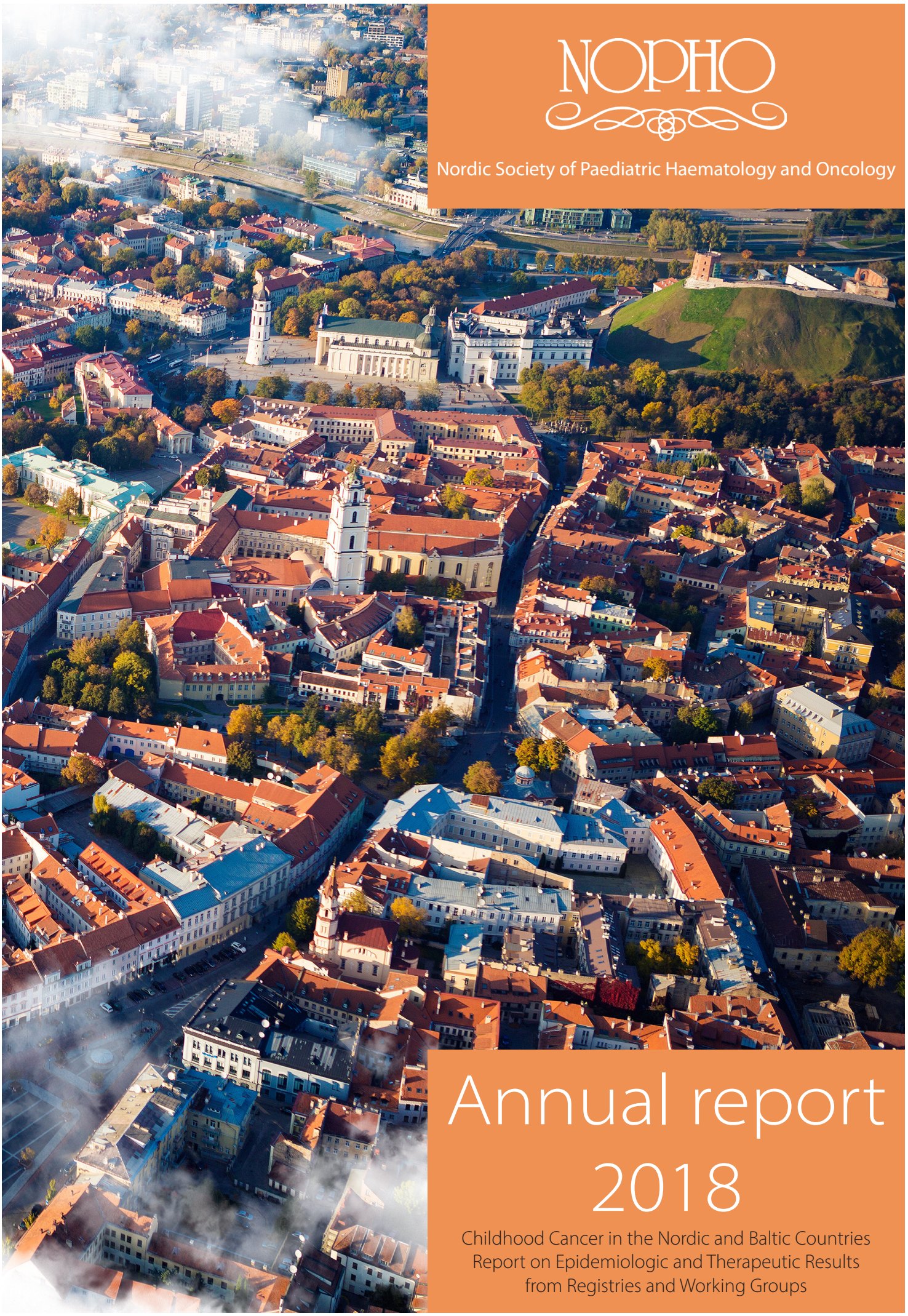

NOPHO

Nordic Society of Paediatric Haematology and Oncology

Annual report 2018

Childhood Cancer in the Nordic and Baltic Countries
Report on Epidemiologic and Therapeutic Results
from Registries and Working Groups

This report is published with financial support from:
The Swedish Childhood Cancer Foundation

Foreword

Dear NOPHO members,

Here you have it for year 2018: the precious NOPHO report, available as a paper edition and on www.NOPHO.org. The report reflects our history and our present. Thank you all for making it true and making it reliable by registering data but also contributing in the working groups for the future.

The quality of registration within NOPHO has traditionally been high and that has given us the basis for our own science but has also made us to be an appreciated collaborator in international projects. We have been collecting data for decades. To keep the data updated needs effort and endurance from individual doctors and nurses taking notes, from data managers in treating centers collecting the data to the registry and from the registry secretariat to check the data reliability, not once but for several times. As seen in a recent paper of cancer treatment results internationally (Allemani C et al, Lancet 391 (10125), 2018), we in the NOPHO countries have been able not only to give first class treatment to our patients but we also have been extremely successful in collecting data to our national registries. Good registration is a tool to transparent science and development. Thank you all for supporting the registry by working so hard for reliable data collection.

During 2017 a big step to secure our data for future has been taken. NOPHOCARE project has been conceived and brought through the evaluation of the authorities. This means that the historical NOPHO registry data are available to the researches during the coming years in a secure and legal way. The soul of this project has been the chair of the LLC Päivi Lähteenmäki: thank you, Päivi, for your huge amount of work to put this project together.

The world has, also during the past year, been changing around us. Everything is not for better. The attempts to intrude to the NOPHO web are reality and we need our webmaster every day more and more to keep our society as private as we want it to be. I wish to thank our webmaster Elisabeth Jensen-Broby Heldrup for seeing the threats to our integrity and for fighting against them. This is one of our big challenges for the coming years: to keep our protocols and society data safe and secure. That, as the registration, is a joint effort to keep this society running.

We have now four joint disease group Committees. Leukemia and Lymphoma, Solid Tumor and Brain Tumor Committees have been joined by a new committee for benign hematology and histiocytosis. The official name for this committee is still pending but this committee will make visible the important work that is being done within the field: benign hematology patients need a huge amount of attention and treatment efforts and not all of these diseases are that benign in their course. Welcome and all the good luck to the new committee.

Thank you all for contributing to NOPHO and enjoy the NOPHO Report 2018. For the first time the NOPHO Annual meeting will be in Vilnius, see you there!

Helsinki/Stockholm, April 18th 2018
Mats Heyman (NOPHO Registry), Jenny Juhlin (NOPHO Secretariat) and Mervi Taskinen (GS)

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NOPHO Board

Members 2017 - May 2018		
Secretary--general	Mervi Taskinen	elected 2016
-elect	Birgitte Klug Albertsen	elected 2016
Treasurer	Peder Skov Wehner	elected 2015
Auditors of accounts	Gustaf Ljungman	elected 2005
	Karsten Nysom	elected 2017
Stand in auditor of accounts	Svein Kolmannskog	elected 2005
Denmark	Peder Skov Wehner	elected 2015
	Lisa Hjalgrim	elected 2014
Finland	Kaisa Vepsäläinen	elected 2016
	Mikko Arola	elected 2017
Iceland	Ólafur Gísli Jónsson	elected 2000
	Solveig Hafsteinsdottir	elected 2013
Lithuania	Jelena Rascon	elected 2016
	Goda Vaitkeviciene	elected 2016
Norway	Anne Grete Bechensteen	elected 2017
	Tove Nystad	elected 2017
	Petter Brandal (radiotherapy)	elected 2012
Sweden	Per Kogner	elected 2015
	Johan Arvidson	elected 2016
Pediatric surgery	Seppo Taskinen	elected 2015
Young NOPHO	Thorgerdur Gudmundsdottir	elected 2016

NOPHO Secretariat and Webmaster

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NOPHO Scientific committee

Members 2017-2018

Sweden	Kees-Jan Pronk (chair)
Denmark	Bodil Als-Nielsen
Finland	Markku Heikinheimo
Iceland	Ragnar Bjarnason
Lithuania	Sonata Trakymiene
Norway	Maria Winther Gunnes
Young NOPHO	Nikolas Herold

The deadline for applications for NOPHO studies is 2 months before each NOPHO board meeting. For the November 2017 term, 6 new applications were submitted and evaluated. For the June 2018 term, the deadline for the applications is April 2nd. For each application term, we have held a 1-2 hour telephone conference some weeks after the application deadline, where the applications have been thoroughly discussed before evaluation notes were subsequently drafted, revised by e-mail, approved and entered into the NOPHO scientific study platform.

During the November 2017 telephone meeting, all proposed candidates for the 2018 NOPHO Lecturer prize were discussed. 3 candidates were selected and presented to the NOPHO board, that subsequently decided on the winner of the 2018 NOPHO Lecturer.

Prior to the application deadline November 2017, Kees-Jan Pronk (SE) succeeded Karsten Nysom as chair of the Scientific Committee. In addition, Maria Winther Gunnes and Bodil Als-Nielsen joined the scientific committee as Norwegian and Danish representatives, respectively.

Lund, March 18th, 2018
Kees-Jan Pronk

Young NOPHO

Young NOPHO Board in 2017–2018

Denmark	Stine Nygaard Nielsen, Sofie Gottschalk Højfeldt
Finland	Anu Vatanen, Laura Madanat-Harjuoja
Iceland	Thorgerdur Gudmundsdottir (Chair)
Lithuania	Audrone Muleviciene
Norway	Simon Kranz, Kirsten Brunsvig Jarvis
Sweden	Nikolas Herold

Last year the annual meeting of Young NOPHO (YN) was held on the 19th of May at the annual NOPHO meeting in Stockholm, Sweden. The minutes from the meeting and the regulations of YN can be found at the NOPHO website. After the annual meeting the YN members had a group photo in the evening sun followed by an invitation for an annual YN dinner sponsored by Barncancerfonden.

In April 2018, 150 persons were registered as YN members (17 from Norway, 49 from Sweden, 38 from Denmark, 23 from Finland, 3 from Iceland, and 20 from Lithuania). We hope that this positive development of increased number of YN members, increased interest, activity and collaboration will continue during the next year.

The status of each YN membership is reviewed on a yearly basis, as according to the YN regulations that state that, NOPHO members who have completed their sub-specialization as paediatric oncologist/haematologist, or who hold a permanent position in this field, as well as researchers who have established their own research group are no longer regarded as YN members. Students working on time-limited research projects within paediatric haematology/oncology are YN members for the duration of this project.

Today, YN is represented by 49 YN members in 35 Working Groups (WG). As WGs are open for one YN member from each country, there is still room for more YN members to engage in this important and exciting area of work within NOPHO. YN members are advised to please contact the respective WG chair or the YN coordinator if they are interested in becoming member of a WG.

In 2018, the board of YN met in Stockholm to plan the next steps and to further increase the activity within YN. The board planned the upcoming **YN annual meeting in Vilnius on 1st of June**. The board decided to:

- To continue with starting each YN annual meeting with a short presentation on NOPHO, YN, the NOPHO-WGs, and the NOPHO educational courses. This is thought as a short introduction to new YN members, that hopefully will become future active NOPHO members.
- The structure of the annual meeting in 2018, will be similar to the 2015-2017 meetings, with a division of the scientific programme (50% research and 50% clinical focus) and with a joint session with NOBOS.
- This year we will, once again, use the topic from the Annual NOPHO meeting and the YN meeting is thought as an introduction hereto. The topics of our upcoming annual YN meeting 2018 are: Epidemiology of solid tumours, the basics of tumour surgery, and radiotherapy in children.
- During the annual YN meeting the YN board will also present some relevant or interesting clinical cases – in the hope of building a clinical case session at the annual YN meetings and hopefully establishing case presentation from other YN members in the future.
- The YN board will select two abstracts that YN members have submitted to the NOPHO meeting, to be presented orally at the annual YN meeting. Two posters, submitted by YN members, will also be selected for a 5-minute rapid fire poster presentation.
- In addition, the next YN board meeting and **a YN meeting including an educational session on "Paediatric Palliative Care" open for all (both YN members and others) that will be in Helsinki 12th – 14th October 2018.**

The YN board would like to thank the Swedish Childhood Cancer Foundation (Barncancerfonden) for supporting all YN related meetings in 2017 and 2018 and the upcoming annual meeting in Vilnius, Lithuania on the 1st of June 2018.

Last but not least we would like to thank all YN members for their activities and energy invested in 2017 to 2018, for making YN a more active and collaborative WG. Thank you!

2nd of May, 2018
On behalf of the YN board,
Thorgerdur Gudmundsdottir
Iceland, YN Chair

Participating clinics/institutions/physicians

Through the years, many colleagues in NOPHO have been involved in treating and reporting of childhood cancer. The main contributors are listed below:

Denmark	Copenhagen	Kjeld Schmiegelow, Thomas Frandsen, Karsten Nysom, Catherine Rechnitzer, Birgitte Lausen, Astrid Sehested, Marianne Ifversen, Lisa Hjalgrim
	Odense	Peder Skov Wehner, Eckhard Schomerus, Niels Fisker, Michael Callesen, Mathias Rathe
	Aarhus	Henrik Hasle, Henrik Schrøder, Birgitte Klug Albertsen, Pernille Edslev Wendtland, Christine Dahl, Torben Mikkelsen, Karin Bækgaard Nissen
	Aalborg	Steen Rosthøj, Erik Østergaard, Ruta Tuckuviene
Finland	Helsinki	Mervi Taskinen, Kim Vettenranta, Pasi Huttunen, Jukka Kanerva, Kirsi Jahnukainen, Virve Pentikäinen, Minna Koskenvuo, Samppa Ryhänen, Helena Olkinuora, Satu Långström, Pauliina Utriainen, Adam Alexandersson
	Turku	Päivi Lähteenmäki, Marika Grönroos, Anu Huurre, Laura Korhonen, Linnea Schuez-Havupalo, Liisa Järvelä
	Oulu	Merja Möttönen, Hanna Juntti, Riitta Niinimäki, Anne Hekkala
	Tampere	Olli Lohi, Mikko Arola, Katriina Parto, Niina Valtanen, Päivi Raittinen
	Kuopio	Pekka Riikonen, Kaisa Vepsäläinen, Jouni Pesola, Tuuli Pöyhönen
Iceland	Reykjavik	Ólafur G. Jónsson, Halldóra K. Thórarinsdóttir, Sólveig Hafsteinsdóttir, Ragnar Bjarnason, Jón Jóhannes Jónsson
Lithuania	Kaunas	Giedre Rutkauskiene, Rosita Kiudeliene, Egle Ramanauskiene, Sonata Argustaite, Justina Klimaite, Ruta Radaviciute
	Vilnius	Jelena Rascon, Goda Vaitkevičienė, Gražina Kleinotienė, Audronė Mulevičienė, Indrė Tamulienė, Natalija Šestel, Ramunė Pasaulienė, Rolanda Nemanienė, Sigita Stankevičienė, Sonata Šaulytė Trakymienė, Vilma Rutkauskaitė
Norway	Oslo	Anne Grete Bechensteen, Ellen Ruud, Heidi Glosli, Bernward Zeller, Inga Maria Johannsdottir, Einar Stensvold, Jochen Büchner, Monica Cheng Munthe-Kaas, Aina Ulvmoen, Charlotte Alme, Marta Maria Dirdal, Kirsten Jarvis, Ida Knapstad, Tale Torjussen. Associate members: Marit Hellebostad, Finn Wesenberg, Eva Widing
	Trondheim	Bendik Lund, Ann Elisabeth Åsberg, Svein Kolmannsskog, Erling Moe, Kristin Solem

	Bergen	Maria W Gunnes, Dorota Malgorzata Wojcik, Anita Andrejeva, Ingrid Kristin Torsvik
	Tromsø	Tore Stokland, Trond Flaegstad, Niklas Stabell, Tove Nystad, Simon Kranz, Ole Mikal Wormdal
Sweden	Stockholm, Solna	Pernilla Grillner, Mats Heyman, Stefan Söderhäll, Niklas Pal, Klas Blomgren, Stefan Holm, Johan Malmros, Per Kogner, Jan-Inge Henter, Jonas Karlén, Ingrid Öra, Petter Svenberg, Trausti Óskarsson, Tatiana Greenwood, Susanna Ranta,Tony Frisk, Tomas Bexelius, Christina Egnell, Johan Hamrin, Nina Mogensen, Karin Strålin, Mari Wilhelmsson, Clary Georgantzi, Karin Henning
	Stockholm, Huddinge	Mikael Sundin, Jacek Winiarski, Peter Priftakis, Kim Ramme, Petra Byström, Gauti Rafn Vilbergsson, Susan Farmand, Lina Ljungholm
	Lund	Jacek Toporski, Helga Björgvinsdottir, Anders Castor, Lars Hjorth, Helena Mörse, Kees-Jan Pronk, Dominik Turkiewicz, Ingrid Öra, Ulf Tedgård, Annika Mårtensson, Rolf Ljung, Marie Eliasson Hofvander, Patrik Romerius, Johan Svahn, Joakim Wille, Ladislav Krol, Nicholas Brodszki, Joana Makari
	Uppsala	Britt-Marie Frost, Gustaf Ljungman, Johan Arvidson, Josefine Palle, Per Frisk, Åke Jakobson, Anders Öberg, Clary Georgantzi, Annika Englund, Natalja Jackmann, Britt Gustafsson, Tania Christoforaki, Arja Harila-Saari
	Gothenburg	Karin Mellgren, Jonas Abrahamsson, Gustaf Österlundh, Marianne Jarfelt, Magnus Sabel, Magnus Göransson, Cecilia Langenskiöld, Lene Karlsson, Elizabeth Schepke, Lars Kawan, Torben Ek, Cecilia Petersen, Diana Ljung-Sass, Lisa Mellström, Aron Onerup, Martin Dalin, Jerker Isaksson, Caroline Jepsen
	Umeå	Ulrika Norén Nyström, Per-Erik Sandström, Caroline Björklund, Mattias Mattsson, Magnus Borssén, Frans Nilsson
	Linköping	Mikael Behrendtz, Britt-Marie Holmqvist, Per Nyman Hartmut Vogt, Irene Devenney, Lisa Törnudd

The Leukemia Registry

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The Solid Tumor Registry

Cecilia Petersen/Mats Heyman (Sweden)
Bem Zeller/Finn Wesenberg (Norway)
Henrik Schröder (Denmark)
Päivi Lähteenmäki (Finland)
Ólafur G. Jónsson (Iceland)

Solid and Brain Tumour Working Groups

Solid Tumour Committee

Chair	Gustaf Ljungman (SE) *2017*
Denmark	Catherine Rechnitzer *2016* Lisa Hjalgrim *2016* Karin Bækgaard Nissen *2017*
Finland	Kirsi Jahnukainen *2016* Hanna Juntti *2016* Jukka Kanerva *2016* Päivi Lähteenmäki *2016* (ST-registry repr.) Sauli Palmu *2017*
Iceland	Halldora Thorarinsdottir *2016* Solveig Hafsteinsdottir *2016* Ólafur G. Jónsson *2016*
Lithuania	Giedre Rutkauskiene *2016* Indre Tamuliene *2016* Rolanda Nemaniene *2016*
Norway	Bem Zeller *2016* Tove Nystad *2016* Dorota Wojcik *2017*
Sweden	Gustaf Ljungman *2016* Niklas Pal *2016* Torben Ek *2016*

Vision updated

- The STC should be a forum for clinical and strategic discussions.
- More than having stationary WG:s the STC could be the forum to form ad hoc WG:s for upcoming protocols or other burning issues.
- The STC should work side by side with the NOPHO Solid tumor registry group.
- The STC may suggest consultation networks within NOPHO for discussion of difficult cases.
- NOPHO countries do not have to join the same international protocols, but if there is consensus– it is possible with NOPHO representatives.
- At least yearly meetings, generally two per year with one meeting at the annual meeting and another one in parallel to the LCC and BTC meetings.
- It is important to have own studies within the group and studies connected to the registry in order to keep it of good quality. The idea of a project to make a common Nordic registration legal and feasible was launched; the NOPHOCARE project.

All Nordic counties have appointed three formal representatives that form the back-bone of the STC but it has been decided to have an open attitude and invite all those with a special interest in the area to participate and contribute. In addition it has been decided that it would be valuable to have members from other disciplines such as radiotherapy, pediatric surgery, pathology, genetics, radiology,

etc. involved in the group to mimic the situation in the tumor board as the solid tumor work indeed is multidisciplinary. However it may be too ambitious in relation to what program we have and therefore we decided to call in other members when relevant and as needed.

The chairman shall be nominated by the national groups rotating between the Nordic countries in a fashion similar to that in other groups. The first country to be responsible was Sweden and the Swedish national Ped Hem Onc group nominated Gustaf Ljungman to be the first chairman and Patrik Romerius to be secretary of the group. The term for the chairman will be two years.

During the past year the STC has had two meetings, one at the annual meeting in Stockholm in May 2017 and one in Vilnius in November 2017.

At the meetings we had reports from NOPHOCARE, discussions about the goals of the STC, how we should work, discussions about the different national treatment recommendations and that they should be placed on the NOPHO website and regularly updated, open phase 1 and 2 trials in the Nordic countries, presentation of the new renal tumor Umbrella protocol , ExPO-r-Net and very rare tumors, liver tumors and the PHITT protocol, diagnostic workflow for neuroblastoma, presentation of the Veritas study for neuroblastoma, report from bone sarcoma meeting in London June 2017, presentation of the Swedish Childhood Tumor Biobank (Barntumörbanken) and many very interesting case discussions that we decided should be a backbone of the coming STC meetings.

For the STC, Gustaf Ljungman, chairman

Brain Tumour Committee

Members of the Brain Tumour Committee board

Coordinator: Virve Pentikäinen (F)
Denmark: René Mathiassen, Christine Dahl, Helle Broholm (neuropathologist)
Finland: Mikko Arola, Virve Pentikäinen, Anne Hekkala, Tuula Lönnqvist (neuropaed)
Iceland: Halldora Thorarinsdottir
Norway: Tore Stokland, Ingrid Kristin Torsvik, Petter Brandal (radiotherapist)
Sweden: Birgitta Lannering, Stefan Holm, Irene Devenney, Christoffer Ehrstedt, Bengt Gustavsson (neurosurg)

Baltic Countries:

Lithuania: Rosita Kiudeliene, Giedre Rutkauskiene
Estonia: Kadri Saks
Latvia: Zhanna Kovalova
Young NOPHO: Kristiina Nordfors (F), Satu Långström (F)
NOPHO Solid Tumor Registry: Mats Heyman

Change of members:

René Mathiassen, Christine Dahl and Satu Långström (YN) joined as new members of the board. Astrid Sehested and Pernille Wendtland Edslev stepped down.

SIOP-E BT working group members from NOPHO (also NOPHO representatives in the SIOP brain tumour working groups and where relevant national coordinators for SIOP protocols)

Medulloblastoma/PNET: Magnus Sabel (S), Anne Vestli (N), Astrid Sehested (DK), Virve Pentikäinen, Mia Westerholm-Ormio (F)
Low Grade Glioma: Tore Stokland (N), Pernilla Grillner (S), Jon Helgestad, Karsten Nysom, Astrid Sehested, Kamilla Rothe Nissen (opthalmologist) (DK), Päivi Lähteenmäki, Tuire Lähdesmäki (F)
High Grade Glioma / DIPG: Stefan Holm, Klas Blomgren (S), Karsten Nysom (DK), Ingrid Torsvik (N), Virve Pentikäinen (F)
Ependymoma: Ingrid Kristin Torsvik (N), Helena Mörse (S), Pernille Wendtland Edslev (DK), Kirsti Sirkiä (F), Satu Långström (F)
CNS Germ cell tumors: Astrid Sehested (DK), Kristin Solem (N), Irene Devenney (S), Anne Hekkala (F)
Craniopharyngioma: Bengt Gustavsson (S) Tore Stokland (N)
AT/RT: Karsten Nysom, chair (DK), Pernilla Grillner (S), Satu Långström (F)
Quality of Survival: Christoffer Ehrstedt
Radiotherapy: Kristina Nilsson (S), Henriette Magelssen (N), Yasmin Lassen (DK)

Brain Tumour Network

NOPHO Brain Tumour Network is a group open to any NOPHO member working with paediatric brain tumours. Annual Brain Tumour Committee meetings are open to Network members. Network cannot be listed on NOPHO web pages because there are many colleagues who are not NOPHO members. Thus, Brain Tumour Committee members in each country will keep list of national Network members and forward relevant messages.

Meetings

Brain tumour committee meetings

Committee meeting was held in in Stockholm on 19th - 20th May 2017 at the NOPHO meeting (minutes and presentations on www.nopho.org). The next committee meeting will be in Vilnius 1st June 2018, also at the NOPHO meeting.

Other brain tumour meetings

The **SIOP-E Brain Tumour Group meeting** was held in in Prague September 7th - 9th 2017.
The **PAENNO 2017 meeting** was held in Visby September 20th - 22th 2017.
Both meetings were well attended by NOPHO representatives and contained excellent program.
SIOP-E BT working group meeting of HGG/DIPG working group was held in Amsterdam November 27th - 28th 2018.

Future brain tumour meetings

The next meeting of the **SIOP-E Brain Tumour Group** will take place in Denver June 29th – 30th 2018 before ISPNO 2018 meeting.
The **ISPNO 2018** meeting will be held in Denver July 1st – 3rd 2018.

NOPHO CNS research projects

The Nordic study of Cerebellar Mutism Syndrome (CMS) in children with brain tumours of the posterior fossa is open in Denmark, Sweden, Finland, Norway, Lithuania, Netherlands, UK and Hungary. The protocol and forms are on the Nopho web site under "protocols". The study database has been developed at CCEG at Karolinska and remote data entry is ongoing. There have been several on-line meetings in the study group. Patient accrual is going well.

Lithium in the treatment of cognitive late effects after cranial radiotherapy is a study proposed by Klas Blomgren and accepted as a NOPHO study by the NOPHO scientific committee and is planned to run in cooperation with Institut Gustave Roussy in Paris and Hospital for Sick Children in Toronto.

NOPHO collaboration in a study of brain tumour diagnostics using methylation array analysis is also anticipated, initiated from Gothenburg, Sweden.

CNS Tumour molecular classification

New WHO classification for the brain tumours was published in May 2016. It reclassifies the major histological brain tumour diagnoses and uses molecular parameters in addition to histology to define tumour entities. New molecular classification has a major impact on prognosis and treatment of many paediatric brain tumours. Accordingly, integrated histological and molecular diagnosis will be required in new international brain tumour treatment protocols. This defines a need for set up of specific diagnostic methods to fulfil the demand of molecular classification. In NOPHO area, common guidelines for molecular diagnosis have been planned in collaboration with Scandinavian Neuropathological Society (SNS). The aim is to have updated guidelines and list of available molecular diagnostic methods on NOPHO web pages as soon as possible.

Participation in brain tumour protocols

The SIOP-E brain tumour working groups work towards international cooperative protocols and registries to improve treatment for brain tumour patients. The NOPHO Brain Tumour Committee participates in this work through elected NOPHO representatives. We intend to have (at least) one Nordic member in the core committees of each of the new SIOP brain tumour protocol. With the present EU legislation, it is necessary to have a national coordinator from each participating country. These coordinators are also members of the SIOP-E working group.

In the beginning of 2018, three phase II-III protocols were open in NOPHO area (SIOP PNET5 medulloblastoma in Finland and Sweden; SIOP CNS Germ Cell Tumour 2 in Norway and Sweden; BIOMEDE in Denmark and Sweden). In addition, several relapse and phase I-II protocols were open and several protocols were also planned to be opened in the near future.

Medulloblastoma

PNET5 protocol for low-risk and standard-risk medulloblastoma contains upfront analysis of molecular markers of tumour biology to stratify patients to low-risk and standard risk treatment. The study questions are about 1) lowering the dose of therapy (both radiotherapy and chemotherapy) for low-risk patients to decrease the late effects and 2) randomising concomitant carboplatin therapy during radio-

therapy for standard-risk patients to increase the effectiveness of the treatment. The protocol was started in Germany September 2014 and is now open also in Finland, Sweden and several European countries. Recruitment has been extended until at least the end of 2021.

There is now an amendment version 12 of the PNET5 protocol in which SHH (Sonic Hedgehog group) activation has to be tested and accordingly, somatic (blood control) preinclusion sequencing of SHH related genes is mandatory for patients with SHH-activated medulloblastoma to find the tumour predisposing syndromes. Other changes include inclusion of clinically high risk patients with WNT activation (favourable biology) in an observational WNT-HR study and new observational arm for TP53 mutated – SHH activated medulloblastomas. The protocol version 12 is ready to be submitted in each participating country. It requires organization of molecular subgrouping in collaboration with national and international reference laboratories.

Protocols for treatment of infant medulloblastoma and high-risk medulloblastoma are in development. The infant protocol (YC/Young Children MB) will have biologically stratified very low and high risk treatment groups and will include radiotherapy for patients > 18 months with poorest prognosis. Protocol was already to be submitted but increased rate of relapses in North American trials led to re-evaluation of the underlying biology of these tumours in collaboration with HIT-group and North American groups. As a result there is a change of the trial design and the protocol will not will not be opened before 2019. The high risk protocol is for clinical HR medulloblastoma patients over 3 – 5 years with non-WNT biology. It has been submitted for funding bodies. It will include randomisation to HART (hyperfractionated accelerated radiation therapy) or standard radiotherapy or high dose chemotherapy and standard radiotherapy.

Atypical teratoid rhabdoid tumour (AT/RT)

At the moment there is no ongoing study protocol, but the European Rhabdoid Registry (EU-RHAB) contains a registry and treatment recommendations. We continue to recommend that patients are discussed with Michael Frühwald in Augsburg, who coordinates the registry, and that patients are reported to the registry. European protocol for AT/RT is being developed.

Ependymoma

SIOP Ependymoma 2 protocol has been opened in France, UK, Italy, Belgium, Czech, Ireland and Spain and is in the process of being opened in the Nordic countries. This protocol has 3 different strata (risk categories) with separate randomisations in each strata. It does not contain novel therapies apart from valproic acid as HDAC-inhibitor and does not require tumour biology testing in preinclusion screening.

Low Grade Glioma (LGG)

The SIOP-LGG 2004 has closed for randomisation in early 2013, but is still open for registration (treatment standard arm). We continue to recommend that all patients with low-grade glioma be registered in the protocol, including patients who do not receive chemotherapy or radiotherapy.

SIOP-LOGGIC protocol is still being worked upon. Patients will be stratified into risk groups (infant, standard risk and diffuse glioma grade II). The planned randomisations include 1) treatment with standard vincristine-carboplatin or vinblastine monotherapy or trametinib (MEK inhibitor) and 2) duration of the treatment. In addition to PFS as defined by MRI imaging, visual and neurological outcome will be included as primary outcome measures. This will necessitate close cooperation with study ophthalmologists for patients with a visual pathway tumour. A separate protocol for treatment of patients with neurofibromatosis 1 and low-grade glioma is also being developed.

High grade glioma and diffuse intrinsic pontine glioma (DIPG)

Infant HGG protocol was agreed but is now planned to be opened as a registry as the cost per patient was too high. The registry will be opened when the sponsor (Gottingen, Germany) gets enough funding.

The SIOP-e DIPG network has developed a DIPG registry which was published in January 2017 and is

ready for use in each participating country after approval of national authorities.

BIOMEDE (Biological Medicine for DIPG eradication) is a protocol for H3K27M positive pontine gliomas. In NOPHO area it is open in Copenhagen/Denmark and in Stockholm/Sweden, and is planned to be opened in Helsinki/Finland. The protocol contains preinclusion screening of tumour biology and biology dependent randomization for targeted medication combined with radiation therapy.

