Report NCU grant

Report submission date:

Main applicant: Peter de nully Brown

Project title: Nordic Lymphoma Group: A Nordic collaboration to combat malignant lymphoma.

NCU grant received (€): 70 000

Project commencement and completion dates: For the year 2010. Grants given for several years previously

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1. Brief description of the project, written in a language understandable to non-scientists (Maximum length: 100 words)

The goals of the Nordic Lymphoma Group, to conduct research into the biology, epidemiology and treatment of malignant lymphoma in the Nordic countries have been pursued in 2009-10 by the continuing accrual to the portfolio of active research protocols including clinical and molecular research. Several large and innovative studies have been closed for accrual during the last 1-3 years and await final publications during the years 2011 and 2012 (large cell lymphoma-, mantle cell lymphoma-, indolent lymphoma-, T-cell lymphoma-, Hodgkin lymphoma and primary CNS lymphoma protocols). These studies are being replaced by follow-up studies by the respective working groups as detailed below.

2. Summarize the major findings of the project (Maximum length: 400 words)

Hodgkin Lymphoma

- The Hodgkin group has submitted an abstract to the lymphoma meeting in Lugano, June 2011, on the results of the Nordic studt of low and intermediate stages of Hodgkin lymphoma. A manuscript will soon be finished. Sweden and Norway have also joined an international study, RATHL, on advanced Hodgkin lymphoma and parts of Denmark are planning to join. Finland has decided not to join due to shortage of personnel.
  Based on the application and need for money for the year 2010, the Hodgkin group was not allocated support from NCU for 2010

Large cell lymphoma:

- CRY-04 study: Final analysis with the median follow-up of three years was performed on May 2010, and the results presented in annual meeting of the American Society of Hematology (ASH) on December 2010. Of the CRY-04 molecular substudies, data on exon-based transcriptome profiling and prognostic impact of serum VEGF levels were also finalized and presented in ASH 2010. Furthermore, an abstract on intergrative genomic profiling and one on clinical utility of PET /CT at end of therapy have been submitted to the Lugano 2011 meeting. Other molecular substudies from CRY-04 material, including tissue microarrays and multiplex ELISAs from plasma are ongoing. Several manuscripts will be submitted for publication on 2011.
- The PET study has included the planned 100 patients and the follow-up data is maturing.

- CHIC study: A new phase II follow-up study for the CRY-04 protocol was finalized on December 2010, and is open for recruitment in all Nordic countries. The purpose is to test whether early CNS prophylaxis given at the beginning of therapy for young high risk DLBCL patients is feasible and could reduce the risk of CNS relapses.

  The fraction of the NCU grant 2010 allocated by the coordination group to the activities of the large cell group has been used for (i) statistics, (ii) meeting activities, (iii) development of new CHIC protocol and (iv) laboratory reagents.

Indolent (low-grade Lymphoma:

- The EORTC/Intergroup study 206981: A manuscript on prolonged follow up and a study on the value of molecular analysis of microscopic residual disease are both published in Journal of Clinical Oncology.
- The second protocol on Rituximab + INF-α in low-grade NHL to which 14,000 € was allocated (of the total 2009 grant to NLG of 70,000 €) will soon have its final analysis. An abstract for the Lugano meeting 2011 has been prepared. As for the CRY04 study, several publications will be submitted for publication during the next two years based on the study and translational investigations.
  The NCU grant has been spent on molecular and immunohistochemical analysis of the two protocols on Rituximab +/- INF-α.
- A new randomized study on upfront treatment of follicular lymphoma in collaboration with the Swiss SAKK group is starting spring 2011.

Mantle cell lymphoma:

- MCLII protocol: In addition to the manuscript published in Blood 2008 (ref 24), another two manuscripts have been published published. One on minimal residual disease and one on predictive factors for response and survival (refs 25 and 26).
- The MCLII is succeeded by:
- The MCLIII, which succeeded in accruing 160 patients July 2009. Preliminary results of the study were presented orally at the ASH meeting 2009 (Abstract 3).
- A new phase I / II study on frontline therapy in elderly patients is open for accrual in the Nordic countries (bendamustin, rituximab, lemalidomide with a dose finding study of lenalidomide as the phase I part of the study).
  To the MCLII and III protocols, 15,000 € was allocated (of the total 2009 grant to NLG of 70.000 €), and were spent on detection of minimal residual disease.

