Nordic Society of Paediatric Haematology and Oncology

NOPHO

Annual Report

2017

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

Foreword

Dear NOPHO members,

The NOPHO report 2017 is ready, and available as a paper edition and on www.NOPHO.org. As always, this would not have been possible without our active members registering data and contributing in the working groups. This is what is has been all about in NOPHO: seeing the bigger picture and the advantage of putting the efforts towards the same goal.

The quality of our registration has been high and will be even better with the growing solid tumor registry. Registration gives us a treasure and basis for good science. Good science together with good clinical practice makes the future. So, a sincere thank you all for keeping our registry fresh and updated. Thank you for being active in the working groups and giving your precious time for collecting and evaluating data for projects, for keeping the protocols running and for representing NOPHO in international collaborative working groups. And thanks to those minds creating the layout of the report and hands on the computer keyboards typing in, copy-pasting and integrating the material to be the NOPHO report 2017: thank you Emma Hovén and Jenny Juhlin!

The world around us is changing, and also NOPHO is moving towards a more international collaboration. NOPHO has been the driving force in creating the present AML-protocol shared widely internationally. Also the next ALL-protocol-to be has strong input from our society having Mats Heyman as the PI. Also the Brain Tumor Committee has actively sought for international collaboration. The several phase 1 centers within the NOPHO area have given us an access to the newest therapies but also invite collaboration from beyond the NOPHO area. These are good examples of that, in spite of more international collaboration, the activity is not elsewhere and the decisions are not taken by the others, but they are as much ours as we want them to be.

Thank you all for contributing to NOPHO and enjoy the NOPHO Report 2017. See you in Stockholm!

Helsinki/Stockholm, March 10th 2017
Mats Heyman (NOPHO Registry), Emma Hovén and Jenny Juhlin (NOPHO Secretariat), Mervi Taskinen (GS)

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NOPHO Board

Members 2016 - May 2017

Secretary- -general -elect	 Mervi Taskinen Birgitte Klug Albertsen	 elected 2016 elected 2016
Treasurer	Peder Skov Wehner	elected 2015
Auditors of accounts	Gustaf Ljungman Birgitte Klug Albertsen	elected 2005 elected 2015
Stand in auditor of accounts	Svein Kolmannskog	elected 2005
Denmark	Peder Skov Wehner Lisa Hjalgrim	elected 2015 elected 2014
Finland	Satu Lehtinen Kaisa Vepsäläinen	elected 2013 elected 2016
Iceland	Ólafur Gisli Jónsson Solveig Hafsteinsdottir	elected 2000 elected 2013
Lithuania	Jelena Rascon Goda Vaitkeviciene	elected 2016 elected 2016
Norway	Bendik Lund Petter Brandal (radiotherapy) Eva Widing	elected 2015 elected 2012 elected 2013
Sweden	Per Kogner Johan Arvidson	elected 2015 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 2016-2017

Denmark:	Karsten Nysom (chair)
Finland:	Markku Heikinheimo
Iceland:	Ragnar Bjarnason
Lithuania:	Sonata Trakymiene
Norway:	Anne Grete Bechensteen
Sweden:	Kees-Jan Pronk
Young NOPHO:	Nikolas Herold

The deadline for applications for NOPHO studies is 2 months before each NOPHO board meeting.

For the November 2016 term, 5 applications were submitted and evaluated.

For the May 2017 term, 6 applications were submitted and are currently under evaluation.

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.

Copenhagen, 12 April 2017
Karsten Nysom

Young NOPHO

Young NOPHO Board in 2016–2017:

Denmark:	Stine Nygaard Nielsen
Finland:	Anu Vatanen, Laura Madanat-Harjuoja
Iceland:	Thorgerdur Gudmundsdottir (Chair)
Lithuania:	Audrone Muleviciene
Norway:	Simon Kranz, Marta Maria Dirdal
Sweden:	Nikolas Herold

Last year the annual meeting of Young NOPHO (YN) was held at the annual NOPHO meeting in Reykjavik, Iceland. The minutes from the meeting and the regulations of YN can be found at the NOPHO website.