CNS Germ Cell tumours

SIOP CNS GCT II protocol for patients with CNS germ cell tumours has been opened in Germany, Sweden, Norway, UK, France, Switzerland and Austria and is planned to be opened in Denmark.

Early phase protocols

Regarding possible experimental therapies in NOPHO, the file ”NOPHO novel therapy trials overview” can be found on www.nopho.org under “protocols” and is updated by Karsten Nysom continuously.

- A phase 1 trial with **afatinib** for relapsed or progressive ERB receptor positive tumors is open in Copenhagen, Denmark.
- The **VINILO** study for relapsed low-grade glioma is now in phase 2 and is open in Copenhagen, Denmark.
- A **dabrafenib** trial for relapsed/progressive BRAF V600 mutated tumors except LGG is open in Copenhagen, Denmark.
- A trial of PD1 inhibitor (**pembrolizumab**) in relapsed/progressive PD1 positive solid tumors including brain tumors is open in Lund, Sweden.
- A phase 1 trial of **tazometostat** for relapsed/progressive INI-1 negative tumors including AT/RT is open in Copenhagen, Denmark.
- **MEMMAT** protocol is a phase 2 trial of multidrug antiangiogenic approach for patients with recurrent or progressive medulloblastoma for whom no known curative therapy exists. The trial is open in Copenhagen, Denmark and in all 6 Swedish centers, and will be opened in Norway during May 2018. The protocol is now paused for amendment after no more access to DepoCyte.
- A phase 2 trial of **dabrafenib and trametinib** for BRAF V600 mutant relapsed or refractory high grade glioma is open in Tampere, Finland and Stockholm, Sweden and will soon be opened in Copenhagen, Denmark.
- A phase 2 trial of **ABT-414** (conjugate of EGFR antibody and chemotherapeutic agent MMAF) in high grade glioma with EGFR amplification is open in Helsinki, Finland.
- A phase 2 trial of **nivolumab and ipilimumab** for relapsed or refractory high grade CNS tumors is open in Stockholm, Sweden.
- A phase 2 trial of **larotrectinib** for tumors harboring a NTRK fusions is open in Stockholm, Sweden and a phase 1-2 trial of **LOXO-195** for tumors with NTRK fusions and resistance to larotrectinib is open in Copenhagen, Denmark.

Radiotherapy

The Skandion Clinic in Uppsala has opened in June 2015, and is now running and treating pediatric patients. Several pediatric brain tumor patients have received proton therapy there and some patients with craniospinal irradiation have also been treated.

A national proton facility is also being constructed in Århus, Denmark and planned to open in fall 2018. Until that pediatric patients from Denmark have been sent to MD Anderson Cancer Center in Houston since 2010. Some pediatric patients from Finland have been sent to Essen Proton Center. Norway has plans for building proton facilities. Until that, pediatric patients are sent to the proton centers in Jacksonville, Florida and Heidelberg.

QUARTET is a prospective SIOPE driven radiotherapy quality assurance program in which radiotherapy dose plans of patients included in SIOPE protocols are previewed on the EORTC data platform by appointed pediatric radiation oncologists. QUARTET is already implemented in the new neuroblastoma LINES protocol and the new EPSSG rhabdomyosarcoma protocol and will probably be included in all

new SIOPE protocols as radiotherapy quality assurance. In already started protocols the QUARTET group and the study PIs will discuss regarding the possibility that countries running these protocols can have the quality control done prospectively by QUARTET. The NOPHO Radiotherapy Working Group will discuss QUARTET at their annual meeting in Stockholm in May 2017.

Use of the NOPHO web in CNS tumour work

We continue to encourage that active SIOPE protocols will be put on the NOPHO web with permission of the protocol PI. Minutes of working group meetings should also be posted if permission is granted by the working group chair. In addition, we plan to have guidelines for CNS tumour molecular classification and list of available molecular diagnostic methods on NOPHO web pages.

Virve Pentikäinen
Helsinki, April 18th, 2018

Retinoblastoma Working Group

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The NOPHO Retinoblastoma group was established after the first joint Nordic Retinoblastoma meeting held in Oslo in April 2013.

Members of this group are ophthalmologists, geneticist, radiologists and paediatricians with special interest in retinoblastoma. There are members from four Nordic countries; Sweden, Denmark, Norway and Finland are members of the group. In the future the NOPHO retinoblastoma group hope for representation in the retinoblastoma group of all countries within NOPHO.

Annual meetings rotate between the Scandinavian countries. This year's meeting was held at St. Erik's Hospital, Stockholm 25-26 January, and we focused on metastatic and relapsing RB. In addition, we discussed how to treat patients with intra-arterial chemotherapy. This is carried out regularly in both Stockholm and Aarhus, and Oslo has plans to start with this treatment form.

The different national guidelines for the treatment of Retinoblastoma are posted on the homepage. Our plan is to enhance the cooperation further, especially international cooperation and discussion of complicated patients.

Publications

2018

Landsend ES, Utheim OA, Pedersen HR, Lagali N, Baraas RC, Utheim TP. *The genetics of congenital aniridia-a guide for the ophthalmologist.* Surv Ophthalmol. 2018;63(1):105-13.

2017

All-Eriksson C, Seregard S, Hansson J. Lakartidningen. 2017;114.

2016

Gregersen PA, Urbak SF, Funding M, Overgaard J, Jensen UB, Alsner J. *Danish retinoblastoma patients 1943-2013 - genetic testing and clinical implications.* Acta Oncol. 2016;55(4):412-7.

2014

Bartuma K, Pal N, Kosek S, Holm S, All-Ericsson C. *A 10-year experience of outcome in chemotherapy-treated hereditary retinoblastoma.* Acta Ophthalmol. 2014;92(5):404-11.

2012

Bagger M, Prause JU, Heegaard S, Urbak SF, Degn T, Kiilgaard JF. *Late onset retinoblastoma presenting with vitreous haemorrhage.* Open Ophthalmol J. 2012;6:23-5.

On behalf of the NOPHO Retinoblastoma Group, Einar Stensvold, Oslo, April 2018

Lymphoma Working Group

Hodgkin and Non-Hodgkin lymphoma

Chair	Lisa Hjalgrim DK (2015)
Denmark	Peder Skov Wehner Lisa Lyngsie Hjalgrim
Finland	Päivi Lätheenmäki Pasi Huttunen Päivi Raittinen
Iceland	Ólafur G. Jónsson Sólveig Hafsteinsdóttir
Norway	Maria Gunnes Erling Johan Moe Monica Cheng Munthe-Kaas
Sweden	Karin Mellgren Susanna Ranta Annika Englund Jonas Karlen Fredrik Baecklund
Young NOPHO	Anne Hekkala (FI) Audrone Muleviciene (LT) Diana Ljung Sass (SE)
Reference pathologist	Ulrika Hansson (SE)

Introduction

The NOPHO Lymphoma group is the combination of the previous Hodgkin Lymphoma (HL) (est. 2014) and non-Hodgkin Lymphoma (NHL) (est. 1992) working groups. It was decided to fuse the two fora at the annual NOPHO meeting in Oulu in May 2015. By thus increasing the number of group members, the idea was to achieve synergy by, e.g., facilitating and improving: 1) The registration of all lymphoma patients in the NOPHO register, 2) The sharing patient experiences and discussing of difficult patients, 3) The involvement of the Nordic countries in international lymphoma protocols and scientific projects, 4) The creation of an infrastructure for handling, shipment, and analyses of bio-samples from patients with various types of malignant lymphomas according to international protocols 5) and to have treatment guidelines also for patients with rare lymphomas and 6) and finally to have an updated Lymphoma working group NOPHO webpage.

Over the last two decades, the treatment of both HL and NHL in children and adolescents has followed European protocols.

The lymphoma Registry

The NOPHO NHL-group has been working with on-line registration of patients for a long time and the web-based register has been open for many years, making reporting easier for all clinics. However, change of the NOPHO lymphoma Registry is in process. The registry will include both Hodgkin and non-Hodgkin patients. The aim is to have more simple registration for all lymphoma patients, with type of lymphoma, disease characteristics, treatment strategy, and importantly better registration of relapse

patients and the relapse treatment strategy. At the moment there is no registration of HL patients in the NOPHO registry (besides Swedish patients) and importantly the registration of NHL patients in registry is dropping, which hopefully will be improved with new international trials opening and the common "NOPHO care project".

Hodgkin Lymphoma

Since approximately 2006 Norway, Sweden, and Denmark have treated their HL patients according to the international **Euro-Net-PHL-C1 protocol**. This is a PET- CT response-tailored protocol with a central board, which evaluates all PET CT scans and standardizes staging and treatment of all included patients. The protocol is now closed and the survival rates are excellent. Since October 2015, the **Euro-Net-PHL-C2 protocol** has opened and all the Nordic countries plan to join within the next year, establishing uniform diagnostic risk stratification and treatment of all Nordic HL patients age 0-18 years at diagnosis. Improving HL registration in the NOPHO database creates a unique opportunity for Nordic scientific projects. Countries where the Euro-Net-PHL-C2 protocol have not been initiated follow the **Euro-Net-PHL-C1-interim protocol**.

A common feasibility NOPHO study (Teddi) using breath hold technique during delivery of radiation to thorax and upper abdomen has been initiated (Lundegaard AY, Radiat Oncol, 2018).

Non-Hodgkin Lymphoma

NOPHO-NHL group joined the **ALCL 99 protocol** for treatment of children with *Anaplastic Large Cell Lymphoma* in 2000 and the protocol is now closed for patient inclusion, but is continuously used as best available treatment in most European Countries. Among more than 400 children included from 15 different countries an EFS of 73% has been be achieved. For ALCL, several new parameters predicting relapse have been identified in the last years. Among them, detection and quantification of minimal disseminated disease (MDD) in bone marrow or blood and low antibody titers against ALK turned out to be powerful prognostic factors for treatment failure. The inverse correlation of high antibody titers and negative MDD suggests a possibly meaningful combination of these parameters to define a very high risk group (HR) of ALCL-patients. MDD positive patients who produce low ALK-antibody titers (≤1:750) constitute a HR group of 20 % of ALCL patients. These HR-patients have a 70-80% risk of relapse with current standard multi-agent chemotherapy, e.g. ALCL 99, and include almost all patients with inherent chemo resistant disease (i.e. those patients who progress during front-line therapy). Another important finding from the international collaboration is that contrary to what is found in many other subtypes of NHL, ALCL relapse can be rescued in more than 70% of the patients. NOPHO contribute with patients to the international ALCL relapse protocol that has now been used in 80 evaluable patients with an EFS and OS of 53±6% and 71±5%, respectively. It appears that Vinblastine monotherapy achieves high remission rates in patients with a late relapse of an ALCL. Furthermore, it appears that autologous SCT was ineffective for patients with relapsed CD3-negative ALCL and that allogeneic SCT achieves a high survival rate for patients with relapse of a CD3 positive ALCL and offers a chance for those with progression during therapy. Work with a new international study, ALCL2 is ongoing and will hopefully be opened in 2018/2019.

NOPHO joined the **EURO-LB 02 protocol** for treatment of children with *lymphoblastic lymphoma* in 2005. Patient accrual to the study had to be prematurely closed at July 1st 2008 due to an excess of toxic deaths, of 3.8 %. 351 patients were registered in the study of which 319 were eligible (66 pB-LBL, 233 T-LBL, 20 ambiguous), and pEFS at 5 years was at 81±2%. The results of the trial have just been published (Landmann E, Hematologica 2017): "The primary aims of this trial were to test whether replacing prednisone with dexamethasone during induction increases event-free survival in the subgroups with T-cell lymphoblastic lymphoma and whether therapy duration could be reduced from 24 to 18 months (factorial design, randomizations). These questions could not be answered due to premature closure of the trial. In induction, 215 patients received prednisone and 104 patients received dexamethasone. The median follow-up was 6.8 years (range, 3.0-10.3). The 5-year event-free survival was 82±2% [12 toxic deaths, 5 secondary malignancies, 43 non-response/relapse (central nervous system n=9; all received prednisone during induction)]. The event-free survival rate was 80±5% for patients with precursor B-cell lymphoblastic lymphoma, 82±3% for those with T-cell lymphoblastic lymphoma, and 100% for patients

with a mixed phenotype. During induction, significantly more grade III/IV toxicities were observed in patients receiving dexamethasone, resulting in significant treatment delays. The number of toxic deaths did not differ significantly. The only variable associated with outcome was performance status at diagnosis. Dexamethasone in induction may prevent central nervous system relapse more effectively than prednisone but produces a higher burden of toxicity."

At the moment NOPHO suggest **EURO LB 02** as best available treatment for patients with lymphoblastic lymphomas. The results of the trial is the backbone for the new BFM and NOPHO driven international LBL treatment protocol hopefully finished and ready to open by 2018 (**LBL 2018**).

The **BFM B-NHL 2013** is approved by the VHP in all of the Nordic countries and has started including patients autumn 2017. Registration of patients data in this protocol are through the Marvin database and NOPHO database. Several NOPHO add on studies are part of this protocol (Quality of life study, immune reconstitution study and CNS flow study). The coordinating NOPHO center is Göteborg.

NOPHO is also contributing with patients to the newly opened European international registry of rare pediatric non Hodgkin lymphomas and is coordinating an international survey over patients with peripheral T-cell lymphomas and a European study and relapsed and refractory NHL.

Finally, a common NOPHO study on CNS status measured with flow cytometry in all lymphoma patients both T-NHl and B-NHL patients has been initiated and recruiting patients in all NOPHO countries.

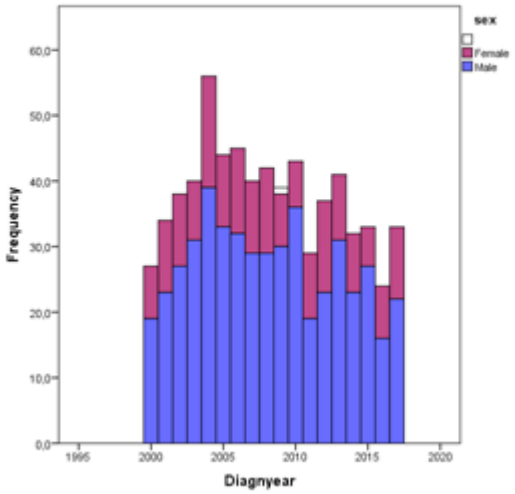
Primary Mediastinal B-Cell lymphoma

There is currently no common treatment protocol within the EicNHL for this small subgroup of NHL patients. Based on the current literature and the NOPHO experience, the NOPHO lymphoma working group recommends treating these patients with the **BFM B-NHL 2004 protocol as backbone chemotherapy adding rituximab to each chemo block**. New treatment **NOPHO guideline** for this disease entity has been put on the NOPHO web.

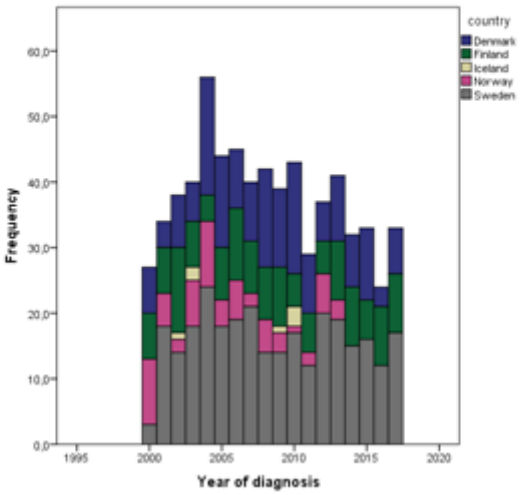
NHL survey of children and adolescens diagnosed with NHL between 2000 and 2017

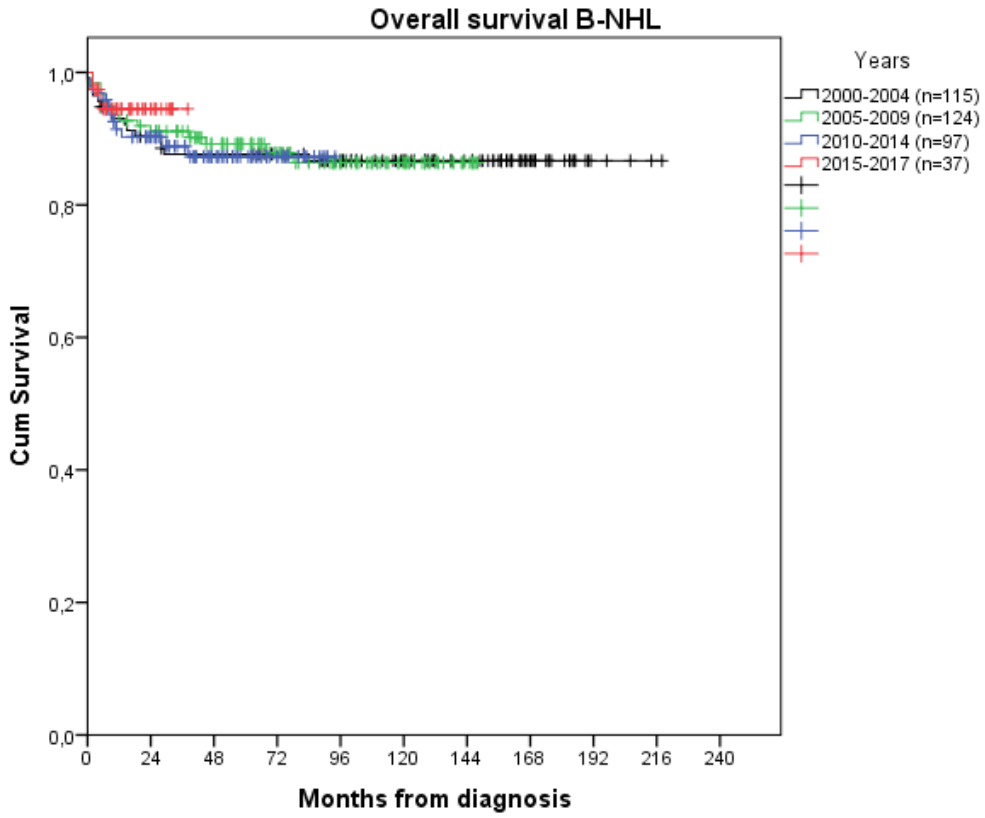
There were 677 reported cases of patients with NHL diagnosed from 1.1.2000 to 31.12.2017 in the five Nordic countries. Patients age 0-18 years have been included in this report. The remaining 677 patients (489 males and 187 females) are reported here below. As can be seen from the figure below the reporting of cases is dropping over the last decade. Patient included from the different countries are as follow: Sweden = 291, Denmark = 173, Norway = 66, Finland = 140 and Iceland = 7

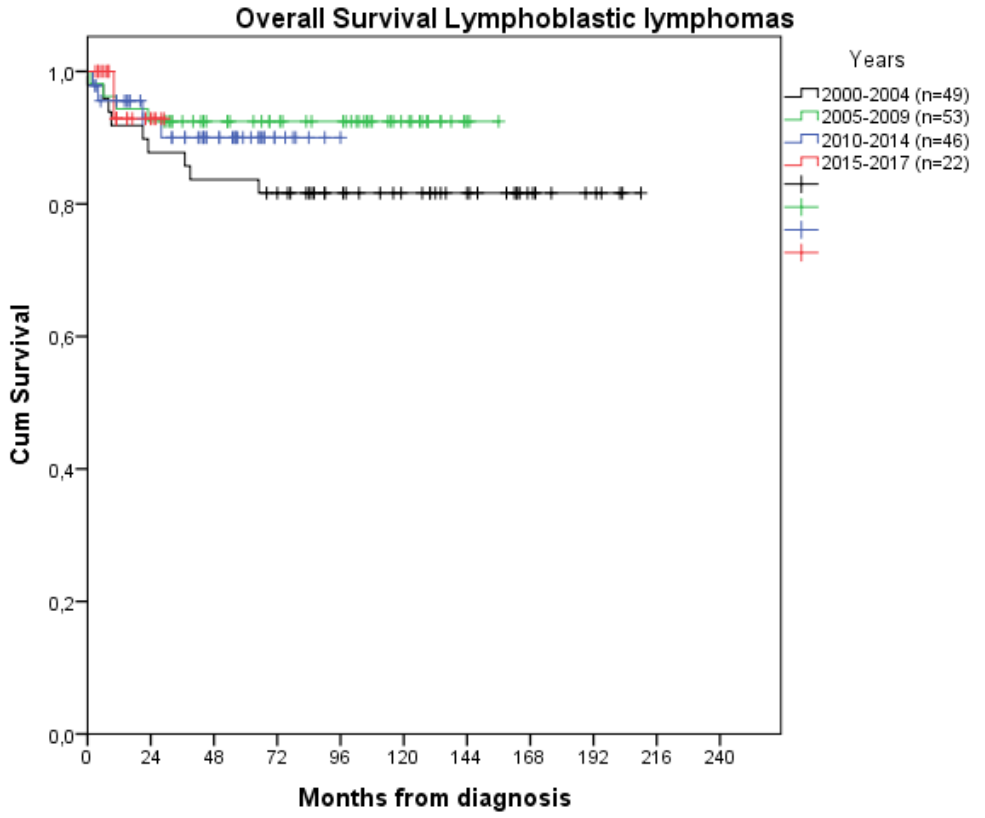
Number of patients over time

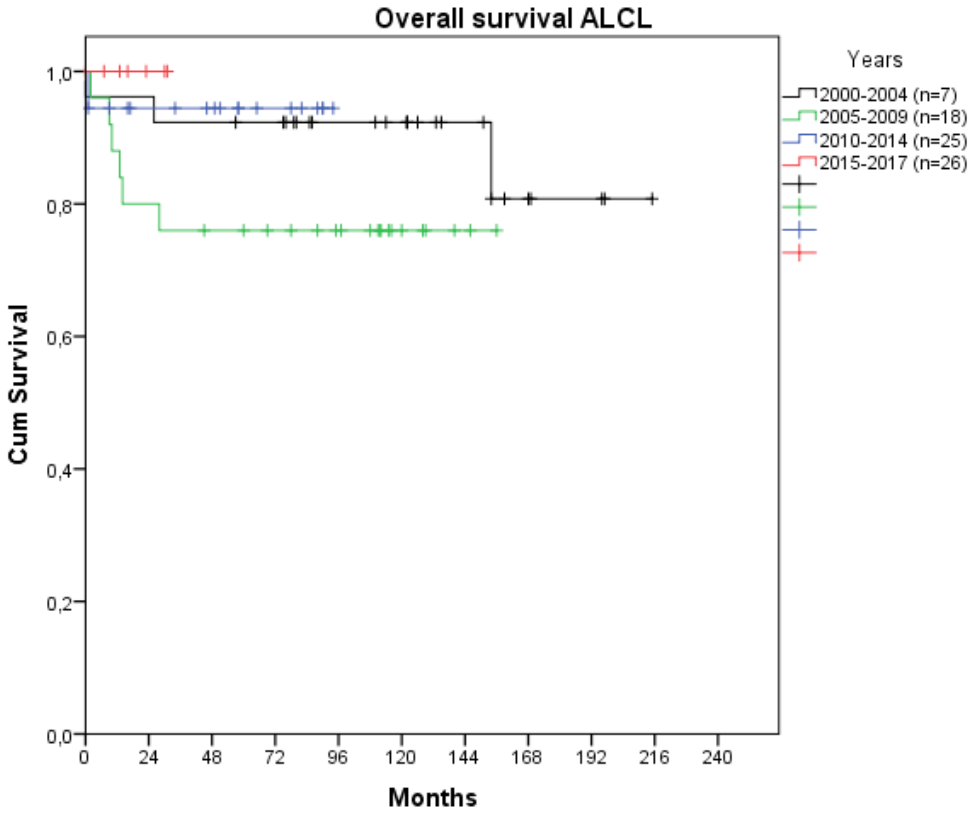


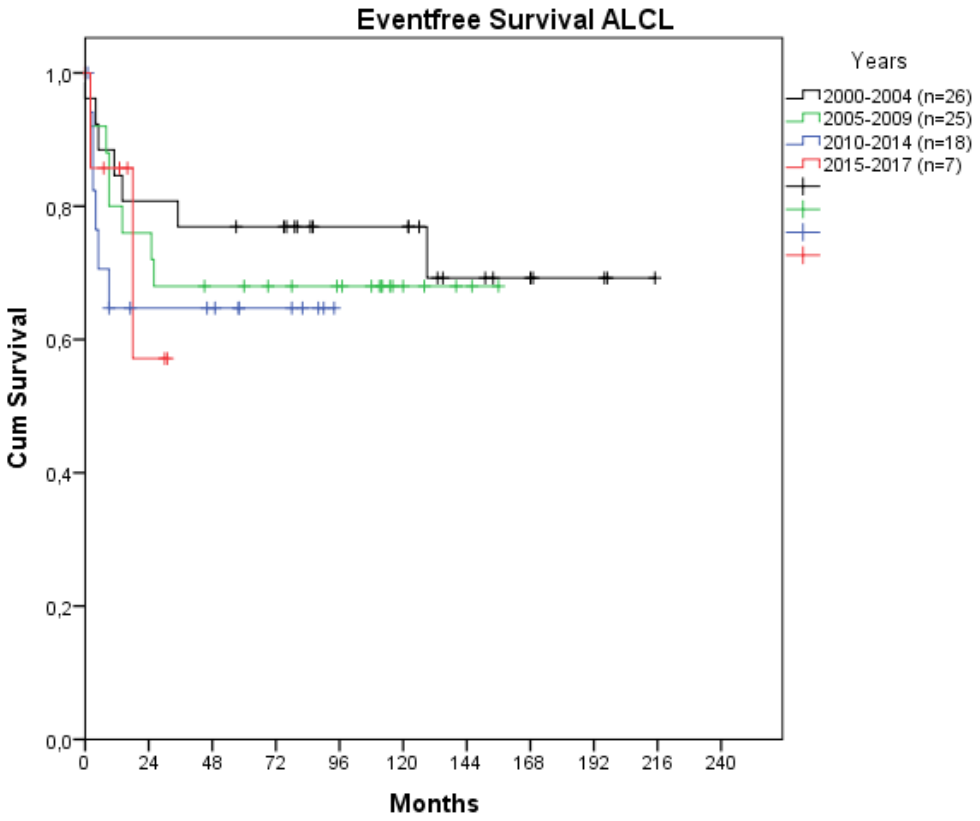
Number of patients per country




Overall survival B-NHL
Years
2000-2004 (n=115)
2005-2009 (n=124)
2010-2014 (n=97)
2015-2017 (n=37)
Cum Survival
1,0
0,8
0,6
0,4
0,2
0,0
0
24
48
72
96
120
144
168
192
216
240
Months from diagnosis


Overall Survival Lymphoblastic lymphomas
Years
2000-2004 (n=49)
2005-2009 (n=53)
2010-2014 (n=46)
2015-2017 (n=22)
Cum Survival
1,0
0,8
0,6
0,4
0,2
0,0
0
24
48
72
96
120
144
168
192
216
240
Months from diagnosis


Overall survival ALCL
Cum Survival
1,0
0,8
0,6
0,4
0,2
0,0
0
24
48
72
96
120
144
168
192
216
240
Months
Years
2000-2004 (n=7)
2005-2009 (n=18)
2010-2014 (n=25)
2015-2017 (n=26)


Eventfree Survival ALCL
Cum Survival
1,0
0,8
0,6
0,4
0,2
0,0
0
24
48
72
96
120
144
168
192
216
240
Months
Years
2000-2004 (n=26)
2005-2009 (n=25)
2010-2014 (n=18)
2015-2017 (n=7)

Summary of the NHL survey

OS for the different types of lymphoma is comparable with what has been described by other groups and is in accordance with last year analyses, but as mentioned before the database lack information about some patients.

The results remain relatively stable over time for B-NHL, pre-B NHL and ALCL. Our Nordic results are well comparable with the results from other groups.

Events in patients with NHL are mainly due to progressive disease or relapse, induction deaths and deaths in CCR.

Data from the NHL registry demonstrates, as other have found, that there is a clear correlation between increasing disease burden at time of diagnosis and decreasing EFs, especially for B-NHL patients.

Overall conclusions

NOPHO takes part in international collaborations for the treatment of HL and NHL. Such cooperation's are necessary to identify patients with specific risk-factors within the very heterogeneous group of lymphoma patients. Moreover, improvement in registration of lymphoma patients in the NOPHO registry will improve the possibility of better surveillance of lymphoma patients with in the region and make it possible for NOPHO to conduct own studies and contribute with data to international studies. Hopefully the common NOPHO care project will help improved registration to the registry. For some NHL subtypes there is clearly need of new protocols.

Lisa Lyngsie Hjalgrim, Chair, Copenhagen, April 2018
Karin Mellgren, Data manager, Gothenburg, April 2018

Publications

Englund A, Glimelius I, Rostgaard K, Smedby KE, Eloranta S, Molin D, Kuusk T, de Nully Brown P, Kamper P, Hjalgrim H, Ljungman G, Hjalgrim LL: ,*Hodgkin lymphoma in children, adolescents and young adults- a comparative study of treatment outcome and clinical presentation*, Acta Oncologica, 2018.

Lundgaard AY, Hjalgrim LL, Rechner LA, Josipovic M, Joergensen M, Aznar MC, Berthelsen AK, Borgwardt L, Johansen C, Loft A, Safwat A, Vaalavirta L, Specht L, Maraldo MV: *TEDDI: radiotherapy delivery in deep inspiration for pediatric patients - a NOPHO feasibility study.* Radiat Oncol 2018.

Landmann E, Burkhardt B, Zimmermann M, Meyer U, Woessmann W, Klapper W, Wrobel G, Rosolen A, Pillon M, Escherich G, Attarbaschi A, Beishuizen A, Mellgren K, Wynn R, Ratei R, Plesa A, Schrappe M, Reiter A, Bergeron C, Patte C, Bertrand Y: *Results and conclusions of the European Intergroup EURO-LB02 trial in children and adolescents with lymphoblastic lymphoma*, Hematologica, 2017.

Leukaemia Working Groups

Leukemia and Lymphoma Committee

Chair	Päivi Lähteenmäki (FI) 2014
Denmark	Peder Skov Wehner, Thomas Frandsen 2014
Finland	Minna Koskenvuo 2017, Mervi Taskinen (re-elected 2017)
Iceland	Ólafur G. Jónsson, Sólveig Hafsteinsdóttir 2013
Lithuania	Ramune Pasauliene 2016, Vilma Rutkauskaite 2017
Norway	Trond Flægstad, Inga Maria Johannsdottir, Bendik Lund 2016
Sweden	Jonas Abrahamsson, Karin Mellgren 2016, Arja Harila-Saari 2016
YN	Audrone Muleviciene (LT)
NOPHO WG-Chairs	
ALL-2008 PI	Kjeld Schmiegelow
ALLTogether	Mats Heyman and Mervi Taskinen
ALL Relapse	Jochen Büchner
ALL WG	Mats Heyman
Adult-ALL-group	Nina Toft
LL Biology	Linda Fogelstrand and Olli Lohi
AML	Jonas Abrahamsson
Biobank	Trond Flægstad
Board chair	Mervi Taskinen
Cytogenetics	Ulrika Norén-Nyström
Event Group	Thomas Frandsen
Infant ALL	Birgitte Lausen
Leukemia registration	Mats Heyman
Lymphoma working group	Lisa Lyngsie Hjalgrim
MDS/JMML	Group co-ordinator Jochen Büchner
MRD-Flow	Hanne Marquart
Ph-ALL/CML	Anders Castor
Pharmacology	Goda Vaitkeviciene
SCT	Carsten Heilmann

The LLC meets twice a year in connection with the Board meeting. The meetings in 2017 were held in Stockholm (May) and in Vilnius (November). The main focus at the meetings has been in the follow-up of the Nordic leukemia protocols, the proceedings of the Lymphoma-WG, and the reports of above mentioned leukemia/lymphoma –related working groups. All these groups report their detailed achievements and efforts under their own titles in this Annual report. As per NOPHO statutes, leukemia- and lymphoma-related NOPHO studies are always evaluated by the LLC before they go to the Board.