T-cell lymphoma:

- The T-01 study: After the publication of the German experience pointing at the occurrence of late relapses in T-cell lymphomas, a decision was taken to publish the final analysis of the NLG-T-01 study with a 5-year median follow-up time (data presented at the EHA 2009 were with 3½ year median follow-up). The analysis results were produced by the NLG statistician Harald Anderson, Lund, in January 2011 and the manuscript is now going to be released to co-authors in its updated version with the longer follow-up allowing us to describe the type and frequency of late relapses. Subset analyses of enteropathy-associated PTCL and anaplastic large-cell TCL were presented as posters at the ASH 2010 in Orlando and an abstract with a subset analysis of angioimmunoblastic TCL has been submitted to the Lugano 2011 meeting (June 2011). A phd in Aarhus and in Oslo will start in 2011 and deal with biological aspects also on the basis of the NLG-T-01 tissue samples.
- The T-02 protocol (ACT-1 trial): After reopening of the trial, accrual has increased steadily and the number of adverse events dropped dramatically. The accrual over the last 6 months (august 2010 – February 2011) has been with 4-6 patients averagely per month. The ACT-1 trial has p.t. approximately 60 patients and the ACT-2 50 patients. With a cumulative number of 110 pts, the ACT trial is already now belonging to the top 3 largest trial ever performed in systemic PTCL. A poster on stem cell harvest feasibility was presented at the ASH 2010 in Orlando and an abstract on hematopoietic recovery after autologous stem cell reinfusion has been submitte to the Lugano meeting 2011.

  The fraction of the NCU grant 2010 allocated by the coordinating group to the activities of the T-cell lymphoma group has been used for (i) meeting activities (clinicians and pathologists), (ii) statistics

(UNI-C data management and conversion from the database to the NLG statistician) and (iii) submission fees for congress abstracts, (iv) laboratory reagents for immunohistochemistry and molecular biology.

CNS lymphoma:

CNS lymphoma protocol consists of a combined multiagent immunochemotherapy regimen based on HD-MTX and HD-Ara-C, intraspinal Depocyte and maintenance temozolomide therapy for responding elderly patients. The CNS lymphoma study was closed at the end of October 2010 after a successful accrual of 67 patients from 12 centers. In the younger age group (18-65 y) there were 39 patients (twenty three male patients, 16 female patients) and in the elderly age group there were 27 patients (twelve male patients and 15 female patients). Median age for the whole cohort was 64 years (55 y in the younger age group, 70 years in the elderly age group). The induction treatment was started in all patients apart from one patient who was excluded from the study as the inclusion criteria were not fulfilled. The response to induction therapy was assessed after 2, 4 and 6 chemotherapy cycles. The great majority of the patients responded to treatment. The overall response rate (CR+PR) was 82.7%. Maintenance treatment was started in 15 of 27 elderly patients and is not completed for all patients as yet. The toxicity was mainly grade 3-4 infections occurring during neutropenia especially after HD-AraC. There were four treatment related deaths.

Support distributed to the PCNSL group has been spent on data management, monitoring and Safety Board expenses.

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

Lymphoid cancer – malignant lymphoma - is the tenth most frequent cancer in the Nordic countries, amounting to a total of 5000 cases annually. Malignant lymphoma, however, comprise many subentities, which in the WHO classification amounts to more than 20 different diseases, each with its own particular malignant phenotype, biology, and treatment option. The Nordic Lymphoma Group has gained considerable insight into the planning and management of clinical studies with translational research aspects. The ”harvest” in term of new insight when running clinical studies is based on hard work over several years. Among the major achievements of NLG during the last years are i) results from Mantle cell lymphoma protocol II which by many throughout the world is considered standard therapy today, ii) preliminary results from Hodgkin lymphoma trial for limited stage disease with the use of smaller radiation fields with lower doses resulting in less long term side effects while maintaining excellent survival and iii) results from two randomized first-line studies in indolent lymphomas showing excellent results with immunotherapy (antibody treatment with or without interferon).