YN continues to be very active. Therefore and, due to the new YN regulations, the membership of all YN members is revised on an annual basis. The YN regulations, 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 YN members. Students working on time-limited research projects within paediatric haematology/oncology are YN members for the duration of this project. According to these regulations, the status of the memberships will be reviewed on a yearly basis.
In April 2017, 113 members (13 members from Norway, 38 members from Sweden, 33 members from Denmark, 22 members from Finland, 3 members from Iceland, and 4 members from Lithuania) have been registered as YN members.
We hope that this positive development will continue during the next year.

Today, YN is represented by 32 YN members in 24 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. Please contact the WG Chair or the YN coordinator if you are interested.

During the last years, the YN Web Portal, a platform for connecting YN, with information and discussions, was launched. The Web Portal has been developed by Elisabeth Broby Jensen and Dragi Petkovski together with YN members. However further development and promotion of the Web Portal is still needed to increase the activity in the forum. The responsible YN board members for the Portal is Stine Nygaard Nielsen. We hope that the activity on the Forum will increase during 2017 and that it will be used to stimulate new research collaboration throughout NOPHO.

In 2017, the board of YN met in Reykjavik to plan the next steps to further increase the activity within YN and to plan the YN annual meeting in Stockholm in May. During the YN board meeting, the board decided to:

- From now on, to start 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 2017, will be similar to the 2016 meeting, again with a division of the scientific programme: 50% research and 50% clinical focus.
- This year we will, once again, use topics from the Annual NOPHO meeting so that the YN meeting is an introduction hereto. The topics of our next YN annual meeting 2017 are: “Novel therapies and bio banking in the Nordic countries”.
- Call for YN members to submit abstracts on interesting clinical cases. The YN board will select two of the most interesting abstracts to be presented at the YN annual meeting. The two presenters will be rewarded with a travel-grant prize.
- Select two abstracts YN members have submitted to the NOPHO meeting, to be presented orally at the YN annual meeting. The two presenters will be rewarded with a travel-grant prize.

The YN board would like to thank the Swedish Childhood Cancer Foundation (Barncancerfonden) for supporting all YN related meetings in 2016 and 2017 and the upcoming annual meeting in Sweden at the 19th of May 2017. The YN board would also like to thank the Icelandic Childhood Cancer Foundation (Styrktarfélag krabbameinssjúkra barna) who supported the YN board meeting in Reykjavik.

Last but not least we would like to thank all YN members for their activities and energy invested in 2016 to make YN a more active and collaborative WG. Thank you!

2nd of May, 2017
On behalf of the YN board,
Thorgerdur Gudmundsdottir, Iceland, YN Coordinator