The roles of still new LL-Biology WG has been discussed during the year. Important conclusions, e.g., regarding the need for presenting all the genetic studies under preparation also to this group during the process of NOPHO study applications. Discussions on the topic "Biobank material and the ethics" started in 2016 and some developments have been achieved during 2017. NOPHO cancer etiology group and LL-Biology group continue the work on clarifying the processes based on different national laws.

The preparations of the new ALLTogether protocol have regularly been discussed at the LLC and the aim is to be able to start a Nordic piloting phase for the backbone protocol after the Board meeting in June 2018.

LLC could also be a forum for discussing tricky patient cases treated on the NOPHO protocols. These may pop up from the help desk or from the questions directly presented to the protocol PIs. Such cases and discussions may even bring up those new clinical problems that LL-Biology group is searching for.

LLC chair represents NOPHO at the I-BFM board. In the Jerusalem meeting, it was decided that the structure of I-BFM meetings will change from the Spring2019 onwards. A one week European Childhood Cancer meeting will be the future format where separate days for Leukemia/lymphoma, brain tumors and solid tumors will be organized within the SIOPE-meeting concept. Importantly, NOPHO has the big task of organizing the I-BFM meeting and Childhood Leukemia/Lymphoma Symposium (CLLS) in 2018. The schedule will be: 18.5.2018 closed meetings, 19.-20.5. I-BFM Annual meeting, and 21-22.5. CLLS. The venue is the Marina Congress Center in Helsinki. Jukka Kanerva is the chair of the organizing committee that includes representation from NOPHO countries.

LLC chair position has to be checked after two year periods. Päivi Lähteenmäki continues as the LLC chair up to June 2018 Vilnius meeting where Norway will take over. THANK YOU ALL FOR GOOD COLLABORATION!

Turku, April 2018
Päivi Lähteenmäki

ALL Working Group

Coordinator	Mats Heyman
Denmark	Thomas Frandsen
	Birgitte Klug Albertsen
Finland	Päivi Lähteenmäki
	Mervi Taskinen
Iceland	Ólafur Gísli Jónsson
Norway	Inga Maria Rinvoll Johannsdottir
	Trond Flaegstad
	Bendik Lund
Sweden	Jonas Abrahamsson
	Anders Castor
	Johan Malmros
Lithuania	Goda Vaitkeviciene
Estonia	Mari Punab
Adult representatives	
Denmark	Nina Toft, Ulrik Overgaard
Finland	Ulla Wartiovaara-Kautto
Norway	Sigurd Liestøl
Sweden	Helene Hallböök
Lithuania	Laimonas Griskevicius
Estonia	Katrin Palk, Kristi Lepik
Young NOPHO	Adam Alexandersson (FI)
	Nikolas Herold (SE)
Chair of the	
Leukemia and Lymphoma committee	Päivi Lähteenmäki
ALL 2008 protocol committee	Kjeld Schmiegelow
Event group	Thomas Frandsen
Infant ALL	Birgitte Lausen
Relapse of ALL	Jochen Büchner
Ph+ ALL/CML	Anders Castor
MRD group	Hanne Marquart
Cytogenetic group	Ulrika Noren Nyström, Bertil Johansson
Pharmacology group	Goda Vaitkeviciene
MDS	Henrik Hasle
LL-Biology	Olli Lohi, Linda Fogelstrand
A representative from	
NOPHO registry	Mats Heyman
General secretary	Mervi Taskinen

The ALL group meets twice yearly, the day after the Leukaemia & Lymphoma Biology group meetings. The meetings during the year from the last report have been held at Arlanda airport (13th of September 2017 and 14th of March 2018) and have been amalgamated with the NOPHO ALLTogether working group meetings. The main task of the working-group is to coordinate ALL-directed activities within NOPHO and to prepare issues for decision by the LLC and the NOPHO board.

The present ALL protocol (NOPHO ALL-2008)

ALL WG has cooperated with the NOPHO ALL 2008 PI-group in the follow-up of the ALL2008 protocol.

The study protocol has recruited 2236 patients from 1.7.2008 to 31.12.2017. Out of those 1881 were children 1-17.99 years from the Nordic and Baltic countries, 355 adults (age 18-45) from the Nordic and Baltic adults. The protocol is now also recruiting adults up to 45 years in Finland (so far 24 patients included). We no longer separate the Baltic patients from the rest of NOPHO in the evaluations, but Lithuania and Estonia did not take part in the randomisations in the NOPHO ALL-2008 protocol. The randomized parts of the protocol have now closed since 1.3.2016, but the protocol is used as best available therapy until the next protocol is launched.

EFS at five years: children: 0.87 , adults: 0.68.

pOS at five years: overall: children: 0.92, adults: 0.74.

The NOPHO ALL-2008 patients have been considered as three defined cohorts:
Cohort 1: Diagnosis 1.7.2008-31.12.2014 (overall publication of outcome comparing children <18 years with young adults 18-45 years). Publication: Toft et al. Leukemia. 2018 Mar;32(3):606-615.
Cohort 2: Diagnosis 1.7.2008-1.3.2016 ("randomization cohort" - with randomized parts starting recruitment from 1.1.2009 in Denmark and Sweden, 11.2.2009 in Norway, 1.6.2009 in Finland and 7.1.2010 in Iceland).
Cohort 3: Diagnosis 1.7.2008- ongoing ("continuation" population-based cohort until the start of the next ALL-protocol).
The final composition of cohort 1 and 2 is in principle fixed, but further scrutiny may still change details in the registration.

The randomised parts:
R1: treatment with or without 6MP increments during consolidation for SR and IR-patients has now been published: Tulstrup et al, Eur J Haematol. 2018 Jan;100(1):53-60.
R2: 2-weekly (total 15 doses) vs 6-weekly (total 8 doses) PEG-Asp during post-consolidation therapy for SR and IR-patients) has been published in abstract form at ASH 2017 (Klug Albertsen et al) and is now prepared for submission for publication of the final paper.
R3: The third randomization exploring the addition of Depocyte to high-risk patients in Maintenance has already been published: Levinsen et al. J Pediatr Hematol Oncol. 2016 Nov;38(8):602-609.

A large number of additional papers have been published or are planned based on the protocol – most of those will be based on Cohort 2, but some add-on studies may extend into Cohort 3, which is one of the reasons why the protocol stratification and treatment intentions should be kept.

The MRD group and database

An important quality-control measure, which is valuable for many of the publications in the NOPHO ALL-2008 trial is the scrutiny of the MRD-file, has been finalized during the last year by Hanne Marquart and Hans Ole Madsen together with the national coordinators and the MRD-labs throughout NOPHO. The MRD-database is planned for revision and may be used as a central hub for MRD-data in the upcoming ALLTogether protocol.

The Cytogenetic group and database

The Cytogenetic group performs annual central review of the genetic aberrations in the ALL-cohort (both adults and children) in all Nordic countries. This review has the last year been extended to the Baltic countries thanks to the work by Ulrika Norén Nyström and Bertil Johansson.

The database, which has been managed for many years by Erik Forestier is now prospectively stored in the MySQL database together with the rest of the NOPHO ALL-data in Stockholm. For this purpose, a web-based access has been developed, so that genetic labs can enter data directly into the database and central review can be performed on-line. The legacy data from the cytogenetic group is planned to be added to this system, but for practical reasons and time-constraints, this work is still largely pending.

International Collaborations

Internationally, the NOPHO ALL working group has been represented in the I-BFM collaborative ALL working group, the Interfant 2006-, EsPhALL- and IntReALL relapse- study groups, the Ponte-di-Legno (PdL) group as well as an ad-hoc working group for the registration and treatment of patients with Mb Down and ALL originally started within the PdL collaboration.

An additional important contribution is the initiative from Kjeld Schmiegelow to the PdL-group to coordinate toxicity-registration internationally. A consensus paper describing definitions of 14 toxicities has been published: Schmiegelow et al. Lancet Oncol. 2016 Jun;17(6):e231-e239 as well as a paper with detailed data on pancreatitis from 18 study-groups: Wolthers et al. Lancet Oncol. 2017 Sep;18(9):1238-1248.

CNS-toxicity and Osteonecrosis have been chosen as second in line for consensus papers compiling clinical data and biologic material for GWAS-analysis. NOPHO-representatives are Arja Harila-Saari and Stavroula Anastasopoulou (CNS) and Riitta Niinimäki and Signe Sloth Mogensen (osteonecrosis).

The next ALL-protocol - ALLTogether

The international collaboration, which started in 2013 to form a consortium for a common ALL protocol ("ALLTogether") has continued and the first complete draft of the protocol is currently in its final stages. The initially participating study groups: NOPHO, UKALL, DCOG and COALL were during 2016-2017 amended with the Belgian group (BSPHO) and Portugal (SHOP) and during the last year Ireland (PHOAI) and France (SFCE) has also joined the consortium. Mats Heyman, Kjeld Schmiegelow and Mervi Taskinen are the NOPHO representatives and Mats Heyman is the coordinating PI.

Because of the considerable delay in starting the experimental parts of the new protocol (need for funding-applications in the different countries as well as coordinated applications to regulatory authorities), as well as the need for large changes in the organisation of the clinical departments with the advent of the new protocol, it has been suggested that the new protocol is used as best available therapy in a pilot-phase excluding the experimental interventions. This proposal has been submitted as a NOPHO-study and will be discussed at the NOPHO-meeting in Vilnius.

The ALL-WG as an ALL forum

Several working- and ad hoc groups - the LL-biology group, the pharmacology group and the event-group have presented their projects to the ALL-group for feedback and discussion.

The ALL WG has also served as discussion-forum for NOPHO-studies pertaining to ALL-issues giving approvals and recommendations for amendments and further handling by the LLC.

Stockholm, Springtime, 2018
Mats Heyman

Leukemia - ALL Registration Working Group

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Introduction

The NOPHO ALL-2008 trial was the third consecutive trial opened for childhood acute lymphoblastic leukemia in the Nordic countries. In contrast to the NOPHO ALL-92 and ALL-2000 trials, adult patients (18-45 years) were included as well as patients from Estonia and Lithuania. The main objective was to improve outcome compared to previous protocols using risk- and response-based strategies, while abandoning the use of central nervous system irradiation. The initial trial design allowed for three separate randomizations:

R1: Randomization between standard dose of 6-mercaptopurine and dose increments during the consolidation I phase, days 36-85 (SR/IR arms). *Closed for recruitment 1.3.2016. Standard arm used thereafter.*

R2: Randomization between intramuscular PEG-asparaginase administered either at two (standard) or six (experimental) week intervals from week 15 to 33 – total dose 8 doses and 15 doses respectively (SR/IR arms). *Closed for recruitment 1.3.2016. Experimental arm used thereafter.*

R3: Randomization between standard triple intrathecal therapy (prednisolone, methotrexate, cytarabine) and liposomal Cytarabine (DepoCyte®) plus prednisolone given at 12 weeks interval during the maintenance phase, weeks 36 to 96 (HR arm only). *Closed for recruitment 03.09.2012.*

All three randomizations are now closed but the trial is still open for the population-based cohort as best available treatment.

The NOPHO ALL registry is a population-based registry for children with ALL in the Nordic countries. Adults and patients from Lithuania and Estonia are registered as well if they are considered for trial participation. From the time the NOPHO ALL-2008 trial was opened 1.7.2008 to 31.12.2017, a total of 2552 adult and pediatric patients have been recruited but 2236 were eligible for the trial (Figure 1). Table 1 describes the annual recruitment of patients eligible for the trial. From the trial start to the closure of R1 and R2 1.3.2016 a total of 1770 patients were eligible for the trial. This cohort will be used as the publication cohort of the trial results.

Figure 1. NOPHO ALL-2008 trial enrollment and exclusions

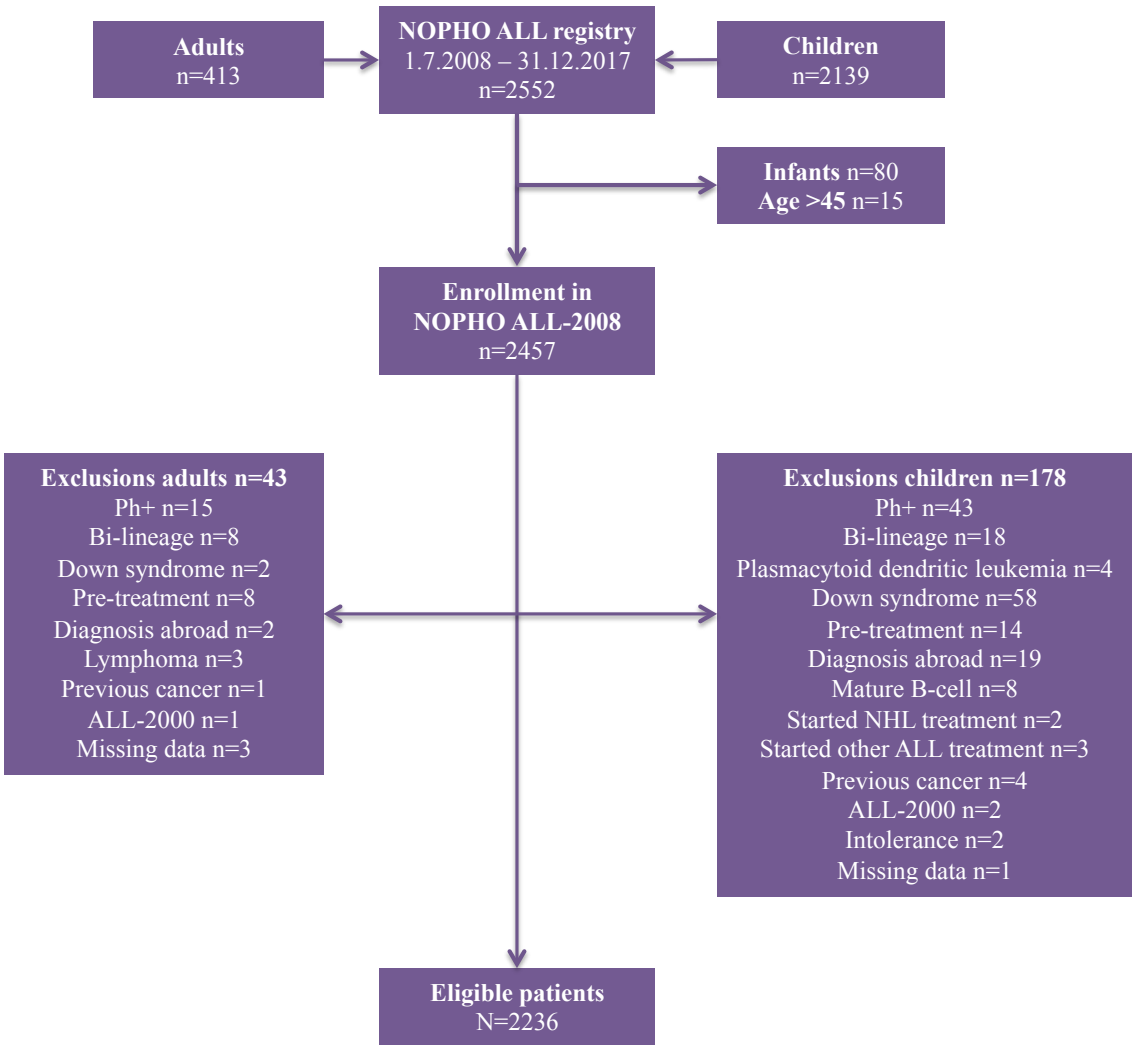


Table 1. Annual trial recruitment by age groups and the number of patients undergoing HSCT in CR1 by year.

Year	All patients	1-17 years	18-45 years	HSCT in CR1
2008	83	78	5	4
2009	206	191	15	16
2010	256	227	29	23
2011	240	196	44	14
2012	213	170	43	18
2013	283	240	43	17
2014	227	185	42	17
2015	217	177	40	17
2016	251	193	58	17
2017	260	224	36	5
Total	**2236**	**1881**	**355**	**148**

In this report we use the last known follow-up time and status available in the NOPHO ALL registry. The registry export used for analyses was made 18.04.2018. For patients with actual follow-up dates <100 days from diagnosis we updated the primary event status and dates based on the information available in the registry (MRD dates, start of specific treatment phases, etc.). Despite our efforts to update the follow-up dates/status, 35 patients registered with a CR1 status have a shorter follow-up time than 100 days. Nearly all of them were diagnosed in 2017. The median follow-up time for surviving patients with a registered CR1 status is now 1587 days (19-3563 days).

Patient characteristics and risk stratification

The characteristics of patients eligible for the NOPHO ALL-2008 trial are described in Table 2. According to the NOPHO ALL registry, eight patients had testis involvement at diagnosis, four children and four adults. Four of them had B-lineage disease and four had T-ALL. In addition, 171 had mediastinal mass at diagnosis, 123 children and 48 adults. Of them 160 (93.6%) had T-ALL. Three patients had concurring testis involvement and mediastinal mass, all with T-ALL.

For the final risk stratification of each patient we used data from the NOPHO MRD and Cytogenetics Working Groups for patients diagnosed 2008-2016. Central reviewing of MRD results and cytogenetics for patients diagnosed in 2017 has not been completed at this point, why we used the MRD data and cytogenetic results available in the registry to assign the final risk stratification based on the "intention to treat" (Figure 2). Two patients could not be assigned a risk group since there was insufficient data for risk stratification. Twenty-one patients died during induction and could therefore not be assigned a risk group. Table 3 describes the relationship between the risk stratification at diagnosis and the final risk stratification.

Table 2. Baseline characteristics, by age groups

Characteristics	All patients n (%)	1-17 years n (%)	18-45 years n (%)
Overall	2236	1881	355
Gender			
Male	1276 (57.1)	1052 (55.9)	224(63.1)
Female	960 (42.9)	829 (44.1)	131 (36.9)
WBC at diagnosis (highest value)			
<100 x 10^9/l	1928 (86.2)	1636 (87.0)	292 (82.3)
≥100 x 10^9/l	308 (13.8)	245 (13.0)	63 (17.7)
Immunophenotype			
Pre-B ALL	1879 (84.0)	1632 (86.8)	247 (69.6)
T-cell ALL	357 (16.0)	249 (13.2)	108 (30.4)
CNS involvement			
CNS1	1940 (86.8)	1621 (86.2)	319 (90.1)
CNS2	197 (8.8)	175 (9.3)	22 (6.2)
CNS3	88 (3.9)	79 (4.2)	9 (2.5)
Missing data	9 (0.4)	5 (0.3)	4 (1.1)
Cytogenetics			
HeH[1]	617 (27.6)	581 (30.9)	36 (10.1)
t(12;21)	436 (19.5)	431 (22.9)	5 (1.4)
t(1;19)	63 (2.8)	56 (3.0)	7 (2.0)
dic(9;20)	32 (1.4)	29 (1.5)	3 (0.8)
iAMP21	34 (1.5)	31 (1.6)	3 (0.8)
MLL rearrangements	71 (3.2)	47 (2.5)	25 (7.0)
Hypodiploidy	26 (1.2)	19 (1.0)	7 (2.0)
Other	545 (24.5)	404 (21.5)	150 (42.3)
Normal	317 (14.2)	229 (12.2)	88 (24.8)
Missing data	85 (3.8)	54 (2.9)	31 (8.7)
Induction stratification			
Non-HR induction	1723 (77.1)	1505 (80.0)	218 (61.4)
HR-induction	513 (22.9)	376 (20.0)	137 (38.6)
Final risk group stratification			
Standard risk	1005 (44.9)	931 (49.5)	74 (20.8)
Intermediate risk	797 (35.6)	656 (34.9)	141 (39.7)
High risk chemo	261 (11.7)	184 (9.8)	77 (21.7)
High risk HSCT	150 (6.7)	92 (4.9)	58 (16.3)
No risk group assigned[2]	2 (0.1)	2 (0.1)	0
Induction Failure	21 (0.9)	16 (0.9)	5 (1.4)

[1]High hyperdiploidy (HeH) includes confirmed HeH, HeH with chromosome number >69 and suspected HeH.
[2]Two patients severely ill during the induction phase, received reduced and highly modified therapy and were not assigned a specific risk group (no d29 MRD). Both achieved CR but relapse occurred as the first event.

Table 3. The relationship between the stratification at diagnosis and the final risk stratification

Final risk group	Non-HR induction	HR induction
SR	1005	0
IR	543	254
HR chemo	54	207
HR HSCT	109	41
Induction failure	10	11
No risk group	2	0
Total	**1723**	**513**

Induction stratification and treatment

The majority of patients (1723, 77.1%) were stratified to the non-HR arm (B-lineage ALL and WBC <100 x 10^9/l at diagnosis) induction therapy and 513 patients (22.9%) to the HR-induction arm (T-ALL and/or WBC ≥100x10^9/l at diagnosis). Among the 513 patients stratified to the HR-induction arm 357 (69.6%) were T-ALL and 156 (30.4%) were B-lineage ALL with WBC ≥100x10^9/l at diagnosis.

Among patient stratified to receive HR-induction, cytogenetic analyses revealed t(12;21) translocation in 29 patients, 28 children and one adult. According to a protocol amendment released in November 2009, patients with B-lineage ALL and WBC ≥100.000 x10^9/l at diagnosis that started HR-induction should be shifted to non-HR-induction if genetic analyses detected a t(12;21) translocation. These patients were not eligible for SR arm therapy or the randomizations and should be stratified to the IR-arm if the MRD-result did not exceed 5% day 29, in which case they would be stratified to the HR-HSCT arm.

The first response evaluation in the treatment protocol is at day 15 during the induction phase. According to the protocol patients receiving HR-induction, patients with MLL rearrangements and patients with hypodiploidy should be switched directly to block therapy if MRD was ≥25% at day 15. In total, 174 (7.8%) patients had MRD ≥25% at day 15. Of them, 66 met protocol criteria for switch to block therapy directly, 61 HR-induction patients and five non-HR induction patients (MLL=3, hypodiploidy=2).

Final risk group

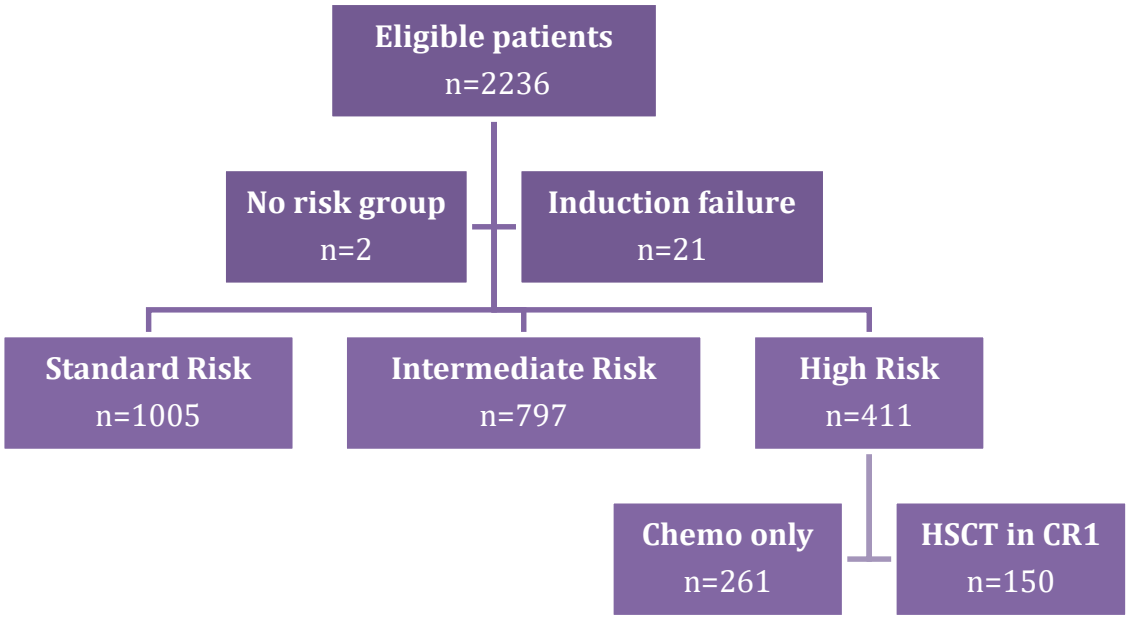
The final risk stratification is based on the induction stratification, cytogenetics, CNS involvement and the MRD response.

The second MRD evaluation is performed day 29 and after that patients are allocated to one of the three treatment arms, SR, IR or HR. In the NOPHO ALL-2008 trial flow cytometry is the method of choice for B-lineage ALL and PCR for T-ALL, with the exception when MRD values are ≥5%, where flow cytometry is preferred since it is more reliable for high MRD values. If a MRD marker is not available patients cannot be allocated to the SR arm. If day 29 MRD is ≥5%, allogeneic HSCT in CR1 is recommended, if a suitable donor is available.

A description of the clinical characteristics by MRD response day 29 is available in our previous report from 2017. In general, MRD response day 29 was worse for adults compared to children. As expected the SR group was the largest group among the pediatric population and IR in the adults population. Furthermore, a higher proportion was allocated to the HR arm among the adult patients.

The final risk group is assigned after the third MRD evaluation, day 79 for SR/IR patients and after the first B-block in HR patients (Figure 2).

Figure 2. Final risk stratification, based on "intention-to-treat"



In the NOPHO ALL-2008 trial the indications for allogeneic HSCT are only based on the MRD response. Patients are assigned to the HR-HSCT group if one of the following criteria is met:

- MRD d15 ≥25% under HR induction and MRD after first A block ≥5%
- MRD d29 ≥5%
- MRD d79 ≥0.1% (must be confirmed with a new MRD day 92)
- MRD after block B ≥0.1% (must be confirmed with a new bone marrow evaluation within one week)
- B-lineage ALL with WBC ≥100.000 x10^9/l at diagnosis and no MRD results available d29 and d79.

After the final risk stratification 150 patients met the criteria for undergoing allogeneic HSCT. According to the ALL registry 148 have undergone allogeneic HSCT in CR1, 115 HR HSCT patients, 25 HR chemo, 6 IR and 2 SR. Of these patients, 96 received non-HR induction and 52 had HR induction. Of the 66 patients that met criteria for block therapy directly after d15 MRD (≥25%), 30 (45.5%) have undergone allogeneic HSCT in CR1. Of the 94 patients with d29 MRD ≥5%, 71 (75.5%) have undergone HSCT in CR1. The annual number of patients undergoing HSCT in CR1 has been relatively stable since 2008 (Table 1).

The NOPHO ALL-2008 trial allowed patients with hypodiploid ALL to undergo HSCT in CR1 although stratified as HR chemo without being excluded from the study. Three of the 25 patients with hypodiploid ALL were stratified as HR chemo but underwent HSCT in CR1.

Protocol adherence

Not all patients were treated according to their assigned risk-group. Protocol adherence was high during the induction phase (Tables 4 and 5) but lower for the treatment administered after the final risk stratification, 97.1% for children and 91.7% for adults (Tables 6 and 7). The most common reasons for non-adherence were discrepancies in the interpretation of MRD and cytogenetics between the clinics and the central review (described in last years report). Other reasons were for example adaptations due to treatment toxicity and a clinical decision based on the physician´s experience or preferences (protocol violation).

Table 4. Protocol adherence – Induction treatment (patients 1-17 years)

Admin\RG	RG=non-HR	RG=HR	Total
Admin=non-HR	1498	4[1]	1502
Admin=HR	5[2]	371	376
Other[3]	2	1	3
Total	1505	376	1881

[1]All patient with B-lineage ALL, hyperleukocytosis and t(12:21) not registered as receiving dexamethasone in the beginning of the induction phase.

[2]All patients were switched to HR induction due to MLL rearrangement

[3]One patient died at the day of diagnosis and two received modified treatment due to toxicity.

Protocol adherence: Risk group = Administered (RG = Adm): 1498+371+4 (included since recommended in the protocol amendment)/1881 **(99.6%)**.

Table 5. Protocol adherence – Induction treatment (patients 18-45 years)

Admin\RG	RG=non-HR	RG=HR	Total
Admin=non-HR	214	2[1]	216
Admin=HR	3[2]	134	137
Total	217	136	353

[1]One patient was treated as non-HR due to spontaneous drop of leukocytes <100 on the day of first treatment but one patient (T-ALL, leu <100) was treated as non-HR due to unknown reasons.

[2]Received HR induction due to unfavorable cytogenetics (MLL n=2, hypodiploidy n=1)

Protocol adherence: Risk group = Administered (RG = Adm): 214+134/353 **(98.6%)**.

Table 6. Protocol adherence - Final risk-group (patients 1-17 years)

Admin\RG	RG=SR	RG=IR	RG=HR-chemo	RG=HR-HSCT	Total
Admin=SR	910	9	0	0	919
Admin=IR	15	633	3	6	657
Admin=HR	2	9	181	85	277
Other	4	5	0	1	10
Total	931	656	184	92	1863[1]

[1]16 patients died during induction and two patients in addition were not eligible for risk group assignment.

Protocol adherence: Risk group = Administered (RG = Adm): 910+633+181+85/1863 **(97.1%)**.

Table 7. Protocol adherence - Final risk-group (patients 18-45 years)

Admin\RG	RG=SR	RG=IR	RG=HR-chemo	RG=HR-HSCT	Total
Admin=SR	67	5	1	0	73
Admin=IR	6	123	0	1	130
Admin=HR	0	8	76	55	139
Other	1	5	0	2	8
Total	74	141	77	58	350[1]

[1]Three patients died during induction

Protocol adherence: RG = Adm: 67+123+76+55/350 **(91.7%)**.

Primary events - children

In the pediatric population the 5-year EFS is now 87% (±1%), the 5-year DFS is 91% (±1%) and the 5-year OS is 92% (±1%) (Table 8). As previously reported, the results in the HR chemo group are disappointing. The 5-year DFS in the HR chemo group is higher than the 5-year OS reflecting the high frequency of deaths in CR1 (10.3%) and a very poor OS after relapse, only nine (26.5%) of 34 patients with relapse are currently alive. The earliest event reported was at the day of diagnosis (two patients with fatal hemorrhage) and the latest event occurred day 2548 (iBM relapse in a child with t(12;21) ALL receiving SR treatment).

Table 8. NOPHO ALL-2008 - treatment-results – all events. Patients 1-17 years treated in Nordic and Baltic centres

Event	BCP WBC<100 n=1505		BCP WBC>100 n=127	T-cell n=249	Total n=1881
Non-responders	0		0	0	0
Death in induction	10		3	3	16
CR-reached	**1495**		**124**	**246**	**1865**
Remission %	**99.3**		**97.6**	**98.8**	**99.1**
CR1, no RG d29*	2		0	0	2
	SR n=931	**IR n=656**	**HR-chemo n=184**	**HR-HSCT n=92**	**CR1 n=1863 (1881)****
Death in CR1	8	13	19	8	48
Relapses	35	46	34	9	124 (126)**
iBM	17	23	26	8	74 (76)**
iCNS	8	13	4	0	25
Testis	0	0	1	0	1
BM+CNS	4	8	3	0	15
BM+testis	3	0	0	0	3
BM+CNS+testis	2	1	0	0	3
BM+Other site	1	1	0	1	3
SMN	9	1	2	0	12
All events	52	60	55	17	184 (202)**
CCR number	879	596	129	75	1679 (1679)**
CCR %	94.4	90.9	70.1	81.5	90.1 (89.2)**
pDFS (60 mo)	0.95 (0.01)	0.91 (0.01)	0.77 (0.04)	0.87 (0.04)	0.91(0.01)***
pEFS (60 mo)	-	-	-	-	0.87 (0.01)
All dead	20	30	45	14	109 (127)**
All alive	911	626	139	78	1754 (1754)**
alive %	97.9	95.4	75.5	84.8	94.1 (93.2)**
pOS (60 mo)	0.97 (0.01)	0.95 (0.01)	0.72 (0.04)	0.83 (0.04)	0.93 (0.01)
Overall pOS (60 Mo)	-	-	-	-	0.92 (0.01)

*Two patients with very severe infectious complications during induction. Long time in ICU and completely modified post-induction therapy. No RG-assignment possible. Both patients relapsed and died of disease.