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

The number of cases of each subtype being diagnosed annually in each country may be small. In order to gain increased knowledge, large, homogeneously treated patient cohorts with a possibility for long-term follow-up are needed.

Nordic collaboration enables us to collect sufficient numbers, to study them clinically and molecularly, and to follow them prospectively and completely to gain highly relevant scientific new knowledge. Also, the Nordic group contributes substantially with patients to joint European randomised trials.

5. Publications resulting from this and previous grants

NORDIC LYMPHOMA GROUP LIST OF PUBLICATIONS 1999 – :

1. Jerkeman M, Johansson B, Akerman M, Cavallin-Stahl E, Kristoffersson U, Mitelman F. Prognostic implications of cytogenetic aberrations in diffuse large B-cell lymphomas. Eur J Haematol 1999 Mar;62(3):184-90.
2. Jerkeman M, Anderson H, Cavallin-Stahl E, Dictor M, Hagberg H, Johnson A, Kaasa S, Kvaloy S, Sundstrom C, Akerman M. CHOP versus MACOP-B in aggressive lymphoma--a Nordic Lymphoma Group randomised trial. Ann Oncol 1999 Sep;10(9):1079-86.
3. Rodriguez-Catarino M, Jerkeman M, Ahlstrom H, Glimelius B, Hagberg H. Residual mass in aggressive lymphoma--does size, measured by computed tomography, influence clinical outcome? Acta Oncol 2000;39:485-9.
4. Amini RM, Enblad G, Gustavsson A, Ekman T, Erlanson M, Haapaniemi E and Glimelius B. Treatment outcome in patients younger than 60 years with advanced stages (IIB-IV) of Hodgkin's disease: the Swedish National Health Care Programme experience. Eur J Haematol 2000;65:379-89
5. Jerkeman M, Kaasa S, Hjermstad M, Kvaloy S, Cavallin-Stahl E. Health-related quality of life and its potential prognostic implications in patients with aggressive lymphoma: a Nordic Lymphoma Group Trial Med Oncol 2001;18:85-94.
6. Osby E, Taube A, Cavallin-Stahl E, Hagberg H, Bjorkholm M. Reproducibility of tumor response e-valuation in patients with high-grade malignant non-Hodgkin's lymphoma. Med Oncol 2001;18:137-40.
7. Messori A, Vaiani M, Trippoli S, Rigacci L, **Jerkeman M**, Longo G. Survival in patients with intermediate or high grade non-Hodgkin's lymphoma: meta-analysis of randomized studies comparing third generation regimens with CHOP Br J Cancer 2001;84:303-7.
8. Amini R-M, Glimelius B, Gustavsson A, Ekman T, Erlanson M, Haapaniemi E, Enblad G. A population-based study of the outcome for patients with first relapse of Hodgkin's lymphoma. Eur J Haematol 2002;68:225-232.
9. Jerkeman M, Aman P, Cavallin-Stahl E, Torlakovic E, Akerman M, Mitelman F, Fioretos T. Prognostic implications of BCL6 rearrangement in uniformly treated patients with diffuse large B-cell lymphoma--a Nordic Lymphoma Group study. Int J Oncol 2002 Jan;20:161-5.
10. Goldkuhl C, Ekman T, Wiklund T, Telhaug R. Age-adjusted chemotherapy for primary central-nervous system lymphoma--a pilot study. Acta Oncol 2002;41(1):29-35.
11. Kimby E. Beyond immunochemotherapy: combinations of rituximab with cytokines IFN-α2a and G-CSF. Sem in Oncology 2002; 29: 7-10.
12. Hagenbeek A, Czuczman M, Ghielmini M, Herold M, **Kimby E**, Solal-Céligny P, Unterhalt M. Rituximab therapy for indolent non-Hodgkin's lymphoma. Anti-Cancer Drugs 2002;13(Suppl 2):S11-S17
13. Osby E, Hagberg H, Kvaloy S, Teerenhovi L, Anderson H, Cavallin-Stahl E, Holte H, Myhre J, Pertovaara H, Bjorkholm M. CHOP is superior to CNOP in elderly patients with aggressive

lymphoma while outcome is unaffected by filgrastim treatment: results of a Nordic Lymphoma Group Randomized trial. Blood 2003;101(10):3840-8.