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
	Odense	Peder Skov Wehner, Eckhard Schomerus, Niels Fisker
	Aarhus	Niels Clausen, Henrik Schrøder, Henrik Hasle, Birgitte Klug Albertsen, Pernille Edslev Wendtland, Christine Dahl, Karin Bækgaard Nissen, Torben Mikkelsen
	Aalborg	Steen Rosthøj, Erik Østergaard, Ruta Tuckuviene
Finland	Helsinki	Kim Vettenranta, Pasi Huttunen, Kirsi Jahnukainen, Jukka Kanerva, Kirsti Sirkiä, Mervi Taskinen, Virve Pentikäinen, Minna Koskenvuo, Samppa Ryhänen, Helena Olkinuora, Satu Långström
	Turku	Päivi Lähteenmäki, Marika Grönroos, Anu Huurre, Laura Korhonen, Linnea Schuez-Havupalo
	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, Jóhann Heidar Jóhannsson
Lithuania	Kaunas	Giedre Rutkauskiene, Rosita Kiudeliene, Egle Ramanauskiene, Sonata Argustaite, Justina Klimaite
	Vilnius	Jelena Rascon, Goda Vaitkevičienė, Gražina Kleinotienė, Audronė Mulevičienė, Indrė Tamulienė, Lina Ragelienė, Mantas Jurkonis, Natalija Šestel, Ramunė Pasaulienė, Rolanda Nemanienė, Sigita Stankevičienė, Sonata Šaulytė Trakymienė, Vilma Rutkauskiatė
Norway	Oslo	Anne Grete Bechensteen, Ellen Ruud, Heidi Glosli, Bernward Zeller, Eva Widing, Inga Maria Johannsdottir, Einar Stensvold, Jochen Büchner, Monica Cheng Munthe-Kaas, Aina Ulvmoen, Charlotte Alme, Marta Maria Dirdal, Kirsten Jarvis. Associate members: Marit Hellebostad and Finn Wesenberg
	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
Sweden	Stockholm, Solna	Pernilla Grillner, Mats Heyman, Stefan Söderhäll, Niklas Pal, Arja Harila-Saari, Klas Blomgren, Stefan Holm, Johan Malmros, Per Kogner, Jan-Inge Henter, Jonas Karlén, Ingrid Öra, Petter Svenberg, Jukka Vakkila, Trausti Óskarsson, Tatiana Greenwood, Susanna Ranta,Tony Frisk, Tomas Bexelius, Christina Egnell, Johan Hamrin, Nina Mogensen, Karin Strålin, Mari Wilhelmsson
	Stockholm, Huddinge	Mikael Sundin, Jacek Winiarski, Peter Priftakis, Kim Ramme, Lena-Maria Carlson, Petra Byström, Gauti Rafn Vilbergsson, Susan Farmand
	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, Caroline Jeppson, Ladislav Krol, Nicholas Brodszki
	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
	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
	Umeå	Ulrika Norén Nyström, Per-Erik Sandström, Erik Forestier, Ulf Hjalmars, 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

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Solid and Brain Tumour Working Groups

Solid Tumour Committee

Chair	Gustaf Ljungman SE
Denmark	Catherine Rechnitzer Henrik Schrøder Lisa Hjalgrim
Finland	Kirsi Jahnukainen Hanna Juntti Jukka Kanerva Päivi Lähteenmäki (ST-registry repr.) Sauli Palmu
Iceland	Halldora Thorainsdottir Solveig Hafsteinsdottir Ólafur G. Jónsson
Lithuania	Giedre Rutkauskiene Indre Tamuliene Rolanda Nemaniene
Norway	Eva Widing Bem Zeller Tove Nystad
Sweden	Gustaf Ljungman Niklas Pal Torben Ek

On November 17-18 2016 the STC held its second meeting arranged by the former secretary general Cecilia Petersen in Stockholm. She initially summarized our positions and conclusions from our initiating meeting in Copenhagen in November 2016:

- 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, favorably two-day 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. Some of these disciplines were represented at the meeting and others remain to be contacted.

The meeting was held in close collaboration with the Nordic registry group and the role of a common Nordic registrations as a back-bone for future collaborative research was agreed upon. It was reassuring the NOPHO board the day preceding our meeting had approved the NOPHOCARE application.

It was decided to try to have STC meeting twice yearly with one meeting at the annual meeting and in parallel to the LCC and BTC meetings.

One of the goals at the meeting was to appoint a chairman for the group. This was difficult and instead it was decided that a chairman should 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. At a later time the Swedish national Ped Hem Onc group nominated Gustaf Ljungman to be the first chairman and Patrik Romerius to be secretary of the group.

At the meeting we had reports from: the INFORM and novel therapies study, the ExPO-r-Net meeting, the NOPHOCARE, about brachytherapy. Furthermore we formed working groups at the meeting to discuss and propose how we could proceed in a number of different issues like: website matters, composition of the STC, strategy issues for the STC, minimal variables in NOPHOCARE, and formation of a very rare tumor group (which was actually formed on-site). For all these issues you can find presentations on the NOPHO website.

It was also decided that an important part of the STC work was to discuss practical issues like what protocols we use and discuss up-coming protocols. We also discussed that it would be valuable to discuss difficult cases and a decision was made to create a common treatment summary overview with information from each country about which protocol is used for which disease and who is the responsible person in the respective country.