** Figures in parenthesis include the outliers without risk-group. For "All Events","CCR number", "All dead", "All Alive" and "alive %", they also include the induction deaths.

***For the risk-groups the estimates correspond to pDFS. In the Total column the pDFS/pOS for the whole group of patients that could be risk-grouped is given. The total overall pEFS and pOS also include the patients who could not be risk-grouped and the induction deaths.

Events since the last survey

Since the last NOPHO report 21 new events have occurred among the patients diagnosed 1-17.9 years (Table 9).

Table 9. Post-induction Events by risk-group (final stratification)

Event	SR	IR	HR-chemo	HR-HSCT	Total
Relapse	6	8	3	1	18
DCR1	0	1	0	1	2
SMN	0	0	1	0	1
Total	6	9	4	2	21

Death in CR1 (n=2)

IR-group: 1 case

A 17-year old girl at diagnosis with B-lineage ALL. CNS1 and received non-HR diagnosis. No identifieable MRD marker but good morpholocial response d15 and d29. Stratified to the HR arm on the basis of hypodiploidy. Death in CR1 approximately two years after diagnosis. The cause of death is not available in the registry.

HR-HSCT: 1 case

A 11-year old boy at diagnosis with B-lineage ALL. CNS1 and stratified to non-HR induction. Stratified to HR-HSCT based on d29 MRD >5%. He received HR-block treatment with insufficient MRD response. Although no stratifying cytogenetic aberrations were detected Ph-like translocation was observed why imatinib treatment was initiated. Death in CR1 7.4 months after diagnosis. The cause of death is not available in the registry.

SMN (n=1)

HR-chemo-group: 1 case

A 16-year old boy at diagnosis with T-ALL. Stratified to the HR arm since MRD d29 was >0.1% (but <5%). Became MRD negative after the first A block. Developed MDS three months after discontinuation of maintenance treatment.

Relapses (n=18)

In the pediatric population 18 relapses have occurred since the last survey. Table 10 describes the type of relapse by the final risk group.

Table 10. Relapses by site and risk-group (final stratification)

Rel site	SR	IR	HR-chemo	HR-HSCT	Total
iBM	3	5	3	1	12
iCNS	2	3	0	0	5
BM+testis	1	0	0	0	1
Total	6	8	3	1	18

Primary events – Adults

Table 11. NOPHO ALL-2008 - treatment-results – all events
Patients 18-45 years mostly treated in Nordic and Baltic adult haematology clinics

Event	BCP WBC<100 n=218		BCP WBC>100 n=29	T-cell n=108	Total n=355
Non-responders	0		0	0	0
Death in induction	0		3	2	5
CR-reached	**218**		**26**	**106**	**350**
Remission %	**100**		**89.7**	**98.1**	**98.6**
	SR n=74	**IR n=141**	**HR-chemo n=77**	**HR-HSCT n=58**	**CR1 n=350**
Death in CR1	1	6	7	4	18
Relapses	10	24	16	17	67
BM	7	10	13	10	43
CNS	0	5	1	0	6
Testis	2	1	0	0	3
BM+CNS	1	1	1	1	4
BM+testis	0	0	1	0	1
BM+other site	0	1	0	1	2
Other site	0	3	3	2	8
SMN	0	0	1	0	1
All events	11	30	24	21	86 (91)*
CCR number	63	111	53	37	264 (264)*
CCR %	85.1	78.7	68.8	63.8	74.4 (74.4)*
pDFS (60 mo)	0.79 (0.06)	0.79 (0.04)	0.72 (0.06)	0.58 (0.08)	0.74 (0.03)**
pEFS (60 mo)	-	-	-	-	0.69 (0.03)
All dead	6	24	22	17	69 (74) *
All alive	68	117	55	41	281 (281)*
alive %	91.9	83.0	71.4	70.7	80.2 (79.2)
pOS (60 mo)	0.87 (0.05)	0.79 (0.04)	0.64 (0.06)	0.61(0.08)	0.75 (0.03)
Overall pOS (60 Mo)	-	-	-	-	0.74 (0.03)

* Figures in parenthesis including induction deaths for "All Events","CCR number", "All dead", "All Alive" and "alive %".

** For the risk-groups the estimates correspond to pDFS. In the Total column the pDFS/pOS for the whole group of patients that could be risk-grouped is given. The total overall pOS also includes induction deaths.

Events since the last survey

Sixteen new events have occurred among the adults. Two induction failures, one death in CR1 and 13 relapses. Table 12 describes the post-induction events by risk group and Table 13 the site of relapse by risk group.

Induction failures (n=2)

A 19-year old female with B-lineage ALL. Hyperleukocytosis at diagnosis, CNS1 and no stratifying cytogenetic aberrations. She received HR-induction. Day 15 MRD was >5% but <25%. Death 33 days after diagnosis. The cause of death was toxic megacolon and cardiopulmonary failure.

A 33-year old male with T-ALL. No hyperleukocytosis and CNS1. He received HR-induction. Day 15 MRD was >25% but was not able to start block therapy. Death 37 days after diagnosis. The cause of death was septic shock and incarceration of the brain.

Deaths in CR1 (n=1)

HR-chemo-group: 1 case

A 33 year old male with T-ALL. WBC <100 x10^9/l at diagnosis and CNS 1. MRD d15<25%. He was stratified to the HR-chemo arm because of day 29 MRD >0.1% (but <5%) and good response during block treatment. He died of pneumocystis jirovecii pneumonia approximately four months after discontinuing HR maintenance treatment.

Table 12. Post-induction events by risk-group (final stratification)

Event	SR	IR	HR-chemo	HR-HSCT	Total
Relapse	4	3	4	2	13
DCR1	0	0	1	0	1
Total	4	3	5	2	14

Table 13. Relapses by site and risk-group (final stratification)

Rel site	SR	IR	HR-chemo	HR-HSCT	Total
BM	3	2	3	2	10
BM+CNS	1	0	0	0	1
BM+testis	0	0	1	0	1
Other	0	1	0	0	1
Total	4	3	4	2	13

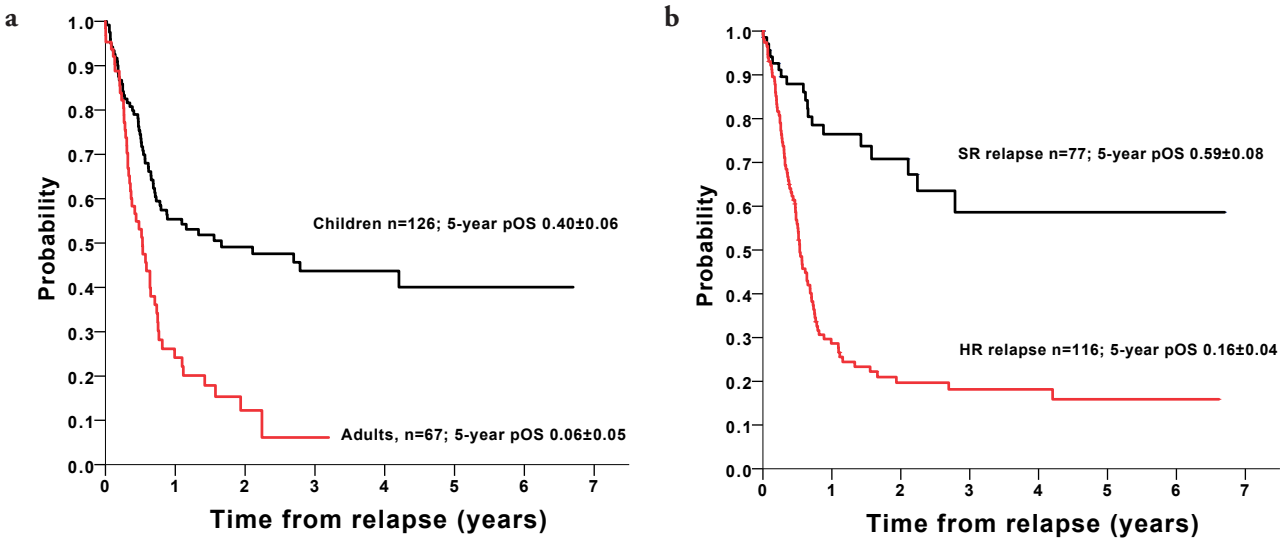
Relapse

In total, 193 relapses have occurred as the first event, in 126 children and 67 adults. Table 14 describes the distribution of relapses by final risk stratification and relapse risk group, as defined by IntReALL (Standard Risk, High risk). The 5-year OS after relapse is now 29% (±5%), 40% (±6%) for children and only 6% (±5%) for adults (Figure 3a). For patients that did not undergo HSCT in CR1 and relapsed (n=166) the 5-year OS is 32% (±5%). In the ALL registry ten patients are registered as "alive after relapse" but have a follow-up time <100 days after first relapse, why the OS numbers in the relapse cohort might be overestimated. The overall survival was better with patients initially stratified as SR and IR compared to HR-chemo/HSCT. This is explained by the higher proportion of SR relapses among SR/IR patients, which generally have a better outcome than HR relapses (Figure 3b).

Table 14. Final risk group vs. relapse risk group and 5-year overall survival

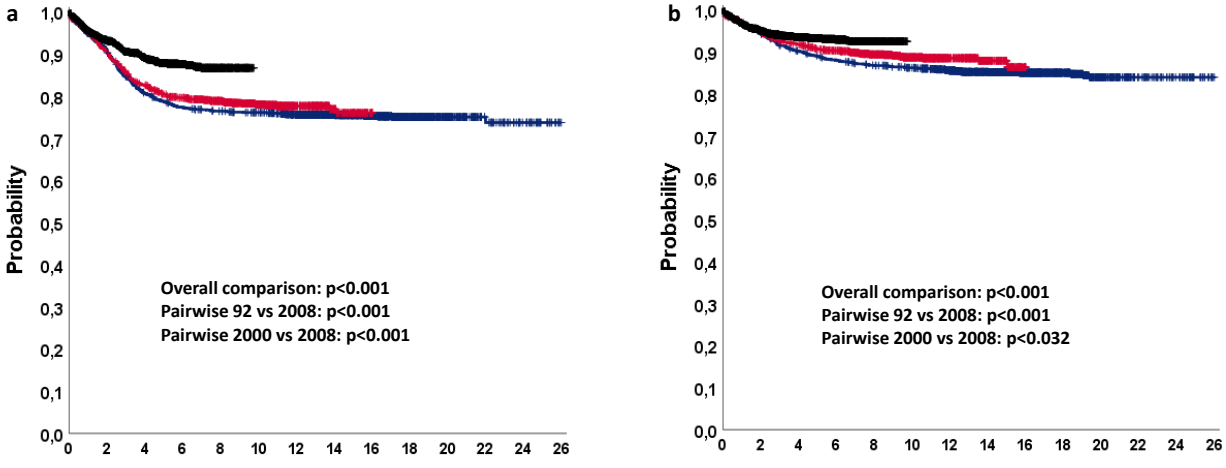
	SR	IR	HR-chemo	HR-HSCT	No RG	Total
All relapses	45	70	50	26	2	193
SR relapse	31	36	5	5	0	77
HR relapse	14	34	45	21	2	116
5-year OS	**55 ±5%**	**34 ±8%**	**16 ±6%**	**12 ±10%**	**0**	29±5%

Figure 3. 5-year overall survival after first relapse; a) by age, b) by relapse risk group



Treatment-results – Survival analyses

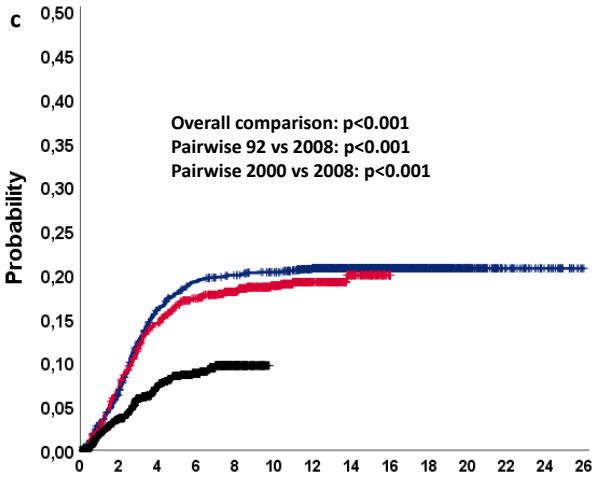
Figure 4. NOPHO ALL-92, NOPHO ALL-2000, NOPHO ALL-2008, Non-B cell ALL 1-<15 years at diagnosis. (a) EFS, (b) OS, (c) cum inc of relapse, and (d) DCR1



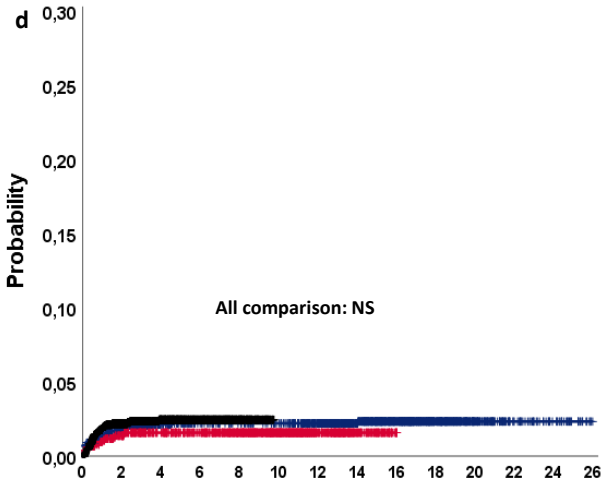
Cohort	Total n	Events	no Event	pEFS (5yr)	pEFS (at FU)
92	1561	386	1175	0.79	0.74
2000	1056	231	825	0.80	0.76
2008	1747	175	1572	0.88	0.87

Cohort	Total n	Deaths	Alive	pOS (5yr)	pOS (at FU)
92	1561	235	1326	0.89	0.84
2000	1056	119	937	0.91	0.88
2008	1747	107	1640	0.93	0.92

Figure 4. NOPHO ALL-92, NOPHO ALL-2000, NOPHO ALL-2008, Non-B cell ALL 1-<15 years at diagnosis. (a) EFS, (b) OS, (c) cum inc of relapse, and (d) DCR1



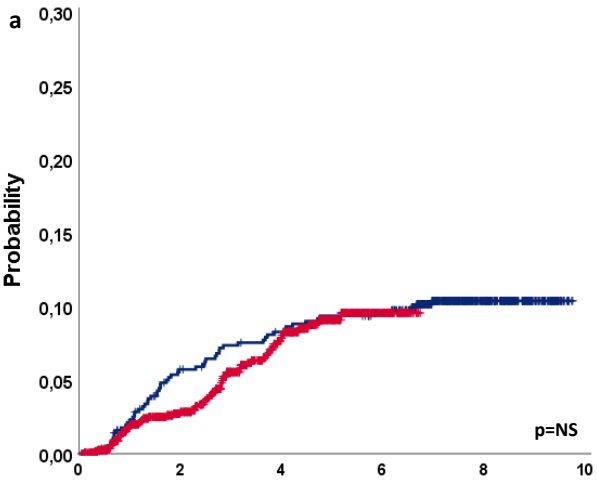
Cohort	Total n	Relpses	no Rel	pRel (5yr)	pRel (at FU)
92	1561	311	1250	0.18	0.21
2000	1056	190	866	0.17	0.20
2008	1747	111	1636	0.08	0.10



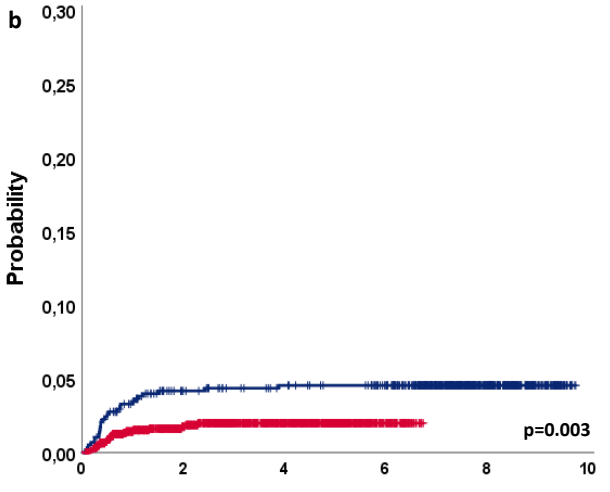
Cohort	Total n	DCR1	no DCR1	pDCR1 (5yr)	pDCR1 (at FU)
92	1561	34	1527	0.022	0.023
2000	1056	16	1040	0.016	0.016
2008	1747	38	1709	0.024	0.024

Results are actually still improving – the very considerable difference in EFS now also shows in OS. The rate of death in CR1 is also dropping. The relapse-rate has halved compared with previous protocols.

Figure 5. NOPHO ALL-2008, Non-B cell ALL 1-<18 years at diagnosis. (a) cum inc of relapse, and (b) DCR1. Early=Diagnosis before 1.7.2011; Late=Diagnosis after 1.7.2011



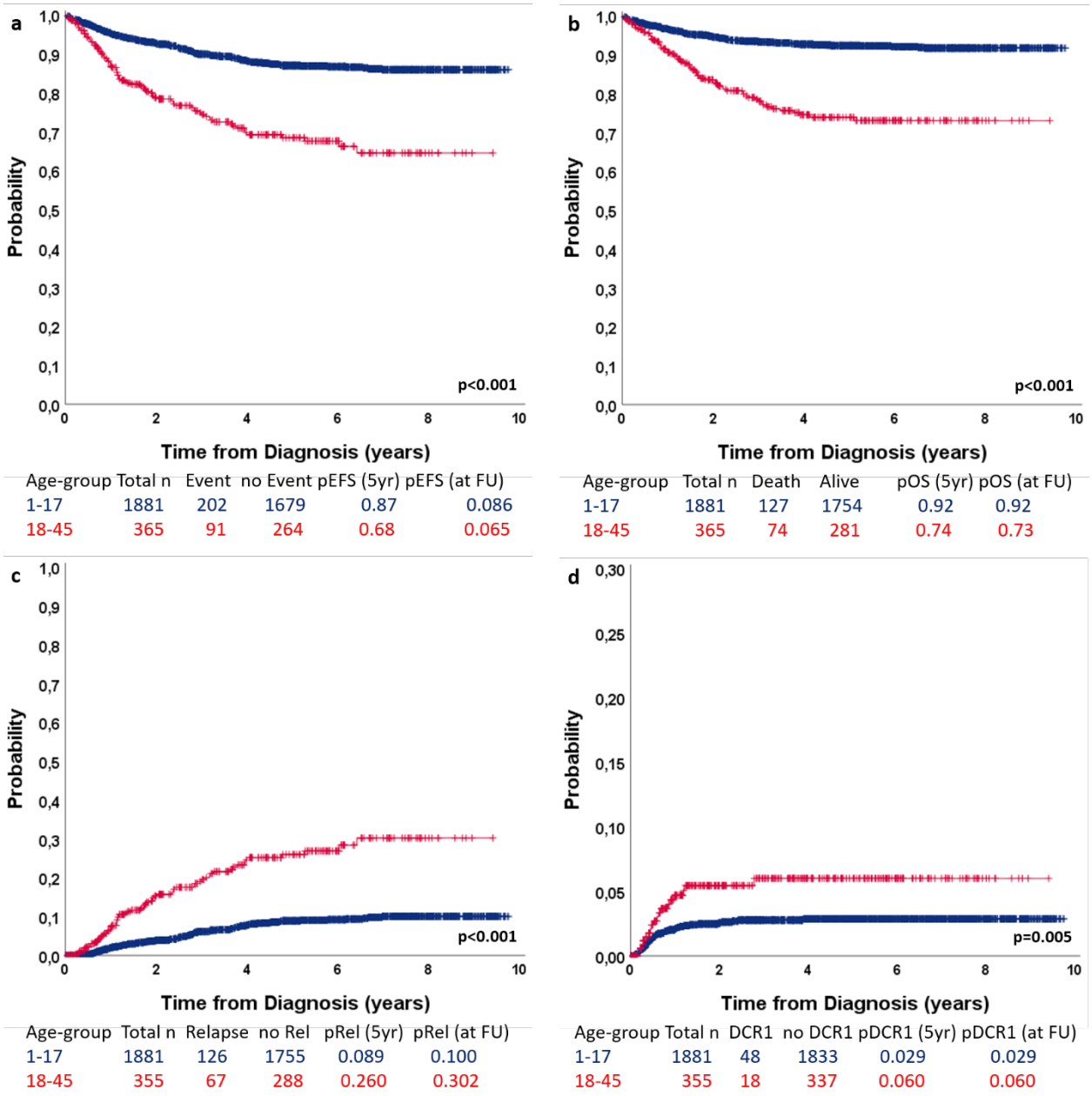
Cohort	Total n	Relapse	no Rel	pRel (5yr)	pRel (at FU)
Early	581	57	524	0.09	0.10
Late	1284	69	1215	0.09	0.10



Cohort	Total n	DCR1	no DCR1	pDCR1 (5yr)	pDCR1 (at FU)
Early	581	26	555	0.045	0.045
Late	1284	22	1262	0.020	0.020

The early toxicity, particularly in the HR-protocol led to amendments, taking effect in the latter part of 2011 that had the desired effect: Treatment-related mortality (TRM) decreased, but the relapse-rate was unchanged and has remained so. The change in TRM is now significant and the overall TRM in the protocol is going down with further recruitment.

Figure 6. NOPHO ALL-2008, NOPHO and Estonian children all patients by age-group (children <17 vs young adults 18-45 years)
(a) EFS, (b) OS, (c) cum incidence of Relapse, (d) cum incidence of DCR1

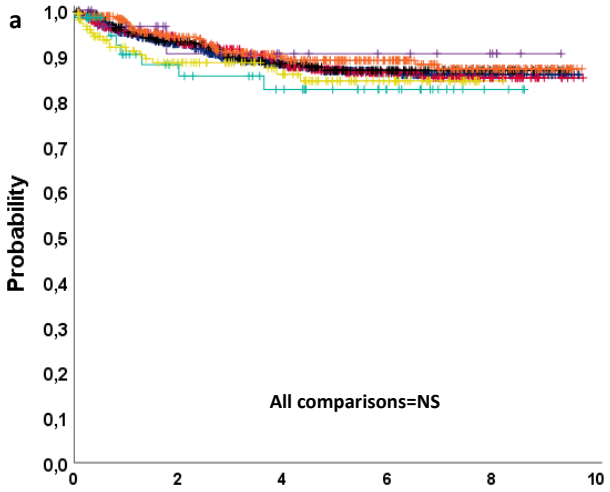


Overall results for children and young adults. The differences are highly significant, also in the risk-stratified analysis, with one exception: the HR-chemo-group (Table 15). The difference is entirely driven by a higher relapse-rate in the older cohort.

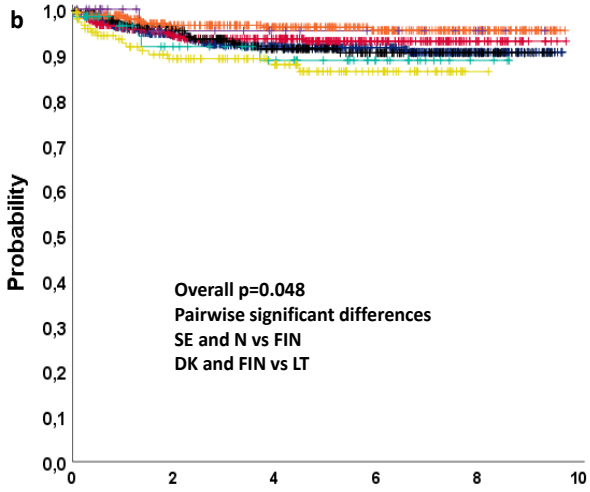
Table 15. Comparison of 5-year EFS for the age-groups stratified by risk-group

Risk-group	1-17 (n)	1-17 EFS	18-45 (n)	18-45 EFS	p-value
SR	931	0.93	73	0.78	<0.001
IR	656	0.89	138	0.75	<0.001
HR-chemo	184	0.66	77	0.62	0.503
HR-SCT	92	0.79	55	0.51	<0.001

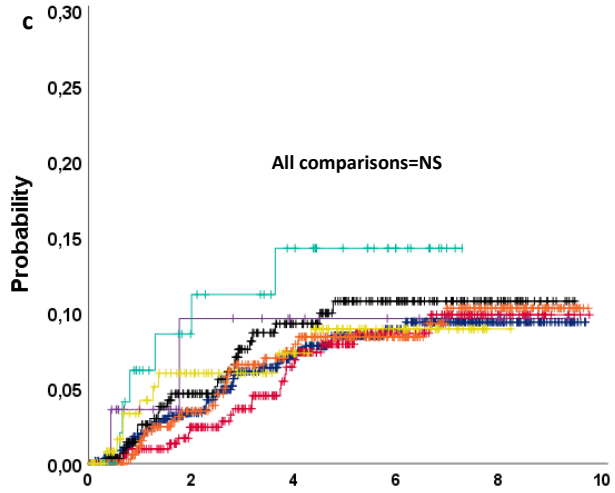
Figure 7. NOPHO ALL-2008, NOPHO and Estonian children <18 by Country
(a) EFS, (b) OS, (c) cum incidence of Relapse, (d) cum incidence of DCR1



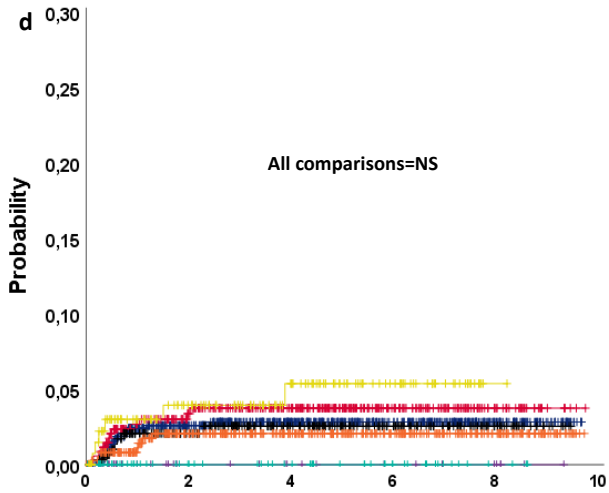
Country	Total n	Event	no Event	pEFS (5yr)	pEFS (at FU)
Sweden	608	69	539	0.87	0.86
Denmark	350	39	311	0.87	0.85
Norway	312	31	281	0.87	0.87
Finland	373	35	338	0.89	0.87
Iceland	31	2	29	0.90	0.90
Estonia	62	8	54	0.83	0.83
Lithuania	145	18	127	0.84	0.84



Country	Total n	Dead	Alive	pOS (5yr)	pOS (at FU)
Sweden	608	47	561	0.92	0.91
Denmark	350	22	328	0.93	0.93
Norway	312	22	290	0.91	0.90
Finland	373	14	359	0.96	0.95
Iceland	31	1	30	0.95	0.95
Estonia	62	5	57	0.89	0.89
Lithuania	145	16	129	0.86	0.86



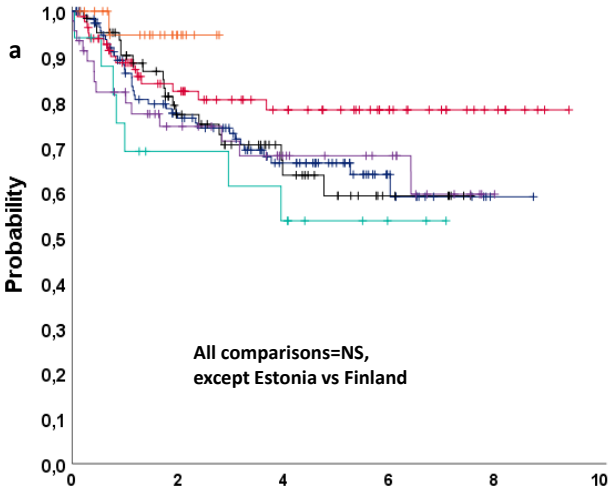
Country	Total n	Relapse	no Rel	pRel (5yr)	pRel (at FU)
Sweden	608	40	568	0.085	0.094
Denmark	350	21	329	0.079	0.098
Norway	312	23	289	0.107	0.107
Finland	373	25	348	0.084	0.103
Iceland	31	2	29	0.096	0.096
Estonia	62	6	56	0.142	0.142
Lithuania	145	9	136	0.089	0.089



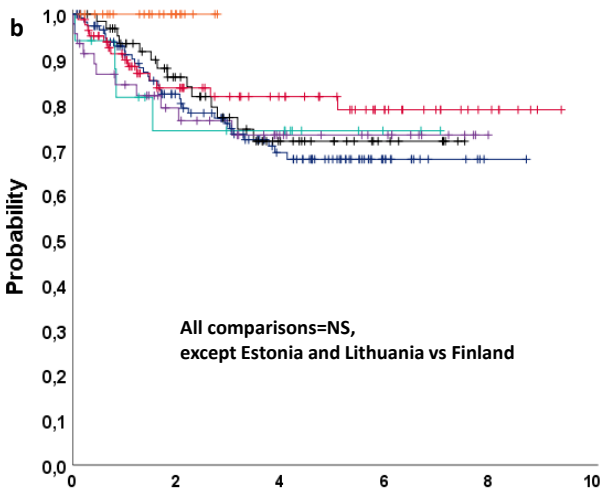
Country	Total n	DCR1	no DCR1	pDCR1 (5yr)	pDCR1 (at FU)
Sweden	608	16	592	0.028	0.028
Denmark	350	12	338	0.038	0.038
Norway	312	7	305	0.025	0.025
Finland	373	7	366	0.021	0.021
Iceland	31	0	31	0.0	0.0
Estonia	62	0	62	0.0	0.0
Lithuania	145	6	139	0.054	0.054

Estonia is a slight outlier in EFS because of a higher relapse-rate (but only 6 relapses in total), and compensates partly with no TRM. Lithuania sticks out with higher death in CR1-rate. However, this may have been due to early problems, since the improvement in the latter part of the protocol has also eradicated this difference (not shown). The detectable differences in OS are mostly the result of early differences in TRM – which have largely disappeared in the later years. Unfortunately, the OS estimates are also somewhat less reliable than EFS, since some patients have insufficient follow-up after relapse.

