

NCU – Summative report for 2013

Report submission date: 28.02.14

Principal investigator: Kjeld Schmiegelow

Project title: EXPLORING AND IMPROVING THIOPURINE/METHOTREXATE MAINTENANCE THERAPY OF ACUTE LYMPHOBLASTIC LEUKEMIA

NCU grant received (€): 50,000

Project commencement and completion dates: 01.01.13 – 31.12.17

1. Briefly describe the project in a language understandable to non-scientists (max. 100 words)

Metabolism of anticancer drugs is highly variable among patients. Therefore, standardized dosing will cause insufficient treatment in rapid metabolizers whereas patients with slow inactivation may suffer excessive side effects. In this project we optimize dosing of anticancer drugs based on the genetics of the patients and drug measurements throughout the treatment period and use this to test if a novel combination of anticancer drugs can improve the prognosis of patients with an adverse drug metabolism profiles.

2. Summarize the major findings of the project (max. 400 words) and

Due to the long term cohort approach in this project testing of the major hypotheses cannot be done until the end of the project. Nonetheless, from the data obtained this far, pharmacogenetic study manuscripts addressing more specific clinical problems have been published (see 5) or are in preparation. These include a) investigations of toxicity after high-dose Methotrexate, b) identification of venoocclusive disease triggering factors, c) impact of gene variants on acute toxicities and late effects.

Sample collection in the cohort study are progressing satisfactory – we receive approximately 100 blood samples each week corresponding to more than 5000 per year. Chemical analysis of these is ongoing as is registration of clinical parameters. Moreover, collection and registration of clinical outcome and toxicity information is ongoing.

The intervention is also in preparation – a mixture formulation of thioguanine suitable for accurate dosing in pediatric patients is being produced and we expect to include the first patient in this part of the study later this year.

3. Describe how the project has increased our knowledge of the prevention, cause and/or cure for cancer (max. 150 words)

See above 2.

4. Outline how Nordic cooperation has added value to this project (max. 100 words)

Since leukemia is rare, research in this heterogeneous disease requires access to large cohorts of patients treated according to identical guidelines in order to get sufficient statistical power for hypothesis testing. The Nordic cooperation with common treatment protocols has not only added to, but is essential for the cohort-based research strategy in this study.

5. Publications resulting from the NCU research grant

Frandsen TL, Heyman M, Abrahamsson J, Vettenranta K, Åsberg A, Vaitkeviciene G, Pruunsild K, Toft N, Birgens H, Hallböök H, Quist-Paulsen P, Griškevičius L, Helt L, Hansen BV, Schmiegelow K. Complying with the European Clinical Trials directive while surviving the administrative pressure - an alternative approach to toxicity registration in a cancer trial. *Eur J Cancer*. 2014 Jan;50(2):251-9. Epub 2013 Nov 11. PubMed PMID: 24231337.

Lund B, Wesolowska-Andersen A, Lausen B, Borst L, Rasmussen KK, Müller K, Klungland H, Gupta R, Schmiegelow K. Host genome variations and risk of infections during induction treatment for childhood acute lymphoblastic leukaemia. *Eur J Haematol*. 2013 Dec 14. [Epub ahead of print] PubMed PMID: 24330153.

Levinsen M, Rotevatn EO, Rosthøj S, Nersting J, Abrahamsson J, Appell ML, Bergan S, Bechensteen AG, Harila-Saari A, Heyman M, Jonsson OG, Maxild JB, Niemi M, Söderhäll S, Schmiegelow K; for the Nordic Society of Paediatric Haematology, Oncology (NOPHO). Pharmacogenetically based dosing of thiopurines in childhood acute lymphoblastic leukemia: Influence on cure rates and risk of second cancer. *Pediatr Blood Cancer*. 2014 Jan 3. [Epub ahead of print] PubMed PMID: 24395436.

Schmiegelow K, Levinsen MF, Attarbaschi A, Baruchel A, Devidas M, Escherich G, Gibson B, Heydrich C, Horibe K, Ishida Y, Liang DC, Locatelli F, Michel G, Pieters R, Piette C, Pui CH, Raimondi S, Silverman L, Stanulla M, Stark B, Winick N, Valsecchi MG. Second malignant neoplasms after treatment of childhood acute lymphoblastic leukemia. *J Clin Oncol*. 2013 Jul 1;31(19):2469-76.

Rasmussen MM, Christensen RH, Gregers J, Heldrup J, Nersting J, Schmiegelow K. Can SLC19A1 80G>A polymorphisms predict risk of extremely delayed MTX excretion after high dose of methotrexate? *J Pediatr Hematol Oncol*. 2013 Jul;35(5):417-8.

Ebbesen MS, Nersting J, Jacobsen JH, Frandsen TL, Vettenranta K, Abramsson J, Wesenberg F, Schmiegelow K. Incorporation of 6-thioguanine nucleotides into DNA during maintenance therapy of childhood acute lymphoblastic leukemia-the influence of thiopurine methyltransferase genotypes. *J Clin Pharmacol*. 2013 Jun;53(6):670-4.