For the STC, Gustaf Ljungman, chairman

Brain Tumour Committee

Members of the Brain Tumour Committee board
Coordinator: Virve Pentikäinen (F)
Denmark: Astrid Sehested, Pernille Wendtland Edslev, Helle Broholm (neuropathologist)
Finland: Mikko Arola, Virve Pentikäinen, Anne Hekkala, Tuula Lönnqvist (neuropaed)
Iceland: Halldora Thorarinsdottir
Norway: Tore Stokland, Harald Thomassen, 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)
NOPHO Solid Tumor Registry: Mats Heyman

Change of members
Anne Hekkala (F) and Giedre Rutkauskiene (Lt) joined as new members of the board.

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: Harald Thomassen (N), Helena Morse (S), Pernille Wendtland Edslev (DK), Kirsti Sirkiä (F)
CNS Germ cell tumors: Astrid Sehested (DK), Kristin Solem (N), Irene Devenney (S)
Craniopharyngioma: Bengt Gustavsson (S) Tore Stokland (N)
AT/RT: Karsten Nysom, chair (DK), Pernilla Grillner (S)
Quality of Survival: Christoffer Ehrstedt
Radiotherapy: Kristina Nilsson (S), Henriette Magelssen (N), Yasmin Lassen (DK)

Brain Tumour Network

It was decided at Bergen and Oulu meetings to set up a Brain Tumour Network open to any NOPHO member working with paediatric brain tumours. At Reykjavik meeting it was planned that the representative of each national brain tumour group sends the names and e-mail addresses of their national Brain Tumour Network members to NOPHO webmaster to have these members added to the Network on NOPHO web pages. However, this is not possible because there are many colleagues who are not NOPHO members. It was therefore decided that all relevant messages will be send to Brain Tumour Committee members who will forward them to national Network members when needed. Board meetings are open to Network members.

Meetings

Board meetings

Board meeting was held in Reykjavik on 27th - 28th May 2016 at the NOPHO meeting (minutes and presentations on www.nopho.org). The next board meeting will be in Stockholm on 19th - 20th May 2017, also at the NOPHO meeting.

Brain tumour meetings

The **SIOP-E Brain Tumour Group meeting** was held in Liverpool before ISPNO meeting June 11th - 12th 2016.
The **ISPNO 2016 meeting** was held in Liverpool June 12th - 15th 2016.
Both meetings were well attended by NOPHO representatives and were a success with excellent program.
SIOP-E BT working group meeting was also held in HGG/DIPG working group (Milan, November 2016) and NF1 opthalmology meeting was held in connection with the European NF1 meeting (Padua, September).
Opening Symposium for the new Treatment and Research Center for Pediatric Oncology and Hematology took place in Heidelberg January 19th - 20th 2017.

Future brain tumour meetings

The next meeting of the **SIOP-E Brain Tumour Group** will take place in Prague September 7th - 9th 2017.
The **PAENNO 2017 meeting** will take place in Visby September 20th - 22th 2017.

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 and is planned to be opened in the UK. 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 during the Paenno meeting in Copenhagen, 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.

WHO 2016 Brain Tumour 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. Most significant changes has been made to classification of diffuse gliomas, medulloblastomas and other embryonal tumours. New classification also includes newly recognized diagnostic entities. Nomenclature has also been changed to consist of a histopathological name of the tumour followed by the genetic features. New molecular classification has a major impact on prognosis and treatment of many paediatric brain tumours. It also defines a goal for set up of specific diagnostic methods to fulfil the demand of molecular classification according to WHO 2016 classification and new international treatment protocols.

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 2017, three phase II-III protocols were open in NOPHO area (SIOP-E 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 radiotherapy for standard-risk patients to increase the effectiveness of the treatment. Molecular tumour analysis is done from fresh-frozen tissue on a national basis. The protocol was started in Germany September 2014 and is now open also in Finland, Sweden, France, Italy and Spain. There will soon be amendment 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 will become mandatory for patients with SHH-activated medulloblastoma to find the tumor predisposing syndromes.

Protocols for treatment of infant medulloblastoma and high-risk medulloblastoma are in development. The infant protocol (YC/Young Children MB) will have biologically stratified low and high risk treatment groups and will include radiotherapy for patients > 18 months with poorest prognosis. Protocol was already to be submitted but funding issues and increased rate of relapses in North American trials have led to some delay and re-evaluation of the protocol. The high risk protocol is still under preparation.