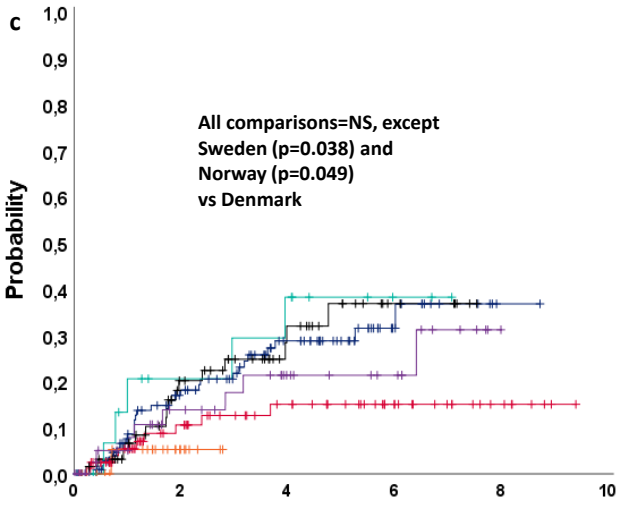
Figure 8. NOPHO ALL-2008, NOPHO and Baltic adults 18-45 years by Country
a) EFS, b) OS, c) cum incidence of Relapse, d) cum incidence of DCR1



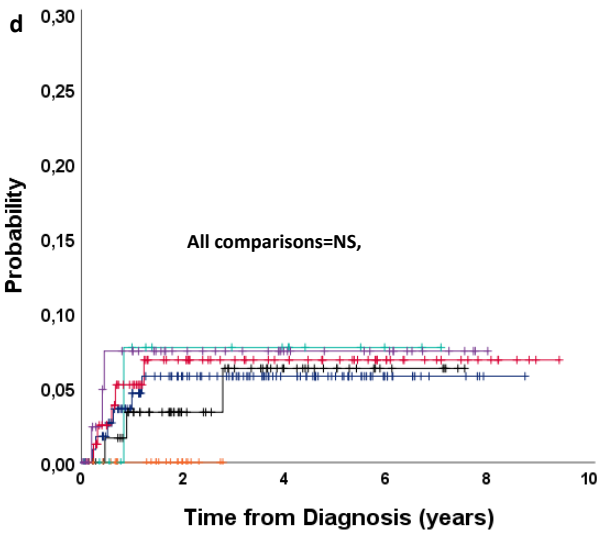
Country	Total n	Event	no Event	pEFS (5yr)	pEFS (at FU)
Sweden	120	35	85	0.67	0.59
Denmark	84	15	69	0.78	0.78
Norway	64	19	45	0.59	0.59
Finland	24	1	23	0.95	0.95
Estonia	17	7	10	0.54	0.54
Lithuania	46	14	32	0.68	0.60



Country	Total n	Dead	Alive	pOS (5yr)	pOS (at FU)
Sweden	120	31	89	0.68	0.68
Denmark	84	14	70	0.82	0.79
Norway	64	14	50	0.72	0.72
Finland	24	0	24	1.0	1.0
Estonia	17	4	13	0.74	0.74
Lithuania	46	11	35	0.73	0.73



Country	Total n	Relapse	no Rel	pRel (5yr)	pRel (at FU)
Sweden	120	28	92	0.29	0.37
Denmark	84	9	75	0.15	0.15
Norway	64	16	48	0.37	0.37
Finland	24	1	23	0.05	0.05
Estonia	17	5	12	0.38	0.38
Lithuania	46	8	38	0.21	0.31



Country	Total n	DCR1	no DCR1	pDCR1 (5yr)	pDCR1 (at FU)
Sweden	120	6	114	0.29	0.058
Denmark	84	5	79	0.15	0.069
Norway	64	3	61	0.37	0.063
Finland	24	0	24	0.05	0.0
Estonia	17	1	16	0.38	0.077
Lithuania	46	3	43	0.21	0.075

The spread of results is more pronounced for the adult group, but the comparisons show few, seemingly spurious significant differences due to the low power. The exception is perhaps the low relapse-rate in the Danish cohort. TRM is considerably higher than in the children, partly reflecting the high fraction of HR-patients and patients transplanted.

Concluding remarks

The NOPHO ALL-2008 trial is closed for recruitment to the randomised studies, but the treatment protocol is still used as the best available treatment in the Nordic countries for both children (≥1 years) and adults (18-45 years). The follow-up time is steadily increasing allowing better capture of events, especially late events such as late relapses and SMNs. To this point, no cases of resistant disease have been registered.

The overall outcome continues to be good, the estimated 5-year OS for children is 93% (±1%) and 74% (±3%) for adults. Although the outcome in the SR and IR arms is very good the outcome in the HR arm has been disappointing. Treatment-related mortality was initially a concern in the HR arm but after the adjustements made according to several protocol amendments (effective for patients diagnosed from about mid 2011) treatment-related mortality has not been more than expected. In total, treatment-related mortality (induction deaths + deaths in CR1) is now 3.9% (3.5% in children and 6.5% in adults) which is comparable to results from recent ALL trials.

The low number of relapses, 8.6% (6.5% in children and 18.9% in adults) is a very positive finding and an important contributing factor to the improved outcome compared to the NOPHO ALL-92 and ALL-2000 trials. Less than one third of relapses are CNS involving which is similar to ALL-92 and ALL-2000 despite the omission of CNS irradiation in ALL-2008. For patients experiencing a relapse as the first event, the outcome is very poor, especially for the HR relapses. The estimated 5-year OS for children is 40% (±6%) and only 6% (±5%) for adults. The outcome after relapse is worse than in the NOPHO ALL-92 and ALL-2000 trials. This finding is very interesting and could suggest that relapses occuring in patients treated according to the NOPHO ALL-2008 protocol are more treatment resistent and/or that the primary treatment is more successful in preventing relapses that generally respond well to relapse treatment.

The balance between survival and toxicity is becoming more challenging. Increasing treatment intensity is not likely to improve the overall outcome, as we have experienced in the HR arm. New therapeutic strategies such as immunotherapy and novel agents need to be implemented in the treatment of patients that respond poorly to the backbone chemotherapy.

The new international ALLTogether protocol is now being finalized and when the recruitment starts the NOPHO countries will enter a new and an exciting era.

This collaboration on an even larger scale is the next rational step in the development, since our statistical margins are decreasing with the improving results. Just as NOPHO has played an important part in the new collaboration, the success of our participation as well as the whole of the protocol depends on the continued fruitful collaboration within NOPHO . The NOPHO ALL registry has proved to be very helpful tool for monitoring the incidence, characteristics and outcome in patients with ALL, especially for children in the Nordic countries where the registry is population-based. The quality of the registration is in general very good and regular updates makes monitoring of events more reliable. This work needs to continue even though we will participate in the ALLTogether trial.

We thank all of the people who contribute to collection of data and registration for your important contribution to the NOPHO ALL registry.

Stockholm, Springtime 2018

Mats Heyman & Trausti Óskarsson

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For details on recruitment and outcome see NOPHO Annual Report ALL2008-section and presentations from previous ALL2008 WG meetings at www.nopho.org.

Meetings

The ALL2008 study committee has merged with the ALL working group, and updates and research on ALL2008 patients are presented at ALL working group meetings and subsequently posted as part of the ALL working group meeting minutes at www.nopho.org. In addition, results and challenges relating to NOPHO ALL2008 has been presented at various meetings in pharmacology WG, MRD WG, ALL event WG, ALL biology WG, and adult ALL meetings. Focus is now only on scientific data exploration and publications.

Protocol/study cohort

By March 1st 2016 (when randomisations were closed) a total of 1908 patients had been registered in the NOPHO ALL2008 register. Of these 141 (7.4%) are excluded from the ALL2008 study cohort due to Down and other ALLpredispositions, previous cancer, mixed phenotype ALL, pre-treatment etc., thus leaving 1469 children and 298 adults in the core cohort for publications.

Randomisations

The protocol was opened July 1st 2008. The three randomised studies opened for children January 1st 2009, but with some delays in entering of patients depending on the approval process in the involved countries. Recruitment has been somewhat below what was projected. Not least R2 (asparaginase at 2

vs. 6 wks intervals) would need several more years of accrual for the study to be sufficiently powered. This reflects poorer recruitment rates (explained by parental refusal and toxicities during consolidation) and somewhat lower relapse rate than originally anticipated. A detailed report was filed to the DSMC December 2015 presenting outcome and toxicity data. Based on these data the DSMC recommended closure of the Rx1 and Rx2, and both studies were closed March 1st 2016. Low dose 6MP and intermittent asparaginase became standards of care. 788 patients have been randomised to Rx1 and 625 to Rx2. Rx1 has been published (Tulstrup, Eur J Haematol 2018) – although 6MP provided borderline significant improvements in fraction of MRD negative patients day 79, no benefit with respect to pEFS was detected. Rx2 results were presented as ASH 2017 and the publication is expected to be submitted by mid 2018. Rx3 (+/- Depocyte in HR maintenance) was closed due to insufficient recruitment and problems with drug supply. The Rx3 study showed borderline significant benefit of Depocyte (Levinsen, J Ped Hematol Oncol 2016).

Toxicity

The compliance to toxicity registration (20 specified toxicities to be registered at 3 months intervals) has been excellent, but reliability differs between the various toxicities. Toxicity profiles for children and adults have been published (Toft, Eur J Haematol 2016; Toft, Leukemia 2018; Rank, Blood 2018). Scrutinization of patient files has revealed that for some toxicities (e.g. peripheral neuropathy) the toxicity data that are routinely captured do not reflect the true incidence. For others including allergy, pancreatitis, thrombosis, and osteonecrosis, the reported toxicity frequencies seem reliable. Approximately 50% of all patients experience one or more of the 20 toxicities. Several of these have been registered in more than 50 patients (allergy, thrombosis, pancreatitis etc) and are being or have been scrutinised in detail (and published). In addition, data on pancreatitis, osteonecrosis, neurotoxicity, and thromboembolism are (or will be) part of the Ponte di Legno Toxicity Working group activities. In general, adults are not more burdened by toxicities than adolescents, but more so for some toxicities, incl. pancreatitis, osteonecrosis and thromboembolism, even in risk group adjusted analyses. Although the simplified MRD-based risk stratification and the major changes in the ALL2008 protocol compared to our previous treatment strategies seem to have reduced the overall relapse rate (especially for T-ALL), the protocol have been somewhat burdened by toxic death. Several amendments to the blocks have aimed to counteract this, and since the latest amendments November 2011 (see www.nopho.org) the toxic death rate for HR-ALL has been acceptable (<5%).

Add-on research

Three large add-on studies are integrated into ALL2008 (see publications):

a. Host genomics: Host DNA has been collected from approximately 90% of the patients. The first ~1300 patients have been exome-enriched SNP-profiled (Illumina Human OmniExome 2.5M). The phenotypes currently addressed are pancreatitis, hyperleukocytosis, CNS leukemia, thrombosis, osteonecrosis, asparaginase allergy, MTX/6MP metabolism, MRD and relapse rates. The first paper on AAP has been published and results are being validated and expanded in a Ponte di Legno study.

b. Maintenance therapy monitoring: Blood sampling has been somewhat below the set target with wide variation between countries and centers. The study has demonstrated strong associations between upstream metabolites and DNA-TGN. This has subsequently been validated in an independent cohort and at strong significant association between DNA-TGN and relapse risk has been shown (HR 0.72 per 100 fmol/micromole DNA for d29 MRD positive patients) (Nielsen, Lancet Oncol 2017). The benefit of adding 6TG to MTX/6MP based maintenance therapy to increase DNA-TGN will be tested in a randomized trial as part of the ALLTogether protocol.

c. Asparaginase antibody and activity monitoring: Sampling has been satisfactory with approximately 8-9 samples having been received per patient.

Publications based on ALL2008 protocol data

1. R**aja R, Schmiegelow K, Frandsen T.** *Asparaginase-associated pancreatitis in children*. Br J Haematol 2012;159:18-27.
2. **Toft N, Birgens H, Abrahamsson J, Bernell P, Griškevičius L, Hallböök H, Heyman M, Holm MS, Hulegårdh E, Klausen TW, Marquart HV, Jónsson OG, Nielsen OJ, Paulsen PQ, Taskinen**

M, Vaitkeviciene G, Vettenranta K, Åsberg A, Schmiegelow K. *Risk group assignment differs for children and adults 1–45 years with acute lymphoblastic leukemia treated by the NOPHO ALL-2008 protocol.* Eur J Haematol 2013; 90: 404-12.

3. **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; 53: 670-4.
4. **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 Methotrexate?* J Ped Hematol Oncol 2013; 35: 417-8.
5. **Vaitkeviciene G, Heyman M, Jonsson OG, Lausen B, Harila-Saari A, Stenmarker M, Taskinen M, Zvirblis T, Asberg A, Groth-Pedersen L, Rageliene L, Schmiegelow K.** *Early morbidity and mortality in childhood acute lymphoblastic leukemia with very high white blood cell count.* Leukemia 2013; 27: 2259-62.
6. **Frandsen TL, Heyman M, Abrahamsson J, Vettenranta K, Åsberg A, Vaitkeviciene G, Pruunsild K, Toft N, Helt L, Bach KF, 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; 50: 251-9.
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11. **Vaitkeviciene G, Matuzeviciene R, Stoskus M, Zvirblis T, Rageliene L, Schmiegelow K.** *Cure rates of childhood acute lymphoblastic leukemia in Lithuania and the benefit of joining international treatment protocol.* Medicina (Kaunas) 2014; 50: 28-36.
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25. **Nielsen SN, Eriksson F, Rosthoej S, Andersen MK, Forestier E, Hasle H, Hjalgrim LL, Aasberg A, Abrahamsson J, Heyman M, Jónsson OG, Pruunsild K, Vaitkevicienė GE, Vettenranta K, Schmiegelow K.** *Children with low risk acute lymphoblastic leukemia are at highest risk of second cancers.* Ped Blood Cancer 2017 (In press).
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28. **Toft N, Birgens H, Abrahamsson J, Griškevičius L, Hallböök H, Heyman M, Klausen TW, Jónsson OG, Palk K, Pruunsild K, Quist-Paulsen P, Vaitkeviciene G, Vettenranta K, Åsberg A, Frandsen TL, Marquart HV, Madsen HO, Norén-Nyström U, Schmiegelow K.** *Results of NOPHO ALL2008 Treatment for Patients 1-45 years with Acute Lymphoblastic Leukemia.* Leukemia 2018; 32: 606-15.
29. **Mogensen PR, Wolthers BO, Grell K, Schmiegelow K, Frandsen TL**. *Association between body mass index and pancreatitis in children with acute lymphoblastic leukemia.* Ped Blood Cancer (In press).

30. **Toksvang LN, De Pietri S, Nielsen SN, Nersting J, Albertsen BK, Wehner PS, Rosthøj S, Lähteenmäki PM, Nilsson D, Nystad TA, Grell K, Frandsen TL, Schmiegelow K.** *Hepatic sinusoidal obstruction syndrome during maintenance therapy of childhood acute lymphoblastic leukemia is associated with continuous asparaginase therapy and mercaptopurine metabolites.* Ped Blood Cancer 2017 (In press).
31. **Mogensen SS, Harila-Saari A, Frandsen TL, Lähteenmäki P, Castor A, Kohonen I, Schmiegelow K, Mäkitie O.** *Early presentation of osteonecrosis in acute lymphoblastic leukemia: Two children from the Nordic and Baltic cohort.* Ped Blood Cancer 2017 (In press).
32. **Henriksen LT, Hojfeldt SG, Schmiegelow K, Frandsen TL, Wehner PS, Schroder H, Albertsen BL - on behalf of the Nordic Society of Paediatric Haematology and Oncology, NOPHO, group.** *Prolonged first-line PEG-asparaginase treatment in paediatric acute lymphoblastic leukaemia in the NOPHO ALL2008 protocol - pharmacokinetics and antibody formation.* Ped Blood Cancer (In press).
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37. **Gerbek T, Ebbesen M, Nersting J, Frandsen TL, Appell ML, Schmiegelow K.** *Role of TPMT and ITPA variants in mercaptopurine disposition.* Cancer Chemother Pharmacol 2018 (In press).
38. **Mogensen PR, Wolthers BO, Grell K, Schmiegelow K, Frandsen TL.** *Association between body mass index and pancreatitis in children with acute lymphoblastic leukemia*. Ped Blood Cancer (In press).
39. **Wolthers BO, Mogensen PR, Frandsen TL, Abrahamsson J, Behrendtz M, Heyman M, Lohi O, Norén-Nyström U, Ruud E, Schmiegelow K.** *Insulin dependent diabetes - a chronic complication to acute pancreatitis in childhood acute lymphoblastic leukemia.* Ped Blood Cancer 2018 (In press).
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41. **Henriksen LT, Hojfeldt SG, Schmiegelow K, Frandsen TL, Wehner PS, Schroder H, Albertsen BL - on behalf of the Nordic Society of Paediatric Haematology and Oncology, NOPHO, group.** *Prolonged first-line PEG-asparaginase treatment in paediatric acute lymphoblastic leukaemia in the NOPHO ALL2008 protocol - pharmacokinetics and antibody formation.* Ped Blood Cancer (In press).
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ALL Relapse Working Group

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(email addresses: see NOPHO webside)

Sweden	Mats Heyman (NOPHO registry) Petter Svenberg (PI SR, HR) Trausti Óskarsson (Young NOPHO)
Denmark	Thomas Frandsen (PI SR, HR) Peder Skov Wehner
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Iceland	Ólafur Gísli Jónsson
Lithuania	Goda Vaitkeviciene (PI SR, HR)
Norway	Jochen Büchner (Chair, PI HR, SCT, CART) Inga Maria Johannsdottir (PI SR) Dorota Malgorzata-Wojcik

The NOPHO ALL relapse WG had one face-to-face meeting (May 19, 2017) and one telephone conference (Feb 16, 2018) since the last report. See minutes on the NOPHO webside.

Current Topics

IntReALL SR

By Feb 2018, around 400 pts were enrolled into the SR trial. The protocol is recruiting patients in Norway, Denmark and Finland; soon also in Sweden after sponsorship has been changed to Karolinska Hospital.

The 2nd randomization in the SR arm is currently stopped as Epratuzumab is no longer available (effectuated by a non-substantial amendment to the SR protocol). A substantial amendment will be necessary when the drug is provided from a new company (new IB and IMPD).

IntReALL HR

DK: co-sponsor contracts are signed, sites will be initiated soon
S: national sponsor changed to Karolinska Hospital. Co-sponsor contract not yet signed
NO: not yet approved due to lack of time
FI: co-sponsor contract signed, not yet date for initiation

ALL-SCT-PED-FORUM study

By March 2018, 27 countries with 102 centers participate in the trial. Open in Norway, Denmark, Sweden and Finland; 50 Nordic patients are so far included. Eligibility includes relapsed ALL patients age 0-18 years with an indication for allogeneic stem cell transplantation.

The last Development Safety Update Report (DSUR) was accepted by the authorities, and recruitment continues unchanged. Protocol version 4.0 with amendments was published in January 2018.

CAR-T study for r/r pediatric ALL

Recruitment of relapsed and refractory (r/r) pediatric B-ALL patients into the global ELIANA CAR-T cell trial (Novartis) is completed; four Nordic patients were treated with CTL019. Results from the trial have recently been published (Maude et al., N Engl J Med 2018;378:439-48.). Since September 2017, an Expanded Treatment Protocol with CTL019 is open in Oslo, recruitment is still ongoing, three patients are included. Contact/PI is Jochen Büchner.

Another CAR-T cell trial for children with r/r ALL has been opened in Uppsala, contact person is Gunilla Enblad (gunilla.enblad@igp.uu.se).

Other phase I/II trials for r/r pediatric ALL

Several drugs for relapsed precursor B-ALL are currently tested in phase I/II trials, including Blinatumomab, Inotuzumab ozogamicin, and Carfilzomib. For more details and contact persons, check the overview of current phase I/II trials on the NOPHO webside, member area, NOPHO Novel Therapy WG.

Next meeting

June 1, 2018, 9 a.m. Main topics will be: upcoming new trials for r/r ALL and T-ALL; how to choose and prioritize the different early phase trials and tailor treatment for patients who are either not eligible for an IntReALL protocol, or have a 2nd or higher relapse; and further discussion on the "International Virtual Biobank for IntReALL" (ViBE/Scopeland).

For the working group

Jochen Büchner
Oslo, April 2018

Events Working Group (EWG)

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	Ruta Tuckuviene (Thrombosis study)	ruta@dadlnet.dk

Since last annual report the NOPHO Events group has twice. The main focus of our work has been the adverse effect monitoring of NOPHO-ALL 2008 protocol; especially toxic phenotypes (both as single projects, as part of the NOPHO SNP studies (GWAS) and as part of The iBFM/PdL toxicity consensus work), toxicity related deaths and fungal infections.

The group participates in the work towards the next ALL protocol – ALLTogether – both regarding recommendations and in the work-up of toxicity registration for the new protocol.

The main issues discussed during the last year:

SAEs in NOPHO-ALL 2008

Focus groups have continued scrutinizing the data on the issues mentioned below and have already reported data in publications and presentations and more publications are on their way:
Pancreatitis, vincristine related toxicity, thrombosis, osteonecrosis, VOD and fungal infections.

PdL/IBFM Toxicity Consensus Definition working group

Consensus definitions has been reached for 14 toxicities. The consensus definitions were published in Lancet Oncology (april 2016).
The first business case from the PdL – toxicity working group will be Asparaginase Associated Pancreatitis and has been submitted. First Author is Benjamin Ole Wolthers.

At the IBFM meeting in Helsinki the PdL toxicity working group will be discussing strategies for capturing the next cases from the working group (ON and Neuro-toxicity)

- Kjeld Schmiegelow is coordinating this international Ponte di Legno toxicity working group.
- NOPHO members working with selected toxicities are participating in this work.

Upcoming ALLTogether protocol

Mats Heyman coordinates the NOPHO participation in the upcoming joint ALLTogether protocol. This process is ongoing.

SNP/GWAS studies

A large number of SNP/GWAS studies are ongoing at the moment

- Infection Related deaths (Bendik Lund)
- Pancreatitis (Benjamin Ole Wolters – published)
- ON (Signe Mogensen – manuscript approved with minor revisions)
- VOD (Thomas Frandsen – published)
- CNS-leukemia (Mette Levinsen)
- Hyperleukocytosis (Goda Vaitkeviciene)
- Thrombosis (Ruta Tuckuviene)

Future work of the group

The function as a reference group for problem ALL patients will continue.

Monitoring and analyzing life threatening adverse events and AE's not directly associated with chemotherapy (e.g. infections) are tasks for the Events Working Group.

Annual evaluation of SAE:s will be performed to find out which SAE:s should be studied in detail.

Toxicities and relapses continue to be the major focus issues.

ALLTogether toxicity registration and subgroups in this area will be a priority

Next meeting Sept 24th , 2018 Copenhagen.

Copenhagen 25.4.2018 Thomas Frandsen

Events group related Publications 2017-2018:

Mogensen PR, Wolthers BO, Grell K, Schmiegelow K, Frandsen TL. *Association between body mass index and pancreatitis in children with acute lymphoblastic leukemia*. Pediatr Blood Cancer. 2018 Apr 18:e27071. doi: 10.1002/pbc.27071. [Epub ahead of print] PubMed PMID: 29667750.

Rank CU, Toft N, Tuckuviene R, Grell K, Nielsen OJ, Frandsen TL, Marquart HVH, Albertsen BK, Tedgård U, Hallböök H, Ruud E, Jarvis KB, Quist-Paulsen P, Huttunen P, Wartiovaara-Kautto U, Jónsson ÓG, Trakymiene SS, Griškevičius L, Saks K, Punab M, Schmiegelow K. *Thromboembolism in Acute Lymphoblastic Leukemia: Results of NOPHO ALL2008 Protocol Treatment in Patients 1-45 Years*. Blood. 2018 Apr 16. pii: blood-2018-01-827949. doi: 10.1182/blood-2018-01-827949. [Epub ahead of print] PubMed PMID: 29661787.

Tulstrup M, Frandsen TL, Abrahamsson J, Lund B, Vettenranta K, Jonsson OG, Marquart HVH, Albertsen BK, Heyman M, Schmiegelow K. *Individualized 6-mercaptopurine increments in consolidation treatment of childhood acute lymphoblastic leukemia: A NOPHO randomized controlled trial.* Eur J Haematol. 2018 Jan;100(1):53-60. doi: 10.1111/ejh.12979. Epub 2017 Nov 9. PubMed PMID: 28983968.7:

Tram Henriksen L, Gottschalk Højfeldt S, Schmiegelow K, Frandsen TL, Skov Wehner P, Schrøder H, Klug Albertsen B; Nordic Society of Pediatric Hematology and Oncology, NOPHO Group. *Prolonged first-line PEG-asparaginase treatment in pediatric acute lymphoblastic leukemia in the NOPHO ALL2008 protocol-Pharmacokinetics and antibody formation*. Pediatr Blood Cancer. 2017 Dec;64(12). doi: 10.1002/pbc.26686. Epub 2017 Jun 29. PubMed PMID: 28660740.

Mogensen SS, Harila-Saari A, Frandsen TL, Lähteenmäki P, Castor A, Kohonen I, Schmiegelow K, Mäkitie O. *Early presentation of osteonecrosis in acute lymphoblastic leukemia: Two children from the Nordic and Baltic cohort*. Pediatr Blood Cancer. 2017 Nov;64(11). doi: 10.1002/pbc.26624. Epub 2017 May 18. PubMed PMID: 28521072.

Wolthers BO, Frandsen TL, Baruchel A, Attarbaschi A, Barzilai S, Colombini A, Escherich G, Grell K, Inaba H, Kovacs G, Liang DC, Mateos M, Mondelaers V, Möricke A, Ociepa T, Samarasinghe S, Silverman LB, van der Sluis IM, Stanulla M, Vrooman LM, Yano M, Zapotocka E, Schmiegelow K; Ponte di Legno Toxicity Working Group. *Asparaginase-associated pancreatitis in childhood acute lymphoblastic leukaemia: an observational Ponte di Legno Toxicity Working Group study.* Lancet Oncol. 2017 Sep;18(9):1238-1248. doi: 10.1016/S1470-2045(17)30424-2. Epub 2017 Jul 20. PubMed PMID: 28736188.

Toksvang LN, De Pietri S, Nielsen SN, Nersting J, Albertsen BK, Wehner PS, Rosthøj S, Lähteenmäki PM, Nilsson D, Nystad TA, Grell K, Frandsen TL, Schmiegelow K. *Hepatic sinusoidal obstruction syndrome during maintenance therapy of childhood acute lymphoblastic leukemia is associated with continuous asparaginase therapy and mercaptopurine metabolites*. Pediatr Blood Cancer. 2017 Sep;64(9). doi: 10.1002/pbc.26519. Epub 2017 Apr 19. Erratum in: Pediatr Blood Cancer. 2018 Jan;65(1):. PubMed PMID: 28423235.

Wolthers BO, Frandsen TL, Abrahamsson J, Albertsen BK, Helt LR, Heyman M, Jónsson ÓG, Kõrgvee LT, Lund B, Raja RA, Rasmussen KK, Taskinen M, Tulstrup M, Vaitkevičienė GE, Yadav R, Gupta R, Schmiegelow K. *Asparaginase-associated pancreatitis: a study on phenotype and genotype in the NOPHO ALL2008 protocol*. Leukemia. 2017 Feb;31(2):325-332. doi: 10.1038/leu.2016.203. Epub 2016 Jul 25. PubMed PMID: 27451978.

NOPHO ALLTogether Working Group

Coordinators	Mervi Taskinen, Mats Heyman
Denmark	Thomas Frandsen
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	Birgitte Klug Albertsen
	Nina Toft
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	Helene Hallböök (Sweden)
	Sigurd Liestøl (Norway)
	Ulla Wartiovaara-Kautto (Finland)
	Laimonas Griskevicius (Lithuania)
	Mari Punab (Estonia)

Representatives in ALLTogether task-forces	
Cytogenetics	Bertil Johansson
MRD	Hanne Marquart and Hans Ole Madsen
CAR-T	Jochen Büchner
Toxicity	Jukka Kanerva, Thomas Frandsen
Asp-TDM	Birgitte Klug Albertsen
SCT	Marianne Ifversen
Osteonecrosis	Riitta Niinimäki
HDM	Torben Stam Mikkelsen, Kjeld Schmiegelow
Maintenance	Kjeld Schmiegelow
CNS	Mervi Taskinen
Regulatory	Mats Heyman
Statistics	Mats Heyman, Matteo Bottai

The ALLTogether-group was formed when NOPHO decided to join the ALLTogether consortium and then took over from the ALL-2016 group.

After most of the structure of the ALLTogether protocol has been finalised, the NOPHO ALLTogether group meetings have in the last year been coordinated with the ALL working-group meetings. This has some advantages, adding the input from the ALL-working-group members, who are not members of the ALLTogether working group and it also economises on travelling. The obvious disadvantage is the risk of over-loading the agenda and not getting enough time for each item.

NOPHO participation has been important in the working-groups of the ALLTogether protocol concerning the core activities defining some aspects of the protocol itself (CNS-, statistics- and SCT) as well as standards and rules for important procedures in the protocol (MRD and (Cyto)genetics.

Kjeld Schmiegelow has promoted one very important aspect of the protocol by writing the part of the protocol pertaining to the intensifying intervention in the IR-high-group called Thiopurine-Enhanced-ALL-Maintenance (TEAM).

The regulatory work has been coordinated from Stockholm for the whole protocol and has been greatly aided by the recruitment of Karin Flood as Trial Manager. The help of Jenny Juhlin from her position in the NOPHO secretariat with time dedicated to support for regulatory issues within NOPHO has also been extremely valuable.

Some features in the ALLTogether draft protocol that has been influenced in a major way by previous NOPHO-experience:

- the inclusion of young adults up to the age of 45 years
- the combination of flow-cytometry and PCR for the measurement of MRD
- the spacing of the CNS-consolidation with high-dose Methotrexate reducing the risk of pre-rescue
- measurement of Asp-activity as a guide to detect inactivators (together with the DCOG-group)
- the reduction of the number of Asp-doses for the higher risk-groups
- the choice of high-risk blocks for the HR-arm
- the TEAM randomisation
- the principles of toxicity-registration

The backbone of the protocol is now almost ready. Compared with the NOPHO ALL-2008 protocol there will also be some major changes, which is mostly in line with our aims for taking part in the collaboration. This will have as a result a major re-organisation of the clinical work in the departments throughout NOPHO. To be able to manage this transition and trimming the altered system for standardised diagnostics and other infrasctructure such as a new reporting system, it was decided to draft the backbone of the protocol as a NOPHO-study, without the randomisations and the experimental interventions (Imatinib for patients with *ABL*-class fusions and Nelarabine for T-cell ALL in front-line high-risk) and suggest that this is run as a pilot-study within NOPHO. This suggestion has been submitted to the Scientific committee and will be discussed at the NOPHO-meeting in Vilnius. If it is approved, we could have our new protocol running before, or possibly from, the beginning of the new year.