14. Linderoth J, Jerkeman M, Cavallin-Stahl E, Kvaloy S, Torlakovic E. Immunohistochemical Expression of CD23 and CD40 May Identify Prognostically Favorable Subgroups of Diffuse Large B-cell Lymphoma: A Nordic Lymphoma Group Study. Clin Cancer Res. 2003;9:722-8.
15. Molin D, Enblad G, Gustavsson A, Ekman T, Erlanson M, Haapaniemi E, Glimelius B. Early and intermediate stage Hodgkin's lymphoma – report from the Swedish National Care Programme. Eur J Haematol 2003;70:172-80.
16. Andersen NS, Pedersen, Elonen E et al for the Nordic Lymphoma Group. Primary Treatment with autologous stem cell transplantation in Mantle Cell Lymphoma. Outcome related to remission pretransplant but not to tumour cell contamination of the autograft. Eur J Haematol 2003;71:73-80.
17. Jerkemann M, Andersson H, Dictor M, Kvaløj S, Åkerman M, Cavallin-Ståhl E. Assessment of biological prognostic factors provides clinically relevant information in patients with diffuse large B-cell lymphoma-a Nordic Lymphoma Group study. Ann Hematol. 2004;83:414-9
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19. van Oers MH, Klasa R, Marcus RE, Wolf M, **Kimby E**, Gascoyne RD, Jack A, van t Veer M, Vranovsky A, **Holte H**, Van Glabbeke M, Teodorovic I, Rozewicz C, Hagenbeek A for EORTC Lymphoma Group,HOVON, 3NCIC CTG Hematology Group (Canada), BNLI, Australasian Leukaemia and Lymphoma Group, Nordic Lymphoma Group, EORTC Data Center. Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin's lymphoma, both in patients with and without rituximab during induction: results of a prospective randomized phase III intergroup trial. Blood 2006;108:3295-301.
20. Björkholm M, Hagberg H, Holte H, Kvaloy S, Teerenhovi L, Anderson H,Cavallin-Ståhl E, Myhre J, Pertovaara H, Ost A, Nilsson B, Osby E. Central nervous system occurrence in elderly patients with aggressive lymphoma and a long-term follow-up. Ann Oncol 2007 Jun;18(6):1085-9.
21. Eva Kimby, Jesper Jurlander, Christian Geisler, Hans Hagberg, Harald Holte, Tuula Lehtinen, Björn Östenstad, Mads Hansen, Anders Österborg, Ola Lindén, and Christer Sundström, on behalf of the Nordic Lymphoma Group: Long-Term Molecular Remissions in Patients With Indolent Lymphoma Treated With Rituximab as a Single Agent or in Combination With Interferon α-2a: A Rdomized Phase II Study anFrom the Nordic Lymphoma Group. Leuk Lymphoma 2008;49:102-12. 22. Geisler CH, Kolstad A, Laurell A, Andersen NS, Pedersen LB, Jerkeman M, Eriksson M, Nordstrom M, Kimby E, Boesen AM, Kuittinen O, Lauritzsen GF, Nilsson-Ehle H, Ralfkiaer E, Akerman M, Ehinger M, Sundstrom C, Langholm R, Delabie J,Karjalainen-Lindsberg ML, Brown P, Elonen E. Long-term progression-free survival of mantle cell lymphoma following intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: A non-randomized phase-II multicenter study by the Nordic Lymphoma Group. Blood 2008 2008;112:2687-93
23. Andersen NS, Pedersen LB, Laurell A, Elonen E, Kolstad A, Boesen AM, Pedersen LM, Lauritzen GF, Ekanger R, Nilsson-Ehle H, Nordström M, Fredén S, Jerkeman M, Eriksson M, Väärt J, Malmér B, Geisler CH for the Nordic Lymphoma Group. Preemptive treatment with rituximab of molecular relapse after autologous stem cell transplantation in mantle cell lymphoma. J Clin Oncol. 2009; 27: 4365-70.