Atypical teratoid rhabdoid tumour (AT/RT)

There is no study protocol as such, but the European Rhabdoid Registry (EU-RHAB) contains a registry and treatment suggestion. 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.

Ependymoma

SIOP Ependymoma 2 protocol has been opened in France and the UK, 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, there are at present changes being made to the study design. Patients will be stratified into risk groups (infant, standard risk and diffuse glioma grade II). 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 opthalmologists for patients with a visual pathway tumor. 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 (Göttingen, 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. It has been opened in France, Copenhagen/Denmark, now also 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.

Relapse 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 for patients with recurrent or progressive medulloblastoma for whom no known curative therapy exists. The primary objective is to evaluate the efficacy of multidrug antiangiogenic approach measured by response 6 months after start of therapy. PFS, OS and toxicity are also examined. The trial is open in Copenhagen, Denmark and in all 6 Swedish centers.

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. This represents the largest step this far in increasing capacity for proton therapy in the Nordic countries.

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 protoncenters in Jacksonville, Florida and Heidelberg.

QUARTET is a prospective SIOPE driven radiotherapy quality assurance program in which radiotherapy doseplans 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. The LGG 2004 protocol is on the NOPHO web. Minutes of working group meetings should also be posted if permission is granted by the working group chair.

Virve Pentikäinen
Chair of the NOPHO Brain Tumour Committee, April 11th, 2017

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. So far there are members from all the Scandinavian countries, except for Iceland. If someone from the Baltic countries is interested to be members of the group, they are welcome.
Annual meetings rotate between the Scandinavian countries. The next meeting will be in Stockholm in May 2017.

The different national guidelines for the treatment of Retinoblastoma are posted on the homepage. In 2016 we published common Nordic guideline which was published at NOPHO web. Our plan is to enhance the cooperation further, especially for international cooperation and discussion of complicated patients.

Publications

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 Aug;92(5):404-11.

Lymphoma Working Group

Hodgkin and Non-Hodgkin lymphoma	
Chair	Lisa Hjalgrim DK (2015)
Denmark	Peder Skov Wehner Lisa Lyngsie Hjalgrim
Finland	Päivi Läthenmäki 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 Kristina Nilsson
Young NOPHO	Maria Henningsson (SE) Audrone Muleviciene (LT)
Reference pathologist	Ulrika Hansson (Sweden)

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.

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. Presently the lymphoma group is working on a study protocol for the lymphoma registry in order to achieve better and complete data registration of both NHL and HL patients in the NOPHO community. 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.

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.

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.

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%. At the moment NOPHO suggest EURO LB 02 as best available treatment for patients with lymphoblastic lymphomas. There is a new LBL protocol with the **EicNHL** being planned and hopefully finished by 2018, which NOPHO is taking part in.

Since 2005 the NOPHO-NHL has used the **B-NHL BFM-04 protocol** for the treatment of children with *B-cell lymphomas.* The work with the new cooperative study between NOPHO and BFM, **B-NHL 2013** is now finalized and approved by the VHP in all of the Nordic countries and will start including patients in the very near future (spring 2017). Registration of patient data in this protocol will be through the Marvin database. **Several NOPHO add on studies are part of this protocol (Quality of life study, immune reconstitution study and CNS flow study).**