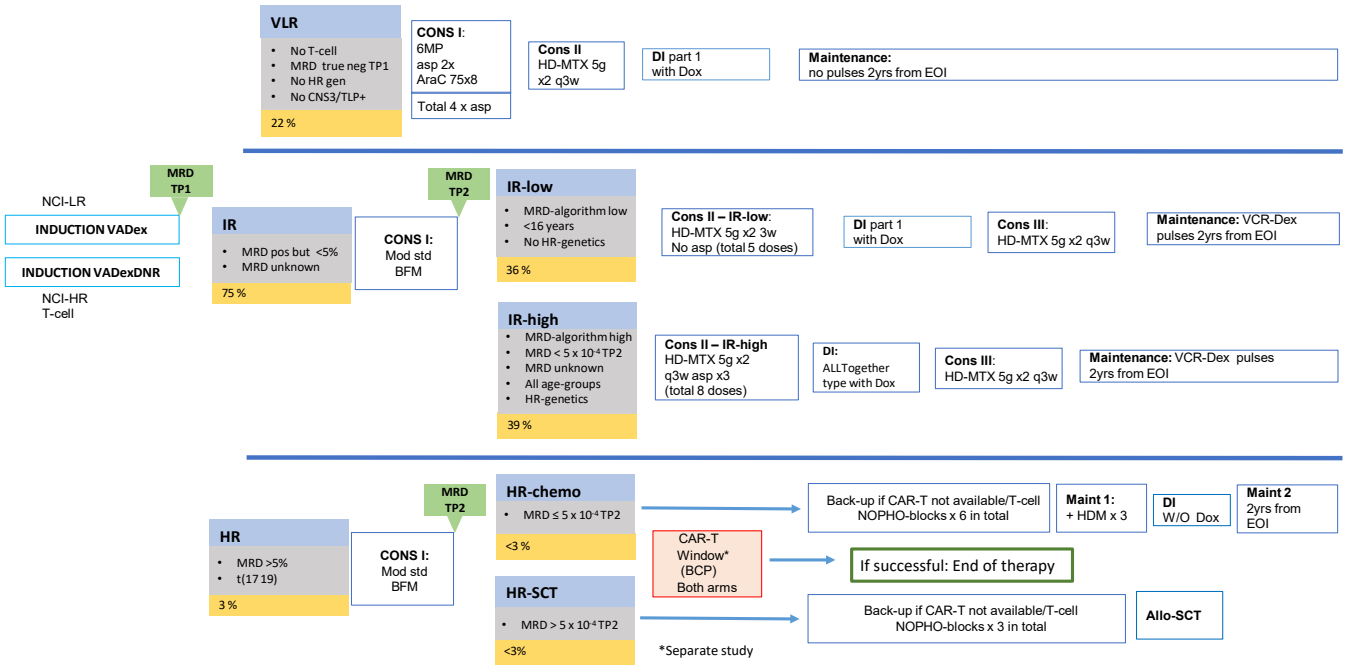
Some of the major changes with influence on the structure of the work in the clinical departments:

- A reduction in the fraction of patients allocated to the high-risk arm (from about 15% to 3% for children <16 and from 35% to 10% for young adults).
- A reduction in in-patient care resulting from the reduction in high-dose Methotrexate courses administered (from 8 for 85% of the patients to 2 for slightly more than 20% of the patients and 4 for 75% of the patients). This is a reduction in the number of courses slightly below 60%.
- An increase in day-care chemotherapy resulting from the introduction of monthly VCR-Dexa pulses throughout maintenance for about half of the patients.

As before, the NOPHO-representation in the protocol-group of ALLTogether is Mats Heyman, Mervi Taskinen and Kjeld Schmiegelow. The representatives in the ALLTogether task-forces are listed above.

Springtime 2018
Mats Heyman

Therapy overview ALLTogether pilot study



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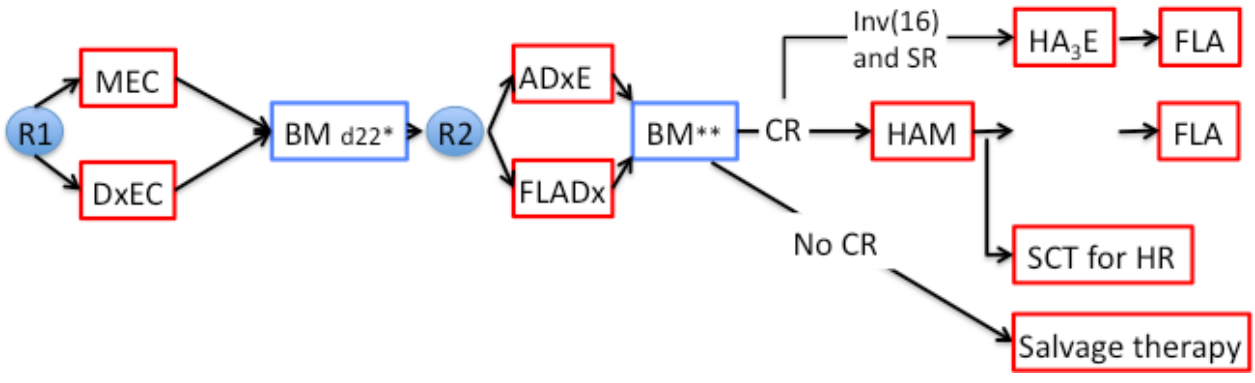

Figure 1. Overview of the current clinical research protocol NOPHO-DBH AML 2012. Evaluation of therapy response is performed on day 22 after the first course and immediately before consolidation. Patients are randomized to receive mitoxantrone or liposomal daunorubicin in course one and to receive ADxE or FLADx as second course. MEC and ADxE are standard arms in non-randomized patients.

Organisation

The group has held two meetings during 2017. One in Haifa, Israel in conjunction with the I-BFM meeting and one in Alicante, Spain. One important function of the meetings have been to be PI meetings for the coordination and supervision of the treatment protocol NOPHO-DBH AML2012. In mid 2016, all centers in Israel started treating according to the protocol followed by some centers in Spain from November 2017. New centers are continuously opening in Spain as the approval processes are completed.

We have continued to act as a platform for facilitating both biological and clinical research in pediatric AML and to include our new collaborators in AML2012 in NOPHO research as well as commencing new research activities together with the Belgian, Dutch, Hong Kong, Israeli and Spanish national AML groups. Cooperation with the NOPHO leukemia biology group has been instrumental in the coordination and planning of, in particular, biological genetics studies.

Several NOPHO AML research projects have been started and pursued during the year and NOPHO has participated in international collaborative scientific studies. The planning of a new supportive care study testing, in a randomized setting, the effect of teicoplanin as antibacterial prophylaxis has been a major task during 2017.

As usual, between meetings, members have frequent mail discussions both regarding individual patient treatment decisions and research issues.

Introduction

NOPHO has from 1984 until 2013 treated children with AML on four common protocols: NOPHO-AML84, -88-, -93 and -2004. The outline for treatment in the respective protocols is demonstrated in figure 2. All protocols have been based on induction therapy with anthracycline, cytarabine and 6-thioguanin with etoposide added from 1988 followed by consolidation based on high-dose cytarabine. Since 1993 a response guided induction strategy has been used, allowing hematological recovery for children in remission after the first course prior to giving the second course. Compared to the previous intensively timed induction this markedly reduced mortality in induction.

From NOPHO-AML84 to NOPHO-AML93, outcome improved significantly and the NOPHO-AML93 had a 5 year EFS of 50%. Overall survival was 65% which at that time was the highest reported in childhood AML.

However, the steady trend towards improvement was broken with the NOPHO AML 2004 protocol. Although survival increased to 70% the EFS5y was disappointingly low at 47%. When analyzing the relatively poor outcome the main conclusions were that the second induction course in the AML 2004 protocol was not intensive enough and that idarubicin seemed to be less effective in patients with RUNX1/RUNX1T1 (t8;21) AML. Therefore, the group worked intensely to produce the new protocol which was finalized in December 2012. The first patients were treated in March 2013.

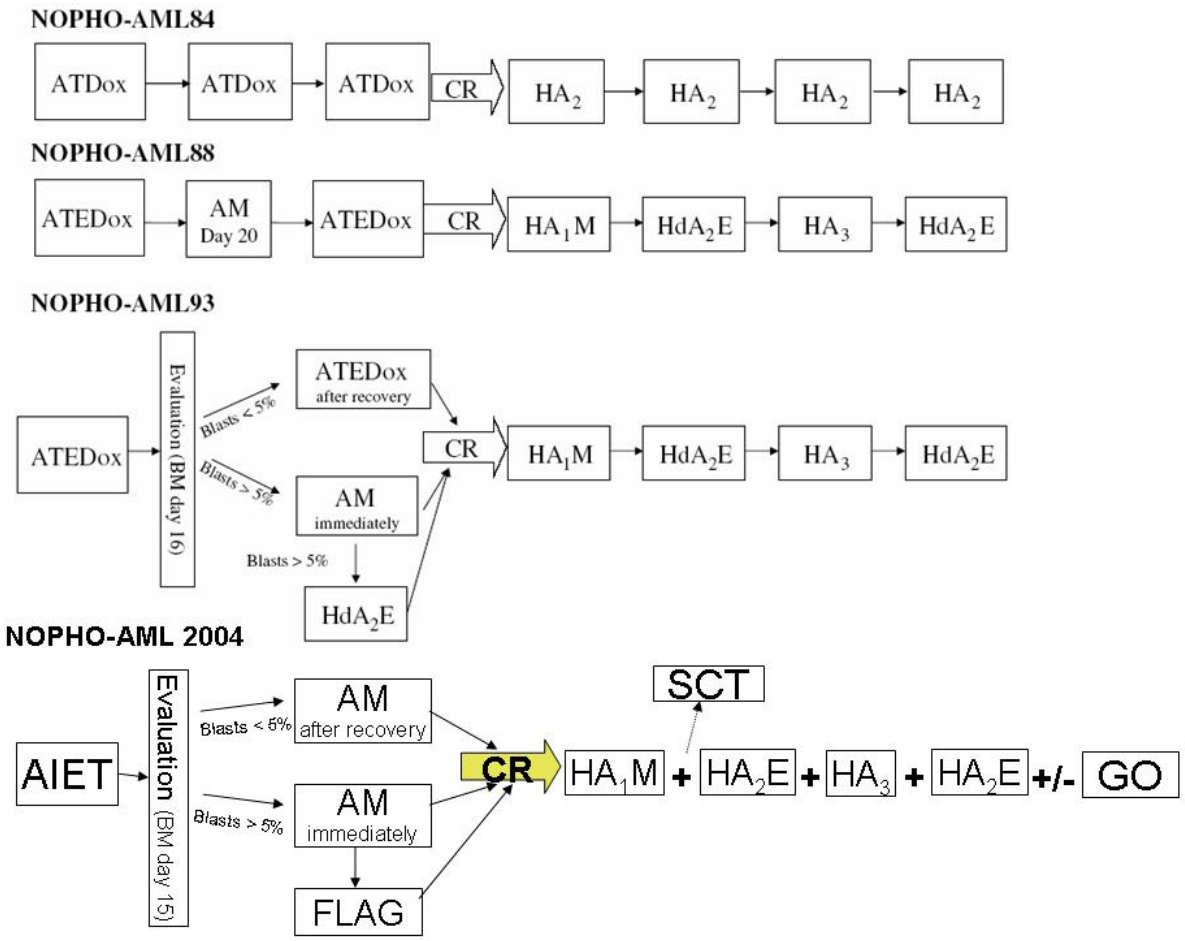

Figure 2. Overview of previous NOPHO treatment protocols from 1984-2012. In AML88 all patients received intensively timed induction with early start of course 2. Since AML93 all protocols have adopted a response-guided timing of the second course, allowing good responding patients to recover peripheral blood values before starting course two.

During 2017 the main work in the AML group has focused on

1. Supervising the efficiency, toxicity and logistic framework for the NOPHO-DBH AML2012 protocol. A major task here is to assure complete registration in the clinical and laboratory (MRD) databases.
2. Implementing the NOPHO-DBH AML2012 protocol in Israel and Spain.
3. Increasing the scientific collaboration with preclinical researchers and between NOPHO and the Belgian, Dutch, Hong Kong, Israeli and Spanish groups.
4. Continued analysis of data generated from previous NOPHO AML protocols.
5. Participating in the European AML group for planning direction of future clinical trials in Europe.
6. Participation in international collaborative research projects.

NOPHO-AML2004

The protocol opened in January 2004 and was officially closed in December 2013. Hong Kong continued to use the protocol as standard of care until September 2016 at which time AML2012 was opened. The 2004 protocol with flow charts and amendments can be accessed at www.nopho.org. The outcome data are mature and much work has been done within the group also during 2017 to analyze and publish data on outcome, disease biology and toxicity. Some publications still remain to be finalized during 2018.

Patient accrual

NOPHO AML-2004 included a randomized comparison of the potential benefit of Gemtuzumab as post-consolidation therapy for standard risk AML. As from the end of 2010, the randomized study had accrued the target number of 120 and therefore was closed for randomization but continued to be used

as standard therapy without Gemtuzumab. Between 2004 and December 2013, when the protocol was officially closed, 323 protocol patients were registered from the Nordic countries and Hong Kong. The protocol was also used as standard therapy for childhood AML in Estonia and Latvia. During 2010-2013 both the Netherlands and Belgium conducted a study based on a modified version of NOPHO-AML2004 (identical treatment except for omission of the third course HAM and no stem cell transplant in first remission). This study recruited 112 patients and had an EFS of 53.5% and OS of 74.5% at three years.

Toxicity

The toxic death rate in AML2004 was relatively low with 3.1% induction deaths and 2.8% deaths in CR1. The frequency of resistant disease was 5%, second malignancy 1.9% and 45% experienced relapse. As the treatment blocks were very intensive, bone marrow aplasia was long and the rate of neutropenic fever very high after each block ranging from almost 100% after the first induction course to 74% after HA3. The acute and long-term cardiac toxicity has been very low but a NOPHO publication in 2016 from the NOPHO-AML88, -93 and -04 protocols showed that, although most patients had normal cardiac function and no cardiac symptoms, left ventricular function was significantly reduced compared to controls.

Outcome

The overall results are stable with a five year EFS of 47% compared to 50% in NOPHO-AML93. The overall survival has improved to 69% from 65% in AML93. Figure 3 shows event-free survival and overall survival compared to previous protocols.

When analyzing the relatively poor EFS it was found that patients with an intermediate response to AIET had a very high relapse rate as did patients with RUNX1/RUNX1T1 regardless of response. The AML group concluded that the second induction course – AM – was too weak in these patient subsets and in 2010 an amendment was made recommending FLADx as second course for patients with RUNX1/RUNX1T1 or an intermediate response to AIET. The amendment is found on http://www.nopho.org. This seemed to markedly improve prognosis for these patients. Similar results were seen in the Dutch/Belgian AML01 protocol which used AIET as first course followed by FLA or FLADx in RUNX1/RUNX1T1 AML.

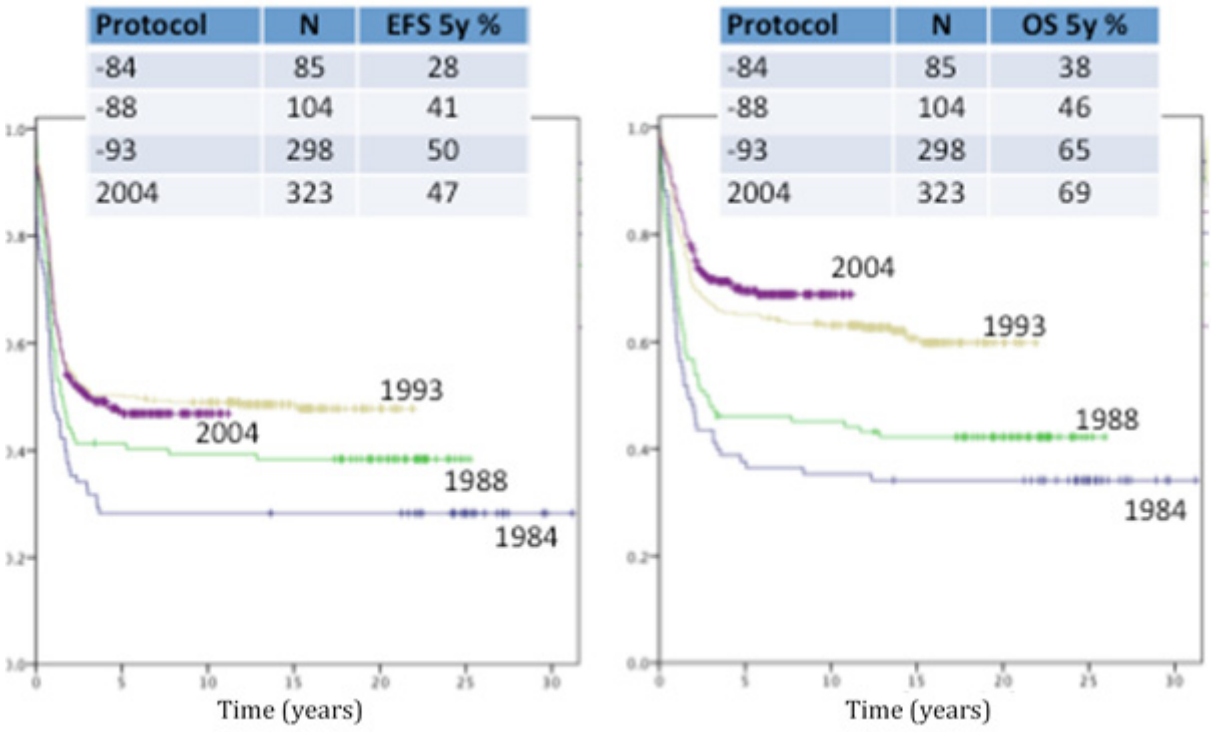

Figure 3. Overall survival (right figure) and event-free survival (left figure) in NOPHO-AML2004 (purple), NOPHO-AML93 (beige), NOPHO-AML88 (green) and NOPHO-AML84 (blue).

Analysis of the results with respect to subgroups is still on-going but it is evident that the changes in induction made in the 2004 protocol affected survival differently for several cytogenetic subgroups. An important conclusion is therefore that, even when using conventional chemotherapy for AML, patients in different subgroups may benefit from tailored therapy.

Stem cell transplant in CR1

In NOPHO-AML2004 high-risk patients were recommended SCT with any matched donor. Initially KMT2A aberration other than KMT2A/MLLT3 was a high risk criterion but interim analysis showed that compliance to the SCT recommendation in these patients was poor and consolidation with chemotherapy resulted in a satisfactory outcome. Thus, an amendment in 2009 removed KMT2A aberrations as a high-risk criterion.

At the same time accumulating evidence indicated that patients with FLT3-ITD mutations without concomitant NPM1 mutation had a very poor prognosis which might be improved by stem cell transplant. Therefore, FLT3-ITD mutations were added as a high risk criterion in an amendment in 2010. In total, only 17% of patients received SCT as consolidation in CR1 or following resistant disease. This is a low rate compared to most other childhood AML protocols.

Gemtuzumab randomization

The results from the randomized study including 120 patients were published 2012 (Hasle et. al. Blood). Gemtuzumab was well tolerated with no toxic deaths. Although GO treated patients had a tendency for later relapses, no effect was observed on either EFS or OS. Thus, the conclusion is that Gemtuzumab neither reduces the relapse rate nor increases survival when administered as post-consolidation therapy. In 2016 we could also show that patients relapsing after GO therapy did not have a significantly worse outcome than patients not receiving GO.

NOPHO-DBH AML2012

The protocol was finalized in December 2012 and the AML2012 database was opened in March 2013. The study has EUDract number 2012-002934-35 and clinical trials identifier NCT01828489. After approval by the competent authorities and setting up of national GCP monitoring the protocol opened in Denmark and Sweden in March 2013, followed by Finland in April and Norway in June. The Netherlands started recruiting patients January 2014 and Belgium in May 2014. Hong Kong started recruiting patients in September 2016 and Israel started using the protocol in summer 2016 but randomizations will commence in 2017. The larger centers in Spain will start using the protocol in spring or summer 2017 following relevant approvals from competent authorities. The MRD group and NOPHO registry have worked very hard in order to set up the logistics and to ensure standardization of MRD flow analyses. MRD analyses are working satisfactorily but there is still some lag in reporting since the MRD database only was ready in spring 2017.

The study is expected to recruit 300 patients within a time frame of six years and will provide a strong basis for biological and clinical add-on research studies.

The main assumptions, which to a large extent were deduced from experiences from AML2004, behind the major changes in standard treatment in AML2012 as compared to AML2004 are that:

- prognosis can be improved by using more intensive induction therapy
- detection of minimal residual disease ≥0.1% by flow cytometry, following the two induction courses identifies a subset of patients with a very poor prognosis when treated with chemotherapy alone
- stem cell transplant can reduce the negative prognostic impact of a poor response to induction therapy

The risk stratification in AML2012 is mainly based on treatment response which we assumed would be possible to evaluate by flow cytometry in the majority of patients. Since MRD flow is very difficult in AML the MRD group have set up strict logistics and a standardized protocol but continuously strive to improve by several quality control procedures. We can already state that this part of the protocol has been a success since around 90% of patients have an evaluable MRD investigation with a sensitivity

of 0.1%. The MRD group meets twice each year and all laboratories partake in twinning so that each patients MRD data is reviewed by two centers. Furthermore, quality control rounds are performed twice yearly where all laboratories review the same data files. All MRD data files are accessible through a common server.

Children with ≥15% leukemic cells after the first course or ≥ 0.1% after the second course are classified as high risk (HR). In addition, patients with FLT3-ITD and no NPM1 mutation are HR patients regardless of response. This is slightly different from more recent AML trials in children that also incorporate more rare gene aberrations with putative poor outcome. However, whether these small subgroups really have poor prognosis with modern treatment and in what way prognosis interacts with treatment response is largely unknown. Given these uncertainties, the NOPHO AML group has decided to keep the risk stratification as originally planned in AML2012. There has been some treatment violations in the protocol where clinicians at times have given HR therapy including SCT to patients with these genetic aberrations. Acknowledging that patient numbers are small, none of the individual study groups will be able to define the "true" prognostic impact of these aberrations and we will join collaborative inter-group studies to extend our knowledge.

Children and adolescents in the HR group are recommended allogeneic stem cell transplant. All other patients are classified as standard risk and receive consolidation therapy with three blocks containing high dose cytarabine. An exception is standard risk patients with CFBB-MYH11 (inv(16)) who only receive two consolidation blocks.

AML2012 includes two randomized studies both aiming at improving treatment outcome. The efficacy and toxicity (in particular cardiac) of mitoxantrone and DaunoXome in the first induction course are compared. The second study compares the efficacy and toxicity of FLADx to the BFM course ADxE. Both studies are evaluated by using MRD flow after the respective courses as primary endpoint.
AML2012 has three other important research aims

1. to evaluate the prognostic significance of measurement of fusion gene transcript levels after the first and second course
2. to perform a comprehensive genetic characterization of the leukemic cells
3. to use fusion gene transcript determinations to detect molecular relapse of AML during follow-up.

As of April 2018, 271 patients have been treated on the protocol. A major setback during 2017 has been that the company producing liposomal daunorubicin has had manufacturing problems and no drug has been available since 1 Nov 2017. Therefore, the randomization was put on hold and an amendment was made giving guidelines how to treat patients until the drug becomes available again. This involved giving the standard arm to all as first course and giving a modified block (ADE - cytarabine, daunorubicin, etoposide) as second course. Unfortunately, none of these patients will be evaluable for more than the third primary aim in the study but we will carefully supervise outcome in also these non-randomized patients. Liposomal daunorubicin will be available again at the earliest in August 2018 thereby delaying the study with almost a year. The other study groups in Europe all have the same problem.

Therefore, the data given below only refers to patients starting treatment on AML2012 until October 2017 and leaves out 53 patients who are diagnosed after this date. This means that all patients have been followed for at least six months at time of analysis. Of the 273 patients treated 194 have been enrolled in at least one of the randomizations. The age distribution is as expected with 20% below two years. As before almost 70% of patients have AML specific genetic aberrations. At present, 10% have CBFB/MYH11 which in good responding patients stratifies to only two consolidation courses. A further 13% have RUNX1/RUNX1T1, 9% KMT2A/MLLT3, 17% other KMT2A rearrangements and 12% FLT3-ITD mutations without concomitant NPM1 mutation. The latter subgroup is a high risk criterion in AML2012.

Adherence to protocol diagnostic and MRD guidelines are excellent. Figure 4 shows that following course one, 94% have an informative MRD examination and that of these 56% have MRD < 0.1%.

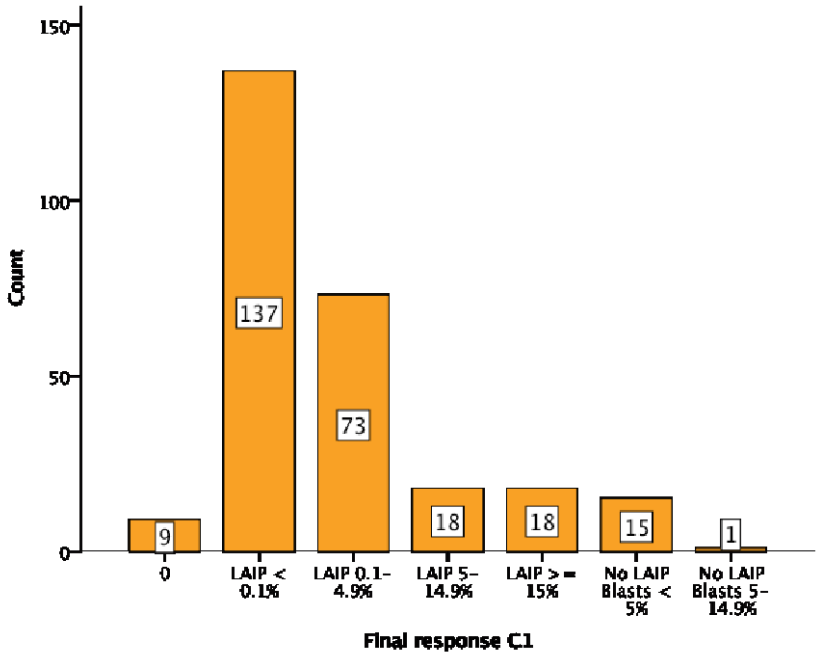

Figure 4. Response to course 1 in AML2012. 0 depicts patients with misregistration. LAIP - leukemia associated immunophenotype.
56% of evaluable patients have MRD < 0.1%.

After course 1 84.3% reached CR. 14% had ≥ 5% blasts at evaluation and proceeded to receive the 2nd course immediately.

AML2012 has very high anti-leukemic effect and following the two induction courses 94.2% reached complete remission. The frequency of resistant disease was 3.9%. Of all patients, 75% were stratified to the standard risk and 18% to the high risk group. Of the patients stratified to HR, almost 20% had FLT3-ITD with good response, 20% FLT3ITD with poor response and the remaining patients poor response as sole high risk criterion. Thus, there is a strong association with FLT3-ITD and poor response to induction. As can be seen in figure 5, that shows Kaplan-Meier plots of disease-free survival and overall survival according to risk group, the risk stratification virtually eliminates the previous difference in outcome.

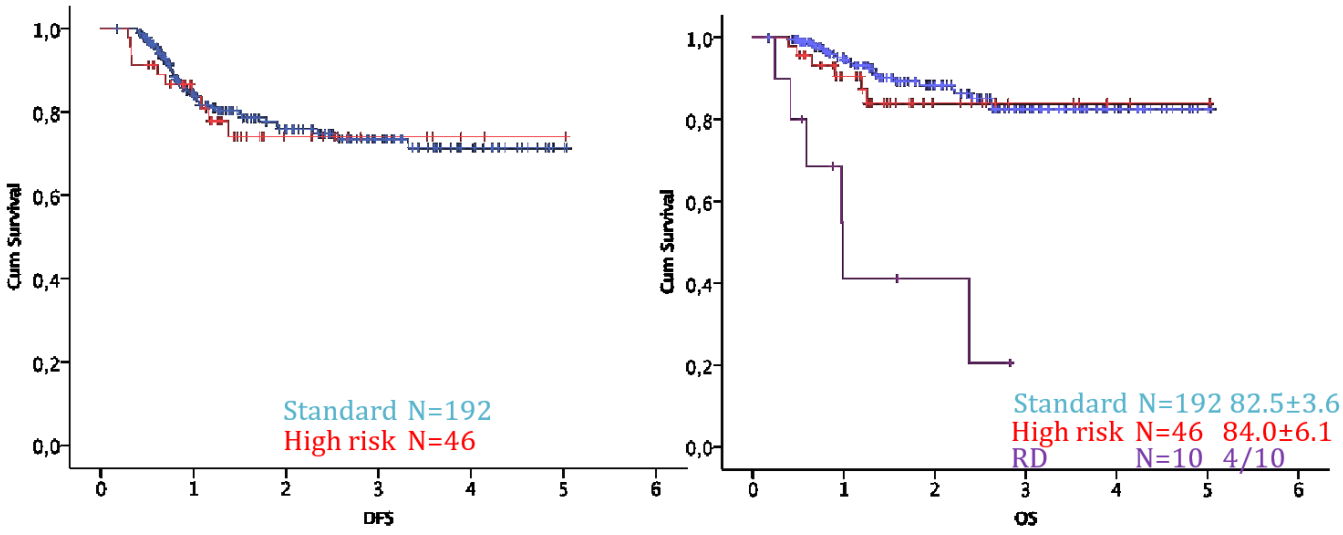

Figure 5. Disease-free survival and overall survival at three years is almost equal in both risk groups. Estimated survival is shown also for patients with resistant disease (RD). Blue curve - standard risk, red - high risk, violet - resistant disease.

The toxicity in AML2012 is, as expected, high but manageable. The frequency of induction death is 1.8%. Fig 6 shows treatment-related mortality (including deaths after SCT in CR1) in AML2004 and AML2012.

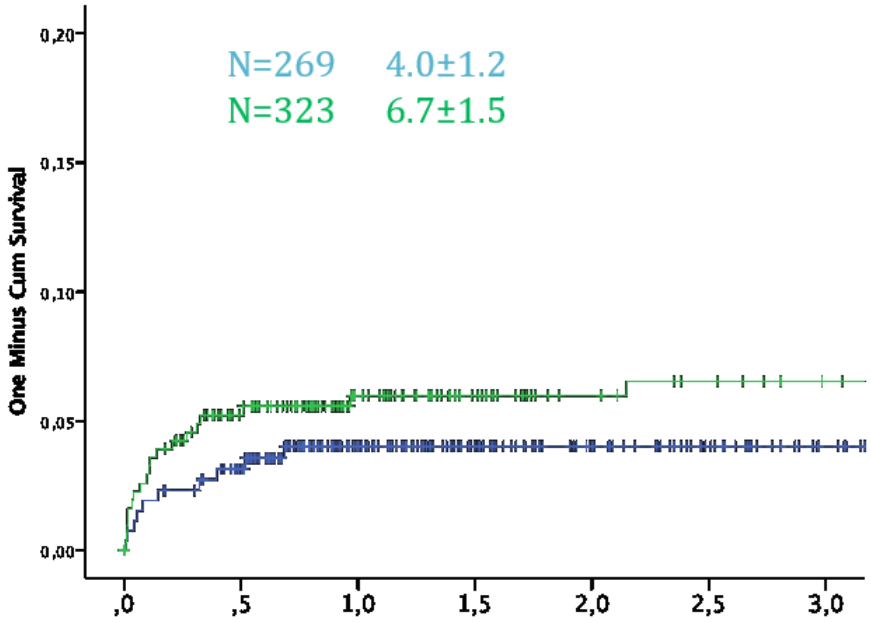

Figure 6. Cumulative incidence of treatment-related mortality (death during induction and death in first complete remission). The difference between the protocols is not statistically significant. Blue AML2012, green AML2004. Note scale on ordinate axis.

The overall treatment-related mortality compares favorably to published data in AML. Registration of specific toxicities shows that around 50% of patients have documented blood-stream infections after the first two courses. After the first course, 14% have typhlitis and 19% require care at ICU. The frequency of specific toxicities however decline with subsequent courses. However, induction therapy for AML is very intensive and many patients experience potentially life-threatening emergencies. Therefore, continued extreme vigilance is necessary and supportive care must be of the highest standard in these patients. Toxicity registration still tends to be delayed for the consolidation courses which is not acceptable in a clinical trial conducted according to good clinical practice. During 2018 special efforts will be dedicated to improving registration.

The follow-up is now sufficiently long to allow more confidence in interpreting results for overall event-free survival in the protocol. Over 90% of relapses in AML2012 occur within 24 months from diagnosis. The data for overall survival must be viewed more cautiously since most patients die at a later time point following relapse. Fig 7 and 8 show a comparison of EFS and OS between AML2004 and AML2012.

