the efficacy of a drug-carrier formulation of cytarabine (DepoCyte) in preventing relapse of high risk ALL.
4. Exploring the neurotoxicity of DepoCyte in a rat model.

Summarize the major findings of the project

The frequency of central nervous system (CNS) involvement in children with acute lymphoblastic leukemia (ALL): This study examines the frequency of CNS involvement at diagnosis by flow cytometric analysis of cerebrospinal fluid. Currently, we have collected and analyzed the presence of leukemic blasts in cerebrospinal fluid from more than 500 patients with ALL. The results from the first 300 patients included in the study was published in 2016 in Pediatric Blood & Cancer (Pediatr Blood Cancer 2016;63:1935-1942). Flow cytometric analysis showed that 29% of patients had CNS involvement, whereas leukemic blasts only were detected in 10% of the spinal fluid samples using conventional cytological examination. By the end of 2017 we will examine the association between CNS involvement detected by flow cytometry at diagnosis and the risk of relapse as well as the localization of relapse (CNS and/or bone marrow).

Mapping of gene expression profiles associated with CNS leukemia: The aim of this study is to identify genes that are differentially expressed in CNS leukemia and explore their biological significance. Gene expression of leukemic cells collected from Danish children with ALL at diagnosis is profiled using microarrays. So far, we have performed profiled 164 patients, including 26 patients with CNS involvement (determined by flow cytometry and/or cytology) and 138 patients without CNS involvement. By comparison of the expression profiles we have identified 56 candidate genes with differential expression. Several of the identified genes have been associated with CNS leukemia in previous studies. The cysteine endopeptidase legumain (LGMN) is overexpressed in a number of cancer types and has been associated with increased migration and invasion of the cancer cells. Higher expression of LGMN in CNS leukemia was validated by QPCR, and multivariant regression analysis revealed an odds ratio of 9.1 for CNS involvement with LGMN expression above the median. Low expression of legumain in normal tissues makes this enzyme a promising candidate for specific targeting of the cancer cells. We expect the results from this study will be published in 2017.

Host genome variants: In the Nordic Society of Paediatric Haematology and Oncology (NOPHO) we have performed these analyses for 1107 children included in the ALL2008 protocol. Within the next year, the more than 2 million host genome variants will be associated with CNS leukemia and be part of regression analyses in combination with presence of CNS leukemia for association with the risk of relapse.

Liposomal cytarabine (DepoCyte) in the treatment of ALL: Toxicity and relapse rate is examined for the 40 ALL patients included in the Nordic HR-ALL Depocyte study (clinical-trials.gov ID: NCT00991744). The results from this study was published in 2016 in Journal of Pediatric Hematology-Oncology (J Pediatr Hematol Oncol 2016;38:602-609). Of the 11 patients treated with liposomal cytarabine, 9 experienced (67%) neurotoxicity at minimum one of the administered doses of Depocyte. In comparison neurotoxicity was only observed for 3 out of 28 patients (11%), who received tripel intratecal therapy with cytarabine, methotrexate and hydrocortisone. At follow up, we observed borderline significant difference in 5 year relapse-free survival between the two treatment arms with Depocyte-treated patients having fewer relapses. Larger, prospective studies are needed to clarify if liposomal cytarabine should be included in the standard treatment of ALL.

Neurotoxicity of DepoCyte in a rat model: In collaboration with Professor Peter Cole, Einstein College, New York, one of our pre-graduate medical students, Anna Thomsen, has completed a toxicity study in a rat model. This study showed reduced cognitive damage at exposure to Depocyte compared to intratecal methotrexate. In time this may lead to leukemia treatment being less toxic to the CNS.

Describe how the project has increased our knowledge of the prevention, cause and/or cure for cancer

Flow cytometric detection of CNS leukemia in the CLEAR project has shown that a much higher proportion of newly diagnosed patients have leukemic cells in the CNS (29%) compared to conventional, less sensitive methods (10%). Within the next year, we will determine whether CNS involvement assessed by flow cytometry is associated with higher risk of relapse. Gene expression profiling of leukemic cells has led to identification of 56 genes that are differently expressed in CNS leukemia. Interestingly, legumain represent a promising candidate for specific targeting of the cancer cells, since this enzyme is overexpressed is CNS leukemia and levels in normal tissues are low. Together, the results from the clinical and pre-clinical DepoCyte studies suggest that treatment with liposomal cytarabine in high risk ALL might be able to improve survival rates with less cognitive toxicity compared to intratecal therapy. In summary, the CLEAR project has added valuable knowledge about the prevalence and the biology of CNS leukemia as well as treatment strategies that potentially could be more effective and less toxic than the current therapy.

Outline how Nordic cooperation has added value to this project

Even though ALL is the most common cancerous disease in children above 1 year, only 220 new cases occur each year in the Nordic and Baltic countries. Therefore a Nordic cooperation is essential for including sufficient patients in the studies conducted as a part of CLEAR. Furthermore, collaboration between pediatric researchers from the Nordic countries enables exchange of expertise between research groups and hospitals. The close collaboration is also reflected by the publications from the project that includes authors from different institutions across the Nordic and Baltic countries.

List the publications resulting from the NCU research grant

Author(s), title, journal and edition	PMID (8 digits, only if possible)
Levinsen M, Marquart HV, Groth-Pedersen L, Abrahamsson J, Albertsen BK, Andersen MK, Frandsen TL, Harila-Saari A, Pronk C, Ulvmoen A, Vaitkeviciene G, Lahteenmaki PM, Niinimaki R, Taskinen M, Jeppesen M, Schmiegelow K. Leukemic blasts are present at low levels in spinal fluid in one third of childhood acute lymphoblastic cases. Pediatr Blood Cancer 2016;63:1935-1942	27447373
Levinsen M, Harila-Saari A, Grell K, Jonsson OG, Taskinen M, Abrahamsson J, Vettenranta K, Åsberg A, Risteli J, Heldrup J, Schmiegelow K. Efficacy and toxicity of intrathecal liposomal cytarabine in first-line therapy of childhood acute lymphoblastic leukemia. J Pediatr Hematol Oncol 2016;38:602-609	27571129

Brief overview of expenditures for last year 1 vedlegg (176848 CLEAR Expenditures 2016.pdf)

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Expenditures for 2016	
Lab technician	21,000 EUR
Running costs for handling of cerebrospinal fluid	3,200 EUR
Total expenditures	**24,200 EUR**

The remainder of the grant will be used in 2017 as specified in the application.