24. Geisler CH, Kolstad A, Laurell A, Raty R, Jerkeman M, Eriksson M, Nordstrom M, Kimby E, Boesen AM, Nilsson-Ehle H, Kuittinen O, Lauritzsen GF, Ralfkiaer E, Ehinger M, Sundstrom C, Delabie J, Karjalainen-Lindsberg ML, Brown P, Elonen E. The Mantle Cell Lymphoma Prognostic Index (MIPI) is superior to the International Prognostic Index (IPI) in predicting survival following intensive 1st-line immunochemotherapy and autologous stem-cell transplantation (ASCT). Blood. 2010; 115: 1530-3.
25. van Oers MHJ, Tönnissen E, van Glabbeke M, Giurgia L, Jansen JH, Klasa R, Marcus RE, Wolf M, **Kimby E**, Vranovsky A, **Holte H**, Hagenbeek A, van der Reijden BA. BCL-2/IgH PCR status at the end of induction treatment is not predictive for progression free survival in relaps BAed/resistant follicular lymphoma: results of a prospective randomized EORTC 20981 phase III intergroup study. J Clin Oncol. 2010; 28: 2246-52.
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28. Jantunen E, d'Amore F. Stem cell transplantation for peripheral T-cell lymphomas. Leuk Lymphoma 2004;45:441-6.
29. Geisler C, Kolstad A, Laurell A, Räty R: Mantle cell lymphoma .- does primary intensive immunochemotherapy improve overall survival in younger patients? Leuk Lymphoma. 2009 Jun 26:1-8. [Epub ahead of print] (Invited paper).
30. Geisler C. Mantle cell lymphoma: are current therapies changing the course of disease?. Curr Oncol Rep 2009;11:371-7 (Invited paper).
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32. Kimby E. Tolerability and safety of rituximab. Cancer Treat Rev. 2005 Oct;31(6):456-73
Kimby E. Management of Stage IV Peripheral T-Cell Lymphomas. Current Hematologic Malignancy Reports. Volume 2 Issue 4. dec 2007 pp. 242-248.

Manuscripts Submitted:

32. P.J. Lugtenburg PJ , Eriksson M, W. van Putten W, Holte H, Biesma DH, van Marwijk-Kooy M, Fijnheer R, Wijermans P, Steijaert M, de Jong D, Lam K, van Imhoff G, van Oers MHJ, Verhoef GEG, Sundström C , Huijgens PC, Sonneveld P for the Dutch HOVON group and the Nordic Lymphoma Group NLG. Two-weekly CHOP chemotherapy with or without rituximab for the treatment of diffuse large B-cell lymphoma in advanced stage poor-risk elderly patients: a randomized phase III trial by the Dutch HOVON and Nordic Lymphoma groups
33. Björn Engelbrekt Wahlin, Christer Sundström, Harald Holte, Hans Hagberg, Martin Erlanson, Herman Nilsson-Ehle, Ola Lindén, Marie Nordström, Bjørn Østenstad, Christian H. Geisler, Peter de Nully Brown, Tuula Lehtinen, Martin Maisenhölder, Anne M. Tierens, Birgitta Sander, Birger Christensson, and Eva Kimby.T cells in tumors and blood predict outcome in follicular lymphoma treated with rituximab
34Björn Engelbrekt Wahlin, Olav Erich Yri, Eva Kimby, Harald Holte[3], Jan Delabie, Birger Christensson, Erlend Bremertun Smeland, Bjørn Østenstad, Peter de Nully Brown, Christer Sundström, and Birgitta Sander Clinical significance of the WHO grades of follicular lymphoma in the rituximab era