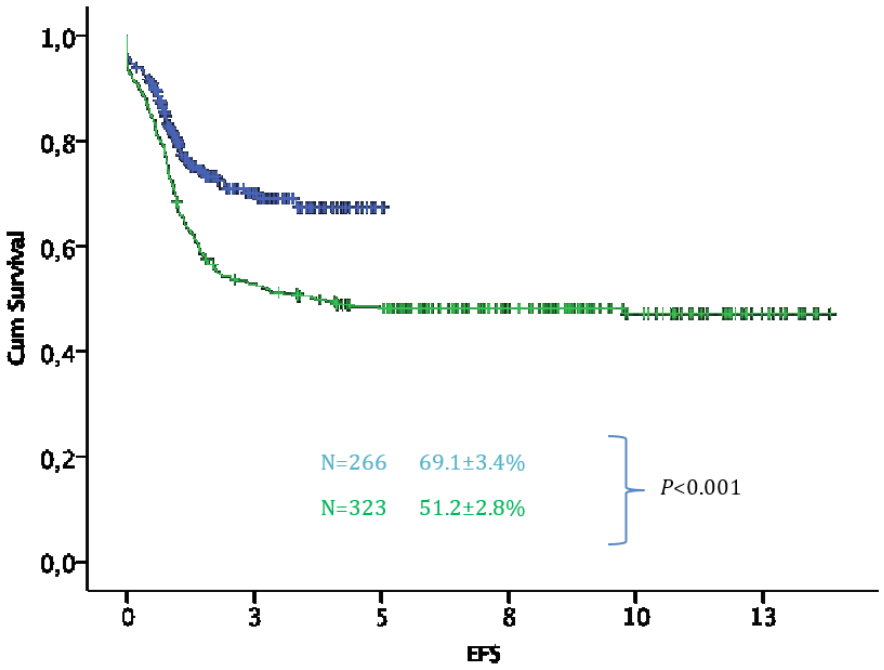

Figure 7. Kaplan-Meier estimates of event-free survival for AML2012 (blue curve) and AML2004 (green curve). Estimates are at three years.

The EFS at three years is 69.1% which is higher than previously published results and significantly better than for AML2004.

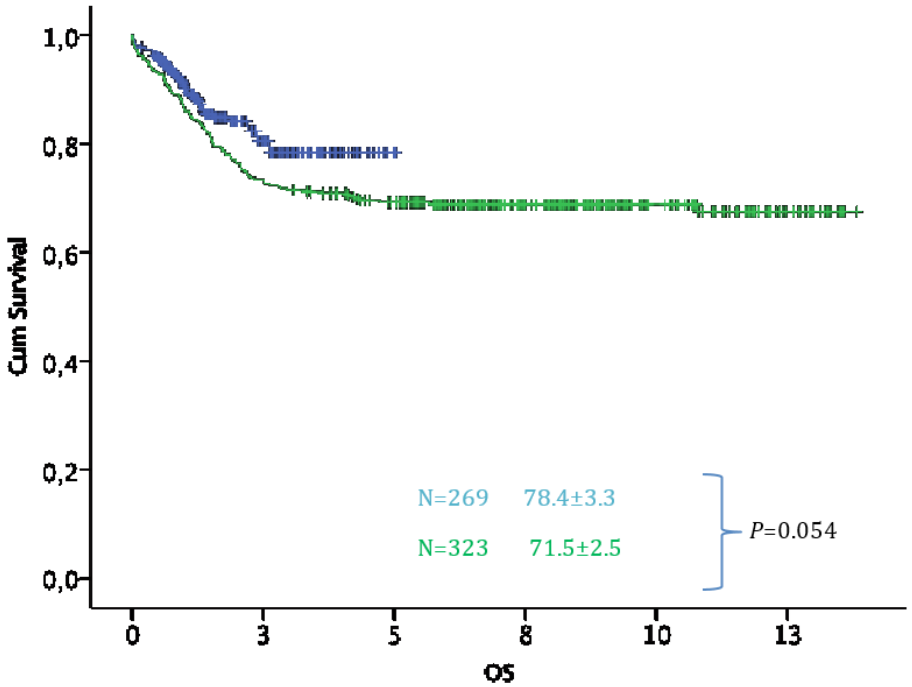

Figure 8. Kaplan-Meier estimates of overall survival for AML2012 (blue curve) and AML2004 (green curve). Estimates are at three years.

Although the curve for overall survival does look very promising, it is still too early to draw definite conclusions. The estimate can both increase or decrease as the follow-up is longer. It should, however, be possible to be more confident in one years time.

The cumulative frequency of SCT in CR1 is 24% which is slightly higher than in AML2004 (17%). This is not entirely due to changes in risk stratification but is also partly explained by a few patients with standard risk who have received SCT and partly because several of the patients with resistant

disease have reached SCT. The total cumulative incidence of SCT at three years is 40% compared to 48% in AML2004, reflecting the lower incidence of relapse (CIR3y AML2012 24.8±3.4%, AML2004 42.3±2.3).

In conclusion, the NOPHO-DBH AML2012 protocol shows very encouraging results. An independent data safety committee reviews the randomized results annually and supports continuation of the study. It is a major setback that we at present have the randomization on hold but, since we now have more countries contributing patients, we expect to reach our target recruitment within 18 months from resuming randomization. The protocol logistics are well functioning and one of our main goals, namely to show that a very demanding flow cytometric MRD determination can be performed in a multi-center setting, has been accomplished. The treatment efficacy is very promising.

Intergroup studies

Myeloid leukemia of Down syndrome

The International DS study ML-DS 2006, which reduced the dose in each course and the total number of courses from 6 to 4 has now been published showing excellent results with an EFS at 5 years of 87% and a cumulative incidence of relapse/non-response of 6% in a cohort of 170 children. A new protocol is under development but the ML-DS 2006 is still used for treatment. The protocol is found at www.nopho.org.

An add-on study on MRD using WT1 analyses is centralized in Aarhus. The protocol and practical information about how to send samples are found at www.nopho.org

AML-M3 APL

In 2009, The NOPHO-AML group recommended joining the international ICC APL study 01 as a registration only study. The outcome in this protocol has been excellent with an OS of 94% at three years. A new protocol, ICC APL study 02, is planned to open during 2018. A major change is that patients with standard risk APL are treated only with retinoic acid and arsenic trioxide. The APL study group have issued interim guidelines for treatment of patients with SR APL which the AML group from 2015 decided to recommend as best available therapy. The guidelines are published on the NOPHO web. High risk patients should continue to be treated according to the old protocol until the final new protocol is approved.

PCR MRD monitoring is mandatory and should be centralized to Aarhus for all Nordic patients.

Data entry will be done centrally.

For the guidelines for APL SR, the ICC APL study 01 protocol for APL HR and PCR MRD invoice please see www.nopho.org

International relapsed AML study

A new relapse protocol has been finalized and approval has been obtained from the competent authorities in Denmark, Finland and Sweden. This new relapse protocol will investigate, in a randomized setting, if addition of Gemtuzumab to FLADx will improve early response. The protocol has been delayed due to change of sponsor and problems with drug delivery but opened in Germany in October 2016. Since the sponsor has changed, amendments must be made in the Nordic countries and submitted to the IEC and CA. This process started already 2016 but has been cumbersome. This study also suffers from the temporary unavailability of liposomal daunorubicin. Meanwhile NOPHO recommendations for relapse treatment can be found at www.nopho.org.

European collaboration

An initiative was made in 2012 by BFM and DCOG, initially aiming at working out a common European AML protocol. A committee was established and representatives from the NOPHO AML group have taken part in meetings twice yearly. Since several study groups have recently started new studies the work

has focused more on finding a common framework to provide a basis for performing studies on novel drugs. This includes finding uniform definitions, risk stratification and response evaluation.

Publications involving the NOPHO AML WG from 2016

- **Wennstrom L, Wendtlant Edsløv P, Abrahamsson J, Maxweell Nørgaard J, Fløisand Y, Forestier E, Gustafsson G, Heldrup J, Hovi L, Jahnukainen K, Jonsson OG, Lausen B, Palle J, Zeller B, Holmberg E, Juliuson G, Stockelberg D, Hasle H**. *Acute myeloid leukemia in adolescents and young adults in the nordic countries – outcome according to pediatric and adult treatment protocols*. Pediatr Blood & Cancer 2016 63(1):83-92.
- **Jarfelt M, Andersen NH, Glosli H, Jahnukainen K, Jonmundsen GK, Malmros J, Nysom K, Hasle H**. *Cardiac function in survivors of childhood acute myeloid leukemia treated with chemotherapy only: a NOPHO AML study*. Eur J Hematol 2016 Jul;97(1):55-
- **Anne M. Tierens, Björklund E, Siitonen S, Marquart Hv, Wulff-Juergensen G, Pelliniemi TT, Erik Forestier, Henrik Hasle, Kirsi Jahnukainen, Birgitte Lausen, Olafur G Jonsson, Josefine Palle, Bem Zeller, Linda Fogelstrand and Jonas Abrahamsson**. *Residual disease detected by flow cytometry is an independent predictor of survival in childhood acute myeloid leukemia: results of the NOPHO-AML 2004 study*. Br J of Haematol. 2016 174(4):600-609
- **Lund Laursen AC, Sandahl JD, Kjeldsen E, Abrahamsson J, Åsdahl P, Ha SY, Heldrup J, Jahnukainen K, Jonsson OG, Lausen B, Palle J, Zeller B, Forestier E, Hasle H**. *Trisomy 8 in pediatric acute myeloid leukemia. A NOPHO-AML study.* Genes Chromosome and Cancer 2016 55(9):719-726
- **Adolfsen Løhmann DJ, Abrahamsson J, Ha SY, Jónsson ÓG, Koskenvuo M, Lausen B, Palle J, Zeller B, and Hasle H**. *Effect of age and body-weight on toxicity and survival in pediatric acute myeloid leukemia: results from NOPHO-AML 2004*. Haematologica 2016 101(11):1359-67
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BLVD
VINTAGE

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The Leukemia Cytogenetic group meet once a year divided in two two-day-meetings. All participants (besides the coordinator) are clinical geneticists working at the laboratories responsible for the cytogentic diagnostics in the Nordic countries. The coordinator, Ulrika Norén Nyström (pediatric oncologist) participate together with Prof. Bertil Johansson in both meetings. In May 2017 the meetings took place in Umeå and the Swedish leukemia patients diagnosed in 2016 were reviewed during the first meeting and in the second meeting the rest of the Nordic leukemia patients. All pediatric AML patients as well as both pediatric and adult ALL patients were evaluated. During the review meetings all diagnostic cytogenetic results are reviewed, such as karyograms, targeted analyses for the mandatory aberrations (FISH- and/or PCR), but also, if they exist, results from SNP-arrays or other types of analyses done at diagnosis are discussed. A complete karyotype is decided, taking into account all diagnostic results we know of for each patient. The genetic group defining the patient in the treatment protocol is finally decided by the "worst counts" –principle.

The Baltic Review

The Baltic countries have not been represented at the meetings so far. But in September 2017 Prof Johansson and Dr Norén Nyström had a separate meeting with representatives from the genetic laboratories in Estonia and Lithuania (see above) where all patients diagnosed and treated according to the NOPHO ALL 2008 protocol in Estonia and Lithuania during 2008 – 2016 were reviewed (adults n=66, pediatric patients n= 198). Representatives from the Baltic countries will from now on be invited to the review meetings.

Cytogenetic results for NOPHO patients diagnosed with ALL and AML in 2016

Briefly, the genetic results at diagnosis in totally 192 children and 58 adults diagnosed with ALL, and 48 children with AML were reviewed at our meetings.

The Cytogentic application in the NOPHO registry

The Swedish genetic laboratories have been piloting the new cytogenetic registration application during the second half of 2017. This will be evaluated during the upcoming annual meetings in April and May 2018 and then hopefully implemented also for the rest of the Nordic and Baltic genetic laboratories. Modifications of the registration application according to the coming ALLTogether protocol will also be discussed.

Umeå 17-04-2018
Ulrika Norén Nyström

Nordic Pediatric Leukemia Biobank Board

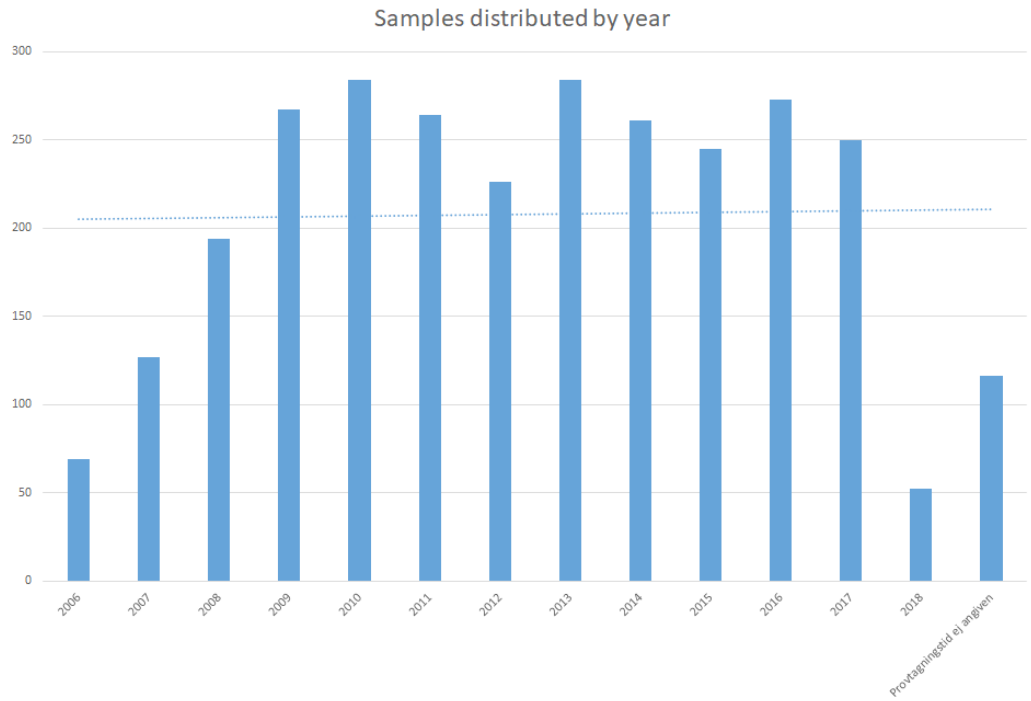
Members

Chair	Trond Flægstad
Denmark	Henrik Hasle
Finland	Olli Lohi
Iceland	Halldóra K. Þórarinsdóttir
Norway	Trond Flægstad
Sweden	Britt-Marie Frost Josefine Palle

Young NOPHO

NOPHO Project representatives:

Kees-Jan Pronk	*Scientific committee*
Mats Heyman	*Leukemia registry*
Yanara Marincevic	*Leukemia Biology*
Sofie Degerman	*Leukemia Biology*



Incident with NOPHO pediatric leukemia biobank's nitrogen tank no. 2.

- The tank contained frozen material from 2465 patients distributed on 8933 vials with cells.
- Background: The power supply for the tank had been interrupted for 11 days. No alarm has gone.
- Reason for interrupted power supply: a fuse on the back of the tank had came off. The fuse wasn´t broken but not in its right place.
- No alarm was sent because the alarm wasn´t right connected/installed. Both tanks are connected together which means that alarm will only react it both are without power.

Action taken to prevent further accident

- The alarm have been fixed.
- Yearly routines have been updated.
- An alarm test will be done on yearly bases.
- The tanks are now included in the system OpenLogger. It is a temperature monitoring system. Alerts will be sent out to laboratory computers if something happens.
- Staff responsible for refilling the tanks of liquid nitrogen have been informed about the incident and what to do if they disover something abnormal.

The damage samples

- The samples were all from the FMCA sample collection and all are from Sweden. Not from the NOPHO biobank.
- The samples can be used for DNA extraction but not for RNA.
- The samples have been frozen again to be saved for future DNA extraction.
- Tests of the damage samples were showing good DNA results.
- Trying to get insurance money for the DNA extractions.

NOPHO pediatric leukemia biobank, Uppsala

New ALLTogether protocol

- The Biobank will collect bone marrow and blood samples at diagnosis and relapse from the Nordic and Baltic countries.

Other issues

How to retrieve samples from the Biobank

The study proposal must be accepted as a NOPHO project by the scientific committee and the board, and will then be reviewed by the biobank board. The Biobank must be acknowledged in scientific papers if the samples are retrieved.

Exception: International studies on rare leukemias where a few samples are asked for.

Constitutional DNA in addition to leukemic DNA

The Biobank want to sample constitutional DNA. For the new ALLTogether protocol, this should be included. For NOPHO ALL 2008, where constitutional DNA is stored at Bonkolab, Copenhagen (another project), and AML at Arhus, there must be an ethical approval for each country (not Sweden) to be able to ship DNA from Copenhagen to Uppsala. This item will be discussed further.

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Organization

The group in its current form Leukaemia & Lymphoma Biology Working Group (LL Biology WG) includes ALL, AML and lymphoma researchers ranging from experimental researchers to pediatric oncologists. The group is open for all NOPHO members and their coworkers with an interest in biology research on leukemia/lymphoma and group members therefore shift over time. Also non-NOPHO members are welcome for an initial meeting before applying for NOPHO membership. Since March 2016, Linda Fogelstrand and Olli Lohi are co-chairs of the group. They have a strong background in basic research and represent diagnostics (Linda) and clinical (Olli) expertise, and have research focus on ALL (Olli) and AML (Linda). The LL Biology WG reports to the LLC, but many of the items are also discussed in the ALL-WG.

Aims

In 2016, the group established the following aims which are still valid:

- Bring together clinicians, experimental researchers and diagnostic experts
- Increase knowledge of ongoing NOPHO biology-related research projects; keep regular updates
- Foster collaboration; increase shared projects, technology/expertise and funding applications
- Enhance and coordinate utilization of NOPHO biobank material
- Plan novel research projects in conjunction with the upcoming novel protocols
- Avoid parallel studies
- Assist the NOPHO Scientific committee (if/when they want assistance) in evaluating and maybe ranking research proposals for the NOPHO Biobank

Meetings and results

The group gathers at biannual meetings which are held back-to-back with the ALL WG meetings. The meetings have a common structure; one scientific theme, presentations of new project proposals (NOPHO projects and local projects), updates of ongoing NOPHO projects and update from the NOPHO biobank. In 2017, the WG held two meetings; in Helsinki in March and in Stockholm in September.

The theme of the Helsinki meeting in March 2017 was 'Translational research - from basic research into clinical setting'. For this theme, invited speakers were Kimmo Porkka, Helsinki, presenting the Finnish Hematology Research Biobank, and Caroline Heckman, Helsinki, presenting her research on 'Individualized cancer systems medicine'.

In the Stockholm meeting in September 2017, the theme was 'Modelling leukemias - advantages and pitfalls'. At this meeting, Bengt Westermark, Uppsala, was invited speaker presenting the 'Authenticity of human tumor cell lines'. Under this theme, we also had several presentations by members of the group,

e.g. concerning leukemia models in mice and zebrafish, testing of cell lines, and bioinformatics. In this meeting, we also had an interactive session inspired by the upcoming ALLTogether protocol. We heard about the planned risk stratification based on genetic aberrations and had group discussions with brainstorming on future biological projects.

The first meeting was financed through company sponsoring and the September meeting by planning grant from the Swedish Childhood Cancer Foundation (3 year grant 2017-2019). Around 30 participants attended the meetings.

The group has during the year given a recommendation to LLC regarding the source of germline DNA for future genetic studies; blood taken during remission. The group has also informed LLC about data handling and consent requirements in genetic studies.

Future perspectives

Meetings will continue to be held biannually, in March and September 2018, both in Stockholm at Arlanda Airport. Meetings will be financed by the planning grant from the Swedish Childhood Cancer Foundation. Travel expenses are covered by the institutions of the participants. The themes of the meetings 2018 will be 'B cell development and signalling – what has gone wrong in ALL' and 'Single cell techniques'.

Olli Lohi and Linda Fogelstrand, April 2018

Infant Leukemia Working Group

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Norway	Anne Grete Bechensteen
Sweden	Anders Castor
	Ulrika Noren Nyström (cytogenetics)
	Mats Heyman (data center)
	Jesper Heldrup (immunophenotyping)
Young NOPHO	Sauli Palmu, Finland

The main activity of the NOPHO Infant Leukemia group is to take care of the international Interfant studies. During 2017 the group has been communicating by email – no WG-meeting was held as a consequence of postponing the update of clinical data in the international Interfant registry in Monza until late 2017.

Status of Interfant-06

The current protocol opened in 2006 with Rob Pieters from Rotterdam as chair of the study. The randomization was closed pr. 1st Aug. 2016 when the target sample size was reached. A new amended version of the Interfant-06-protocol (version 16b) was released in November 2016 with changes in the Asparaginase treatment; only PEG-asparaginase should be used, doses should not be dose-adjusted according to age, and asparaginase drug- and antibody levels should be monitored.

The registration of clinical data and outcome from new and old patients is still ongoing. The update of clinical data has been postponed to early spring 2018. As a consequence, no international annual report was made and no meeting was held in the international Interfant group in 2017. The next international report and meeting is expected to come in May 2018.

Status of Interfant-06 and Infant ALL in NOPHO

The protocol was approved in Finland in 2006 and in Denmark in 2011, thus solely Danish and Finnish patients could be randomised to experimental AML-like therapy. Almost all patients treated according to Interfant-06 in Denmark, Finland and Sweden are registered in the Monza-database, irrespective of protocol status.

The MLL-PCR-MRD-measurements are mandatory in MLL-rearranged patients, and the analyses are free of cost for the diagnostic sample and sample from time point 4. All centres are still recommended to send samples from MLL-rearranged infant ALL patients from diagnosis and Time Point 4 to the MRD-lab. in Copenhagen.

Ongoing studies:

- **A retrospective study in the Nordic infant ALL patients** was approved by the NOPHO Board and Scientific Committee in Nov. 2012. The plan is to describe and analyse survival data of the cohort of

infant ALL patients from the beginning of NOPHO registry up to 2012.

- **A study of maintenance treatment in infant ALL patients** was approved by the NOPHO Board and Scientific Committee in Nov. 2012. The national members of the working group acts as national PI's.
- **The SNP study in Infant ALL** was approved by the NOPHO Board and Scientific Committee in Nov. 2011. The study is both a retrospective and prospective study. The national members of the working group acts as national PI's.

Publications on Infant ALL-studies, where NOPHO is involved

- **Mann G, Attarbaschi A, Peters C, Schrappe M, Lorenzo P De, Hann I, Rossi G De, Felice M, Lausen B, LeBlanc T, Szczepanski T, Ferster A, Janka-Schaub G, Rubnitz J, Silverman L B, Stary J, Campbell M, Li C K, Suppiah R, Biondi A, Vora A, Valsecchi MG and Pieters R on behalf of the Interfant-99 Study Group.** *Improved outcome with hematopoietic stem cell transplantation in a poor prognostic subgroup of infants with mixed-lineage-leukemia (MLL)-rearranged acute lymphoblastic leukemia - Results from the Interfant-99 Study.* Blood 2010; 116 (15): 2644-2650.
- **Van der Linden M, Valsecchi MG, De Lorenzo P, Möricke A, Janka G, Leblanc TM, Felice M, Biondi A, Campbell M, Hann I, Rubnitz JE, Stary J, Szczepanski T, Vora A, Ferster A, Hovi L, Silverman LB and Pieters R.** *Outcome of congenital acute lymphoblastic leukaemia treated on the Interfant-99 protocol.* Blood 2009; 114: 3764-3768.
- **Lönnerholm G, Valsecchi MG, De Lorenzo P, Schrappe M, Hovi L, Campbell M, Mann G, Janka-Schaub G, Li CK, Stary J, Hann I, Pieters R; Interfant-99 study group.** *Pharmacokinetics of high-dose methotrexate in infants treated for acute lymphoblastic leukemia.* Pediatr Blood Cancer. 2009 May; 52(5): 596-601.
- **Pieters R, Schrappe M, De Lorenzo P, Hann I, De Rossi G, Felice M, Hovi L, LeBlanc T, Szczepanski T, Ferster A, Janka G, Rubnitz J, Silverman L, Stary J, Campbell M, Li CK, Mann G, Suppiah R, Biondi A, Vora A, Valsecchi MG.** *A treatment protocol for infants younger than 1 year with acute lymphoblastic leukaemia (Interfant-99): an observational study and a multicentre randomised trial.* Lancet 2007; 370: 240-250.

Copenhagen 17th April 2018
Birgitte Lausen
Chair of the NOPHO Infant Leukemia working group

Pharmacology Working Group

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	Kjeld Schmiegelow
	Henrik Schrøder
Finland	Jukka Kanerva
	Riitta Niinimäki
	Samppa Ryhänen
Iceland	Ólafur G. Jónsson
Norway	Bendik Lund
	Tove Anita Nystad
Sweden	Arja Harila-Saari
	Cecilia Langenskiöld
	Johan Malmros
	Malin Lindqvist Appel (Pharmacogenetic)
	Ranaa El-Edelbi (Chair of Pharmacists wg)
	Staffan Eksborg
	Jesper Heldrup (MTX)
Lithuania	Goda Vaitkeviciene
Young NOPHO	Louise Tram (DK) (stepping down Young NOPHO)
	Nina Mogensen (SE) (stepping down Young NOPHO)
	Samppa Ryhänen (FI) (stepping down Young NOPHO)
	Stine Nygaard Nielsen (DK)
	Thommy Svahn (SE)

NOPHO Pharmacology group met twice last year, on September 19, 2017 and February 6, 2018.

Pharmacology group continued working on the studies started in the earlier years mainly in the platform of the NOPHO ALL2008 protocol, however, several new projects were started and ideas on new projects were generated.

TEAM study - Thiopurine Enhanced ALL Maintenance therapy (Kjeld Schmiegelow)

The Nordic/Baltic NOPHO ALL2008 maintenance therapy study found 10-fold interindividual differences in DNA-TG during maintenance therapy, ranging from 100 pmol/µg to 1000 pmol/µg. In addition, DNA-TG levels were significantly associated with the risk of relapse, but only for post-induction MRD-positive patients. For IR-high patients the study showed a 37% reduction in relapse hazard per 100 pmol/µg DNA increment in DNA-TG.

Based on these and other PK/PD studies from the 92/2000/2008 NOPHO ALL protocols, TEAM has been confirmed as a randomized study to evaluate the improvement in disease-free survival by adding very low dose 6-TG to 6-MP/MTX-based maintenance therapy in pediatric and adult patients (1- 45 yrs) with newly diagnosed B-cell precursor or T-cell ALL treated according to the intermediate risk high group of the ALLTogether protocol. TEAM will be run as an intention-to-treat study.

Patients in TEAM-arm will receive 6MP+6TG+MTX from day 1. 6TG dose will be increased by 2.5 mg/m^2 at 2 weeks intervals until maximum tolerated dose (max. 12.5 mg/m^2). Blood samples will be

taken at 3 month intervals (or more frequently) to measure DNA-TGN to keep the level of DNA-TGN ≤1,500 fmol/µg.

TEAM pilot is currently run in Denmark (Copenhagen), Finland (Helsinki) and Norway with 19 patients included so far. All have achieved goal of more than median value of DNA-TG in the maintenance-study. The aim is to include 30 patients. Results will be available when we start the protocol.

Suggestion is to run TEAM Pilot in the other NOPHO centers when the ALLTogether Pilot-study starts in the NOPHO.

Pilot study on Allopurinol use during maintenance phase of ALL (Jonas Abrahamsson)

The aim of the study is to investigate if adding of allopurinol in patients with wildtype TPMT leads to an increment in 6TG and reduction in 6MMP levels without increasing myelosuppression or other side effects. Opened in Sweden in April 2017, pending approval in Finland. Study population – patients with ALL treated according to ALL2008 protocol and wild type TPMT, during the maintenance-2 phase with no additional chemotherapy apart from intrathecal therapy. Sixty patients are anticipated.

Ten patients included so far. Two SAEs reported. So far metabolites have behaved as predicted. Slow recruitment is thought to be due to misconception on the need of central line for blood sampling. However, blood can be obtained by capillary sampling as in other maintenance studies.

Asparaginase studies

NOR-GRASPALL 2016 pilot study (Birgitte Albert Klug/ Line Stensig Lyngaard)

Single-arm multicenter, multinational pharmacokinetic/pharmacodynamic and safety study of Eryaspase (GRASPA®) for the patients with hypersensitivity to PEG-Asparaginase, diagnosed with Ph- ALL. GRASPA will replace the remaining doses of PEG-asp when a patient develops hypersensitivity. The patients will have 1-7 doses which depending on how many PEG-asp doses they have received. Patients 1 to 45 years old are included. Participating countries: Denmark, Sweden, Norway, Iceland, Finland, Lithuania and Estonia; pediatric and adult centers.

The study opened in April, 2017 and is planned to be continued until. The target is to involve 25 children and 5 adults. In February 2018, study had 11 active sites, with 6 patients included, 16 doses administered. None of the patients had any reactions to GRASPA.

Allergic reactions to PEG-Asparaginase, Anti-PEG antibodies and silent inactivation (Sofie Gottschalk Højfeldt)

13% of patients treated according to the NOPHO ALL2008 protocol experience an allergic reaction to PEG-asparaginase. The study was performed making a speculation that some patients may have a genetic predisposition to development of allergy to PEG-asp. GWAS studies revealed the HLA-DQA2 variant rs3998359 on chromosome 6 to have the strongest association with allergic reactions to PEG-asp. The SNP is in close proximity with the genes reported to be associated with total IgE-levels. The study was presented as an oral presentation at ASH meeting, 2017.

The study is continued with the aim to evaluate IgG antibodies to PEG-Asparaginase. No patients with PEG-asparaginase enzyme activity had or developed anti-PEG antibodies during treatment.
Conclusion: IgG responses to repeat PEG-asparaginase administration are not the primary driver of PEG-asparaginase inactivation. The abstract was submitted to SIOP 2018.

TDM of asparaginase (Birgitte Klug Albertsen)

Extended sampling for asparaginase TDM was started in February 2017 with the aim to identify no-activity patients, to study the pharmacokinetics in depth and to build a database for ALL2008 and for ALLTogether. Sweden, Norway, Denmark, Finland and Lithuania are participating. In ALLTogether dose individualizing from the 3rd dose (day 32) based on the previous level. The centers will have to cover the shipment by standard mail and the analysis of the samples (≈ € 10/sample???). The result and recommandation will appear in ”REDCap”.

HD MTX (Jesper Heldrup, Torben Mikkelsen)

International collaboration with Cincinnati, US (Jesper and Kjeld from NOPHO) was fruitful with the publication 'Consensus Guideline for Use of Glucarpidase in Patients with High-Dose Methotrexate Induced Acute Kidney Injury and Delayed Methotrexate Clearance', Ramsey LB (…) Schmiegelow K (…) Heldrup J. in Oncologist. 2018.

HD MTX database data will be included into the 'Impact of BMI in patients with ALL' project run by Stockholm team (description below).

Vincristine neurotoxicity studies

Retrospective studies run in Vilnius and Lund. Almost half of the patients received one to eight reduced VCR doses due to neurotoxicity (Vilnius study). Comparison of 30 and 60 min infusion did not reveal statistical evidence in neurotoxicity reduction (Lund study, will be presented at annual NOPHO meeting in Vilnius).

Impact of BMI on outcome, treatment related toxicity and pharmacokinetics in patients with ALL (Christina Egnell Gustafsson, Arja Harila-Saari, Susanna Ranta, Mats Heyman)

New study proposal from Stockholm. The aim of the study is to analyse impact of overweight and obesity or underweight on development of treatment-related toxicity, pharmacokinetics of antileukaemic drugs and survival in children with ALL treated with the Nordic protocols. The ultimate goal is to individualize treatment in order to avoid under- and overtreatment and contribute to a development of interventions to improve outcomes in this at-risk population.

The study was approved by the Pharmacology wg as a NOPHO Pharmacology group study. National PIs from the countries that provided data to high dose MTX database will be needed.

A new initiative on the Pediatric oncological pharmacology course

The idea raised by Finn Wesenberg, Jesper Heldrup few years back. Discussed again in the Pharmacology group and was supported by the Pharmacology wg and Pharmacists wg.
Pharmacists in the Nordic countries do not get specific education in pediatric oncology/hematology. On the other hand, physicians feel the need of basic knowledge in pharmaceutical issues such as mechanism of action of cytostatic agents, principles of PK/PD, drug-drug compatibility etc. The nurses would probably be interested as well.

First teleconference on the issue held in March 7, 2018. The idea will be presented for discussion in Vilnius in June at the ECC and Board group meetings.

Next meeting: Tuesday September 25, 2018 in Copenhagen.

Goda Vaitkevičienė
Chair of the NOPHO Pharmacology WG
April 20, 2018

Other Disease Working Groups

Thrombosis and Haemostasis Working Group

Chair	Ruta Tuckuviene (DK)
Denmark	Birgitte Klug Albertsen, Marianne Hutchings Hoffmann
Estonia	Kadri Saks
Finland	Pasi Huttunen, Kaisa Vepsäläinen
Iceland	Ólafur Gísli Jónsson
Norway	Ellen Ruud, Jon Helgestad
Lithuania	Sonata Trakymiene
Sweden	Susanna Ranta, Ulf Tedgård, Tony Frisk
Young NOPHO	Nadine Gretenkort Andersson (SE), Kirsten Jarvis (NO), Cecilie Utke Rank (DK), and Satu Långström (FI)

1. **Meetings:** The Working Group meets twice a year. Last meeting was held in Copenhagen on 18th January 2018. The next meeting is planned on 31st August 2018.

2. **New members:** Cecilie Utke Rank (DK), and Satu Långström (FI)

3. **Status on ongoing registration of thromboses.** The WG continues to obtain the detailed information on TE in NOPHO ALL 2008 protocol. The comprehensive registration of clinical characteristic continues in children and adults in NOPHO ALL 2008 protocol. Eleven children and six adults with thromboses were reported in 2017 (Kirsten Jarvis).

4. Cecilie U. Rank et all scrutinized **TE in children and adults in NOPHO-ALL2008** protocol. Study reports the cumulative incidence of TE is 7.9% (95% CI 6.6–9.1) during therapy of ALL among patients 1–45 years of age. Patients ≥10 years are at highest risk of TE during treatment with ASP with a 2.5-year absolute risk of TE >15%. The hazard of DCR1 was significantly increased (≥5-fold) for younger patients <18 years with TE compared to patients <18 years without TE. The paper is in press.

5. **GWAS** among TE patients with ALL is ongoing. GWAS meta-analysis resulted in two potential top SNPs and associated genes in 92 cases (61 NOPHO, 31 Australian) with thrombosis and ALL. Data is validated in Australian and St. Jude groups, although without statistically significant founding. Marion Mateos et al are working on the paper.

6. **Status on PhD study** (Kirsten Jarvis). The ph.d project includes four substudies: 1) SNP-association study, 2) Mortality, 3) CSVT-outcome , 4) Asymptomatic CVL-related TE study. The major part is a SNP study, and Kirsten currently works on setting up the model for it.

7. **TE in ponte di Legno (pDL)/ I-BFM.** TE is the toxicity of interest in pDL. The data form and protocol are under development by pDL toxicity group.

8. The establishment of **Benign Haematology Committee** was suggested by NOPHO general secretary Mervi Taskinen, and approved by NOPHO Board Meeting in November 2017. The Thrombosis WG supported the Committee. We suggest Ulf Tedgård to be a representative of the Thrombosis WG.

9. **Pulmonary embolism study** in children and adults with ALL is under the process of the writing (Cecilie L. Bjerg, Ruta Tuckuviene).

10. **Future plans:** Thrombosis WG suggests establishing **Thrombosis Registry** in all children and adolescents with malignancies and a **pilot study on thrombosis in ALL-Together** in Nordic and Baltic countries.

Aalborg, April 2018
Ruta Tuckuviene
Chair of the NOPHO Thrombosis and Haemostasis Working Group

Red Cell Disorders Working Group

Chair	Ulf Tedgård (SE) 2012
Denmark	Birgitte Lausen, Niels Clausen, Pernille Wendtland Edslev Mimi Kjærsgaard (DK) associated member
Finland	Kirsi Jahnukainen, Nina Valtanen, Ulla Wartiovaara-Kautto
Iceland	Ólafur G. Jónsson
Norway	Anne Grete Bechensteen, Einar Stensvold
Sweden	Jan-Inge Henter, Rolf Ljung, Magnus Göransson
Young NOPHO	Annika Mårtensson (SE), Audrone Muleviciene (LT), Niina Valtanen (FI), Szymon Klafkowski (NO)

1. **Meetings:** The Working Group has had no formal meetings during the last year. Informal meetings has been held as members of the working group has met at the annual NOPHO meeting in Stockholm May 2017 and the EuroDBA meeting in October.
   The **next WG meeting is planned to take place in September or October 2018**, preliminary in Malmö, Sweden.
2. **New members:** Nina Valtanen (FI), Ulla Wartiovaara-Kautto (FI) and for Young NOPHO Szymon Klafkowski (NO).
3. **Status on ongoing registration of patients with transfusion dependent anemias in the Nordic/ NOPHO Transfusion Registry (NTR).** Registration has started in Sweden but mainly with patients from Lund/Malmö and Stockholm. Patients with Thalassemia, DBA and Sickle Cell Anemia are enrolled.
4. Work regarding update of NTR is ongoing by Dr Peter Priftakis and Ulf Tedgård. Over the years personal has changed at the Childhood Cancer Registry and work with NTR has not had the highest priority.
5. Questions regarding Quality of Life will be added to the registry as part of a study project led by Margareta Stenmarker. QoL as both PROM and PREM will be added and the plan is that it is done by the patients/parents directly online and also be used as part of the ordinary follow-up at the regular doctor visit.
6. In the future NTR will hopefully be able to collaborate with other European registries under the supervision of ENERCA.
7. The establishment of **Benign Haematology Committee** was suggested by NOPHO general secretary Mervi Taskinen, and approved by NOPHO Board Meeting in November 2017. The NOPHO Thromboembolic WG supported the idea of Benign Haematology Committee. The information regarding a Benign Haematology Committee will be sent to the members of the Red Cell Disorders WG in order to have their opinion before the NOPHO meeting in Vilnius.

Lund, April 2018
Ulf Tedgård
Chair of the NOPHO Red Cell Disorders Working Group

Histiocytosis Working Group

Coordinator	Jan-Inge Henter	jan-inge.henter@ki.se
Denmark	Marianne Ifversen (HLH) Bodil Als-Nielsen (LCH)	marianne.ifversen@regionh.dk bodil.elise.thorhauge.als-nielsen@regionh.dk
Finland	Satu Lehtinen Marika Grönroos	satu.lehtinen@ppshp.fi marika.gronroos@tyks.fi
Iceland	Halldóra Þórarinsdóttir	halldorathorarins@yahoo.com
Norway	Maria Gunnes (HLH) Monica Munthe-Kaas (LCH)	maria.gunnes@igs.uib.no uxmomu@ous-hf.no
Sweden	Jan-Inge Henter Tatiana Greenwood	jan-inge.henter@ki.se tatiana.greenwood@ki.se
Lithuania	Jelena Rascon	jelena.rascon@gmail.com
Young NOPHO	Marie Meeths	marie.meeths@ki.se

Langerhans cell histiocytosis (LCH)

LCH-IV has now been opened in Denmark, Sweden and Norway. In countries where LCH-IV is not opened, the recommended treatment is LCH-III.

LCH-IV

For LCH-IV, each country has a separate coordinator. Finland is planning to enter LCH-IV.
Denmark: Karsten Nysom karsten.nysom@regionh.dk
Sweden: Jan-Inge Henter jan-inge.henter@ki.se and Désirée Gavhed desiree.gavhed@ki.se
Norway: Monica Munthe-Kaas uxmomu@ous-hf.no

LCH-IV includes altogether seven interconnected studies "strata" (*recruitment July 2017*):
STRATUM I: First-Line Treatment (*Group 1= 102; Group 2 = 118*)
STRATUM II: Second Line Treatment for non-risk LCH (*n = 35*)
STRATUM III: Salvage Treatment for Risk LCH (*n = 11*)
STRATUM IV: Stem Cell Transplantation for Risk LCH (HSCT) (*n = 0*)
STRATUM V: Monitoring and Treatment of Isolated Tumorous and Neurodegenerative CNS-LCH (*n = 4*)
STRATUM VI: Natural History and Management of "Other" SS-LCH (*n = 201*)
STRATUM VII: Long-Term Follow-up (*n = 3*)

Recruitment is slower than expected to Stratum I and II. Stratum I will take another 5-6 years to reach the final sample size. NOTE: There is an Amendment in Stratum II, Initial course: "Add PRED to all VCR/ARA-C pulses until week 24".

Some other studies on LCH in the literature

In 2010, the group of B Rollins reported on "Recurrent BRAF mutations in Langerhans cell histiocytosis". Badalian-Very G, et al. Blood. 2010 Sep 16;116(11):1919-23. Treatment for patients with BRAF V600-mutants such as with Vemurafenib has been reported to have prolonged efficacy in adult patients with BRAF V600-mutant Erdheim-Chester Disease (n=22) and LCH (n=4). Diamond EL, et al. JAMA Oncol. 2018 Mar 1;4(3):384-388.

In a recent paper, it is stated that two combined treatments (i.e. trametinib plus dabrafenib and vemurafenib plus cobimetinib) that target two different kinases in the BRAF/MEK/ERK pathway, and thereby provides the simultaneous prohibition of both MEK and BRAF, is associated with more durable response rate than BRAF monotherapy and that it can overcome acquired resistance.
Faghfuri E, et al. Mitogen-activated protein kinase (MEK) inhibitors to treat melanoma alone or in combination with other kinase inhibitors. Expert Opin Drug Metab Toxicol. 2018 Mar;14(3):317-330.

The role of BRAF/MAPK inhibition in the treatment of LCH has been reviewed in:

- Abla O & Weitzman S. Hematology Am Soc Hematol Educ Program 2015; 2015: 565-70
- Kolenová A, et al. Targeted inhibition of the MAPK pathway: emerging salvage option for progressive life-threatening multisystem LCH. Blood Adv. 2017 Feb 2;1(6):352-56

From the Histiocyte Society Meeting 2017

1. Vemurafenib study in Europe (Jean Donadieu/Johan Visser)

35 patients: Refractory LCH (n=29) and ND-CNS-LCH (n=6). Vemurafenib dose 20 mg/kg/day; min. 2 months. Skin rash common problem, but manageable. Median fo-up = 13 months.
Refractory LCH: Median age 1 yr. Risk organ involvement: n = 22. Time from diagnosis to start of treatment = 0.8 yrs. Quick full response (100%). In 19 patients the treatment had been discontinued. This resulted in 10 reactivations that were successfully retreated with Vemurafenib.
ND–CNS-LCH: Time from LCH diagnosis to start of treatment was 11 yrs. Partial response in 1 patient, no response in the others.

Conclusions: Monotherapy in active refractory disease resulted in 100% response in a short time. Good safety profile, and no keratoacanthomas. Can be administered as outpatient therapy. It is concluded that 3 months treatment time too short. In this study, ND-CNS-LCH does not improve with Vemurafenib (but there is experience in US and UK of patients responding to Vemurafenib and Dabrafinib, and it is then important is to start early).

2. NACHO (North American Consortium for Histiocytosis)

Phase II Study of Clofarabine in patients with recurrent or refractory LCH study still going (LCH-CLO). https://www.nacho-consortium.org/lch-clo.html

In 2018 opening a phase II MEK2-inhibitor study for LCH.

Hemophagocytic lymphohistiocytosis (HLH)

HLH-94: The Histiocyte Society protocol HLH-94 was based on the combination of chemotherapy and immunotherapy (VP-16, steroids and cyclosporin A), followed by HSCT. This protocol was succeeded by the HLH-2004 protocol. The final HLH-94 study summary was published in 2011 *(Trottestam H, et al. Blood 2011;118:4577-84).*

HLH-2004: This study was opened in January 2004 and closed for recruitment Dec 31, 2011. The main difference compared to the HLH-94 protocol was that cyclosporin A (CSA) was initiated upfront instead of at week 9. Five-year survival in children with (n = 168) and without (n = 201) family history/genetically verified FHL was 59% and 64%, respectively. The results are presented in *Bergsten E, et al. Blood 2017;130:2728-2738.*

NOTE: The Histiocyte Society recommends the HLH-94 protocol as standard of care, since it could not be shown that HLH-2004 was superior to HLH-94. Many nevertheless use CSA as a bridge to HSCT in primary HLH, starting not earlier than week 3, when dexamethasone is tapered (see guidelines

below). The HLH-2004 diagnostic criteria (5/8 criteria) are still recommended.
There is no new international treatment study on HLH planned. Currently minor studies are performed on alemtuzumab in primary HLH and on emapalumab (anti-IFN-gamma) and ruxolitinib (a Janus kinase (JAK) 1/2 inhibitor) in both primary and secondary HLH.

Recommendations on the use of the HLH-94 protocol: Guidelines on the use of the HLH-94 protocol in clinical practice has been prepared by the HLH Steering Committee of the Histiocyte Society, including co-authorship of Tatiana von Bahr Greenwood, AnnaCarin Horne, and Jan-Inge Henter (submitted).

HLH Registry: In preparing for a new international HLH study an HLH Registry is open for (1) all patients with primary immunodeficiencies predisposing to HLH, and (2) patients with active HLH that is not secondary to underlying conditions such as rheumatological disease, malignancy, metabolic disease or Leishmania infection. The study center is in Germany. In Sweden, a nation-wide ethical application for joining the Registry has been submitted. The study objectives include to:

- Collect data relevant for the assessment of feasibility and design of future interventional studies on the treatment of HLH, and the international patient recruitment potential for a future trial
- Collect data on current standard of care, time to transplant, and outcome after 1 year

In case of clinical questions you are welcome to contact Jan-Inge.Henter@ki.se or Tatiana.Greenwood@ki.se.
For pre-treatment sampling for diagnostic purposes, contact Yenan.Bryceson@ki.se.

Novel Therapy Working Group

Members 2017-2018

Denmark	Karsten Nysom (chair), Kjeld Schmiegelow
Finland	Sanna-Maria Kivivuori, Olli Lohi, Matti Korhonen, Susanna Ranta (Young NOPHO)
Iceland	Halldora Thorarinsdottir
Norway	Trond Flægstad, Jochen Büchner
Sweden	Stefan Holm, Ingrid Øra, Jacek Toporski, Mats Heyman

The working group had a physical meeting during the annual meeting in Stockholm. Minutes are on the NOPHO web site. This year, a meeting is planned Saturday 02 June 07:30-09:30.

There are now Nordic ITCC centres in Copenhagen, Stockholm, Gothenburg and Tampere.

More and more early phase trials are becoming available in the region. An up-to-date overview of all early phase trials and all phase 3 trials with targeted agents, open for children or adolescents with cancer in any Nordic or Baltic country, is maintained by the working group and available at www.nopho.org under "Protocols". More and more patients are referred between the Nordic and Baltic centres for therapy on such trials, in line with the ambition of the working group members.

Copenhagen, April 18th, 2018 Karsten Nysom

NOPHO novel therapy working group – Overview of ongoing trials – Updated 17 April 2018 Page 1 of 4

Phase 1-2 trials

Trial (link)	Targeted agent	Other agents	Diagnoses	Age	Open in	Phase	Contact
VINILO	Nilotinib	Vinblastine	Low grade gliomas – relapsed or refractory in all patients; newly diagnosed in NF1 patients	0.5-20.9y	Copenhagen	2	Karsten Nysom
BEACON	Bevacizumab	Temozolomide, irinotecan, topotecan	Relapsed HR neuroblastoma	1-21.9y	Copenhagen	2	Karsten Nysom
ITCC-015	Azacitidine	-	Relapsed MDS or JMML	1-17.9y	Aarhus	1	Henrik Hasle
BI 1200.120	Afatinib	-	Relapsed or refractory intra- and extracranial tumours with confirmed ErbB pathway deregulation, shown in study biomarker pre-screening	1-17.9y	Copenhagen	1	Karsten Nysom
AZA-AML-004	Azacitidine	-	First molecular relapse of AML with known t(8;21), inv(16), t(9;11), NPM1-mutation, or FLT3-ITD-mutation	0.25-17.9y	Copenhagen	2	Karsten Nysom
rEECur EuroEwing link	-	Topotecan, cyclophosphamide, irinotecan, temozolomide, gemcitabine, docetaxel, ifosfamide	Recurrent or primary refractory Ewing sarcoma	4-49.9y	Bergen, Oslo, Trondheim, Tromsø, Copenhagen, Aarhus, Helsinki, Turku, Oulu, Tampere	2	Dorota Malgorzata Wojcik, Heidi Glosli, Erling Moe, Tove Nystad, Karsten Nysom, Henrik Hasle, Jukka Kanerva, Päivi Lähteenmäki, Riitta Niinimäki, Mikko Arola
MEMMAT	Bevacizumab	Thalidomide, celecoxib, fenofibrate, etoposide, cyclophosphamide, liposomal cytarabine	Relapsed or progressed medulloblastoma	0-19.9y **at original diagnosis**	Copenhagen, Gothenburg, Stockholm, Uppsala, Lund, Umeå, Linköping	2	Karsten Nysom, Magnus Sabel, Stefan Holm, Anders Öberg, Helena Mörse, Mattias Mattsson, Irene Devenney

Late Effect Working Group

Chair	Riitta Niinimäki
Denmark	Catherine Rechnitzer Niels Clausen
Finland	Mervi Taskinen Kirsi Jahnukainen
Iceland	Halldora Thorarinsdottir Solveig Hafsteindottir
Norway	Inga Maria Johannsdottir Einar Stensvold
Sweden	Johan Arvidson Cecilia Petersen
NOPHO solid tumour registry	Finn Wesenberg
NOPHO leukaemia registry	Mats Heyman
Young NOPHO	Gitte Sorensen Jan Bernd Stukenborg Simon Kranz Trine Gade Bonnesen Thorgerdur Gudmundsdottir

Meetings

Group had a meeting during the NOPHO Annual meeting, Stockholm 20 May 2017.

Nordic late effect activities

1) Long-term follow-up (LTFU) clinics in NOPHO countries

The goal of the LE WG is that the collaboration between LTFU clinics in NOPHO countries will increase both clinically and scientifically.

Collaboration between LTFU clinics in Finland

All five university hospitals in Finland have established LTFU clinics since the spring of 2016. The first joint meeting was organized in January. The clinics are using the modified British model and international harmonization guidelines that are being translated to Finnish. BCB Medical (a Finnish software company) has developed an electronic platform, which will work as a quality register for childhood cancers.

LTFU clinic in Iceland

The LTFU clinic opened in September 2016. Guidelines from the international harmonization group, SALUB and COG have been used. Survivorship passport has been written using SALUB form with influence from Gothenburg and London.

LTFU clinics in Sweden

In Sweden there are four LTFU clinics. Gothenburg is the oldest clinic, and the others are in Uppsala, Stockholm and Umeå.

2) The Nordic Centre for Fertility Preservation for Boys after Cancer Treatment

Cryopreservation and storage of the samples are done in the national centers. Multicenter biobank has been established in Stockholm. The consortium has representatives from all the Nordic and Baltic countries.

The website of NORDFERTIL (www.nordfertil.org) is online. This project is closely connected to the late effect group, so the link is on the website of the late effect working group.

The risk of infertility varies with type of conditioning. It is important to inform all patients undergoing hematopoietic stem cell transplantation about the risk of infertility and available preservation options. The recommendation made by a panel of fertility specialist within the EBMT has been published in Bone Marrow Transplantation in Feb 2017 (Dalle, et al.)

3) Current follow-up guidelines after ALL treatment in Nordic countries and The ALLTogether

Current follow-up guidelines after ALL treatment have been collected, and the ALL relapse detection study is ongoing by ALL relapse WG. They are basis for future discussion on follow-up guidelines.

The ALLTogether protocol is coming soon. The follow-up after the treatment will be planned together with other countries. The protocol includes several late effect related items, like decreased toxicity (randomized studies) and new agents for HR therapy.

Pancare activities

Pancare had 19th meeting in Lund, May 3-5 and 20th meeting in Lubeck, October 3-5.

Collaboration with NOBOS

Collaboration with NOBOS is ongoing and the LE WG meetings are joint meetings.

Late effects studies in Nordic countries

Gitte Sorensen presented her PhD project on late effects after childhood ALL on LE WG meeting May 2017.

Oulu, April 2018
Riitta Niinimäki

Pharmacists Working Group

Sweden	Ranaa El Edelbi Magnus Dahlander Mattias Paulsson Hilanah Shabo Tamara Al-Ani Sofia Jönsson Madeleine Persson
Norway	Margrete Einen Gunn-Therese Lund Sørland Siri Utby Maria Larsen Kajsa Rinstad
Lithuania	Monika Grigentyte Laimis Dambrauskas
Finland	Sanna Veijalainen Ulla Taipale Taija Heikkinen
Denmark	Sigrid Otnes SørenBisgaard Johansen Kathrine Bruun Svan Louise Larsen Maria Kaaberbøl Thorberg

Meeting

The Pharmacists Working Group had one physical meeting November 10th in Gothenburg. We also had monthly meetings via Lync/Skype.

Projects

The main focus of the working group is the development of an educational material for the extravasation guideline (online education).

We are also working with a second project, the oral chemotherapy project where we initially want to collect and share information concerning e.g. administration via enteral feeding tubes and safe handling of oral cytotoxic agents in the Scandinavian and Baltic countries. The aim is to develop shared instructions and ensure equal access to oral chemotherapy suitable for enteral administration.

Ranaa and Magnus are also helping the NOPHO pharmacology group to set up an education in pharmacology and pharmacokinetics for both pharmacists and doctors.

Presentations

The NOPHO pharmacist group submitted an abstract to the 2018 congress of the European Association of Hospital Pharmacy (EAHP) and were selected for an oral presentation as one of two abstracts in the category. Sanna and Margrete held both the oral presentation and presented the poster.

Ranaa El Edelbi
Chair of the NOPHO Pharmacists WG
Stockholm, April 3, 2018

NOPHO/NOBOS Working Group on Ethics (WGE)

Denmark	Trine Brøner, nurse Gitte Petersen, nurse Astrid Sehested, physician Pernille Wendtland Edslev, physician
Finland	Kristian Juusola, nurse
Iceland	Sigrún Þóroddsdóttir, nurse
Norway	Grete Nathalie Ringheim, nurse
Sweden	Cecilia Bartholdson, nurse Anders Castor, physician Sara Karlsson, nurse Pernilla Pergert, nurse (chair) Jennie Stigmar, nurse Lisa Törnudd, physician (secretary)

The intention of the NOPHO/NOBOS Working Group on Ethics (WGE) is to be a Nordic competence group that offers Clinical Ethics Support (CES) and puts the ethical questions within paediatric oncology on the agenda, by developing and disseminating knowledge and methods. The aims of CES include supporting healthcare professionals to handle ethical issues and to reflect on what should be done in treatment and care. Approaches for CES include, for example, Ethics Case Reflection (ECR) sessions in the team and ethics education. During 2017 the main focus of the WGE has been to develop, deliver and evaluate a course in facilitating ECR sessions.

Organisation

The group has had one 2-day meeting during 2017 and has delivered an ethics training program with two parts.

Meetings of the WGE during the last year

26-28 Mars 2017, Dragør, Denmark
15-16 January, 2018, Malmö, Sweden

Completed course arranged by the WGE (partly replacing regular meeting)

27-29 September 2017, Sigtuna, Sweden
15-16 Mars 2018, Sigtuna, Sweden

Upcoming meetings of the WGE

2 June, 2018, Vilnius, Lithuania
24-26 October, 2018, Reykjavik, Iceland

Funding

Pergert (co-applicant: Castor) has received grants for the WGE for 2018-2020 (PL2017-0002) from the Swedish Childhood Cancer Foundation. The Danish Børnecancerfonden funded the 2-day meeting in Dragør.

Activities of the WGE during the last year

Much of the CES is performed locally by the members, who have been inspired and enabled by their participation in the WGE. Local CES performed by members includes: offering and facilitating ECR sessions in healthcare teams and/or in committees; teaching ethics to nursing and medical professionals/students; performing research projects in clinical ethics; serving as members of national, regional or local clinical ethics committees/societies.

The WGE has been jointly involved in education and research projects, and has continued to work with the Open Space method during meetings. Open space groups have worked on the following ideas:

- Ethics course: guiding ECR sessions, see below
- Nordic study on communication over language barriers, moral distress and the ethical climate in childhood cancer care, see below
- future work on genetics/palliation
- joint session on ethics at the NOPHO/NOBOS meeting in Vilnius

Ethics course: guiding ethics case reflection (ECR) sessions

A course in handling ethical issues and facilitating ECR sessions have been offered to healthcare professionals in Nordic pediatric oncology. The course briefly covered the theory of ECR but was first and foremost a skills course; including the implementation of ECR sessions at the pediatric oncology centres. The first part of the course was a 3-day introduction (sept 2017) to guiding ECR sessions followed by a period in which the participants practiced and implemented ECR sessions in their clinical setting. The second part of the course was a 2-day follow-up (march 2018) where participants could fine-tune their knowledge and skills. The WGE has been collaborating with Dr Molewijk at VU University in Amsterdam, and the course management team consisted of, apart from Bert Molwewijk, Anders Castor, Pernilla Pergert and Lisa Törnudd. Twenty-four healthcare professionals (physicians, nurses and a social worker) completed both parts of the course including: one from Norway, two from Iceland, one from Finland, four from Denmark (representing two centres), and seventeen from Sweden (representing all six pediatric oncology centres). Until March 2018, the Swedish participants had performed twenty-four ECR sessions about ethical issues at their centres. Cecilia Bartholdson is performing an evaluation of the training and the implemented CES and Pergert has been granted separate funding from the Swedish Childhood Cancer Foundation (PR2016-0020) for the research project entitled "Evaluation of ethics support – What is the impact of moral case deliberations on pediatric oncology?".

A Nordic Study on communication over language barriers, moral distress and the ethical climate in childhood cancer care

The WGE has been an expert reference group in a multi-site cross-sectional survey performed in Nordic (Sweden, Denmark, Norway, Finland and Iceland) pediatric oncology using a questionnaire with, apart from socio-demographic items, three instruments:

- Communication over Language Barriers-questionnaire (CoLB-q)[1]
- Moral Distress Scale-Revised (MDS-R)[2]
- Hospital Ethical Climate Survey-Shortened (HECS-S)[3]

Data collection has already been finalized in Sweden and the study will be performed in the other Nordic countries. During 2017, members of the WGE have been involved in the process of translating and culturally adapting the English translation of the Swedish questionnaire to Danish and Norwegian, following recommended procedures.[4]

Presentations on ethics at international conferences from the group or with group members as co-authors during 2017

- 49th Congress of the International Society of Paediatric Oncology (SIOP), Washington DC, USA, October 12-15, 2017
  - o **Bartholdson, C**. (2017) High levels of intensity of moral distress among healthcare professionals – A national study in pediatric oncology. (SIOP Meeting Abstract) Pediatric Blood & Cancer, 64, (Suppl. S3), p.S97.
  - o Invited speakers at the plenary Symposium 3 "Ethical Issues in Paediatric Cancer":
    - **Pergert, P**. Ethical issues in intercultural care.
    - **Castor, A**. Ethical issues in end-of-life care

Publications on ethics from the group or with group members as co-authors

Original articles 2017

- **Bartholdson, C.**, Molewijk, B., Lützén, K., Blomgren, K., & **Pergert, P**. (2018) Ethics case reflection sessions: Enablers and barriers, Nursing Ethics, 25(2):199-211. DOI: 10.1177/0969733017693471
- af Sandeberg, M., Wenemark, M., **Bartholdson, C.**, Lützén, K., & **Pergert, P**. (2017) To change or not to change – Translating and culturally adapting the paediatric version of the Moral Distress Scale-Revised (MDS-R), BMC Medical Ethics Feb 20;18(1):14. PMID: 28219363

On behalf of NOPHO/NOBOS Working Group on Ethics
Pernilla Pergert, Stockholm, April 2018

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1. Granhagen Jungner J, Tiselius E, Wenemark M, Pergert P. Development and evaluation of the Communication over Language Barriers - questionnaire (CoLB-q) in paediatric healthcare. **Patient Education and Counseling**. 2018;In press.
2. af Sandeberg M, Wenemark M, Bartholdson C, Lutzen K, Pergert P. To change or not to change – translating and culturally adapting the paediatric version of the Moral Distress Scale-Revised (MDS-R). **BMC Medical Ethics**. 2017;Feb 20;18(1):14.
3. Pergert P, Bartholdson C, Wenemark M, Lützén K, af Sandeberg M. Translating and culturally adapting the shortened version of the Hospital Ethical Climate Survey (HECS-S) – Retaining or modifying validated instruments. **BMC Medical Ethics**. 2018;In press.
4. Beaton DE, Bombardier C, Guillemin F, Ferraz MB. Guidelines for the process of cross-cultural adaptation of self-report measures. **Spine (Phila Pa 1976)**. Dec 15 2000;25(24):3186-3191.

Radiotherapy Working Group

Chair	Yasmin Lassen
Denmark	Akmal Safwat Yasmin Lassen
Finland	Kristiina Koskela Merja Korpela Satu Lehtinen
Iceland	Vacant
Norway	Petter Brandal
Sweden	Kristina Nilsson Ulla Martinsson Jonas Karlén
Lithuania	Vacant

The NOPHO pediatric radiotherapy working group had its 3rd annual meeting at the annual NOPHO meeting in Stockholm in 2017. The main discussion point was radiation quality assurance through the new SIOPE initiative QUARTET. All children included into SIOPE protocols will in general be included in this quality assurance program, where radiotherapy target delineation and dose plans will be validated before start of the radiotherapy treatment by SIOPE reviewers so that radiotherapy protocol violations can be prevented. The QUARTET initiative has already organized this for the neuroblastoma Lines protocol, the SIOPE brain tumour group is working on implementing QUARTET into their protocols and all new protocols will have included this radiotherapy quality assurance. We discussed this in the working group and all present members agreed on recommending the board of NOPHO that quality assurance for children in SIOPE protocols should be done by the QUARTET reviewing system. This has been brought further to the NOPHO board.

In the frame of the working group meeting we also organised a workshop discussing irradiation of nephroblastoma in the new UMBRELLA protocol for Wilms tumours. Geert Janssens, a pediatric radiation oncologist from Utrecht, NL, was invited as expert in the field. The Swedish Childhood Cancer Foundation had funded the costs of his invitation and the working group is very thankful to Kristina Nilsson for having organized this funding possibility and to Geert Janssens for coming.

For 2018 we are planning a workshop about the SIOPE ependymoma II protocol. We will prepare a dummy run study comparing target delineation and planning between centers in the Nordic region. If possible we would like to publish our results in a peer reviewed journal.

Yasmin Lassen, for the NOPHO Radiotherapy Working Group

Figure 1. Photo from the NOPHO Radiotherapy Working Group Workshop on Radiotherapy of pediatric nephroblastoma, May 2017 Stockholm.

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