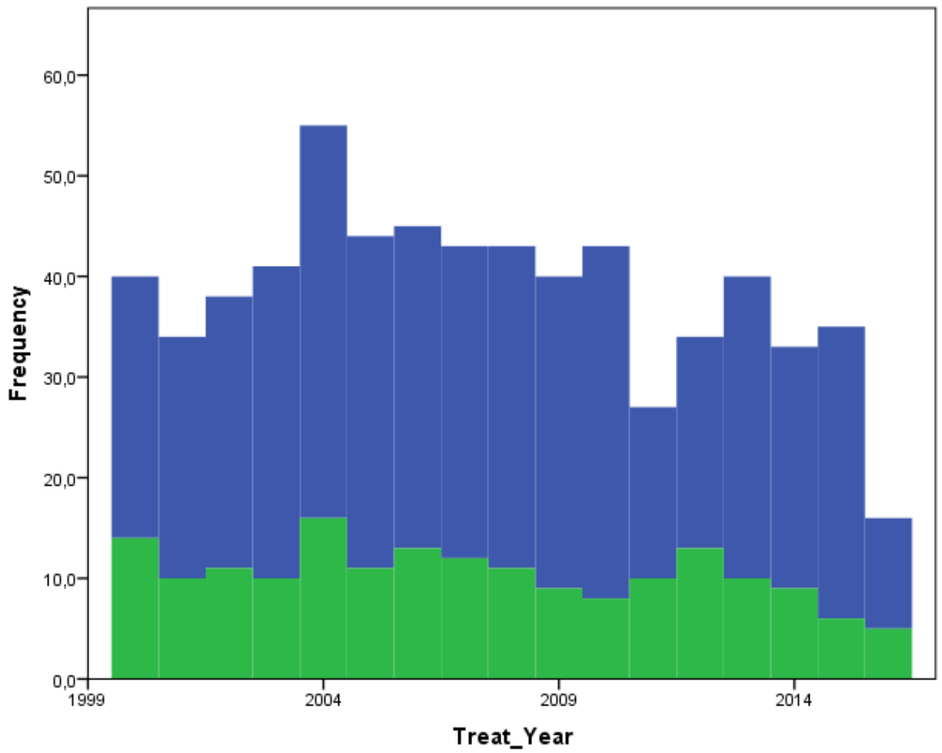
NOPHO is also contributing with patients to the newly opened **European international registry of rare pediatric non Hodgkin lymphomas** and is coordinating an international survey over patients with peripheral T-cell lymphomas.

Finally, a common NOPHO study on CNS status measured with flow cytometry in all lymphoma patients has been initiated.

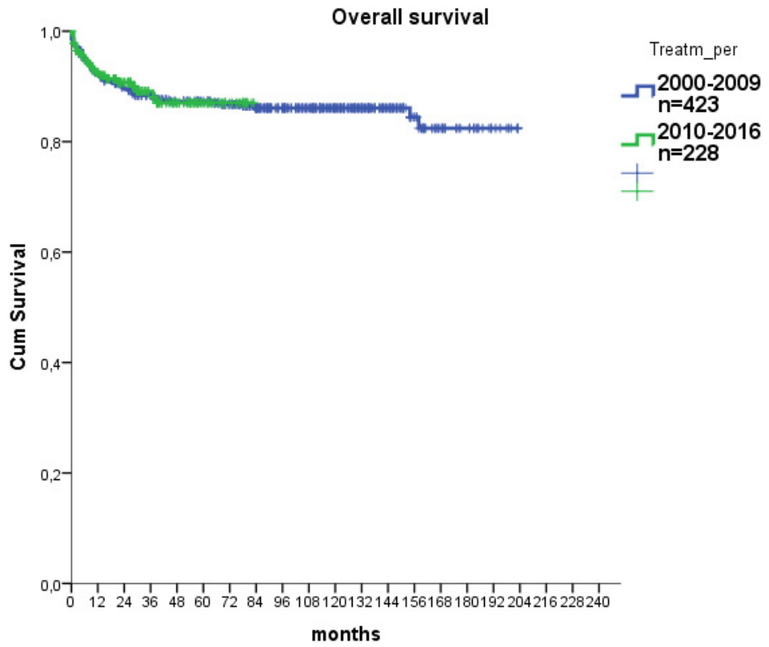
NHL survey of children and adolescens diagnosed with NHL between 2000 and 2017

There were 651 reported cases of patients with NHL diagnosed from 1.1.2000 to 31.12.2016 in the five Nordic countries. Patients age 0-18 years have been included in this report. 19 patients were excluded from the analysis because of missing data. The remaining 651 patients (473 males and 178 females) are reported here below. As can be seen from the figure below the reporting of cases is dropping over the last decade.

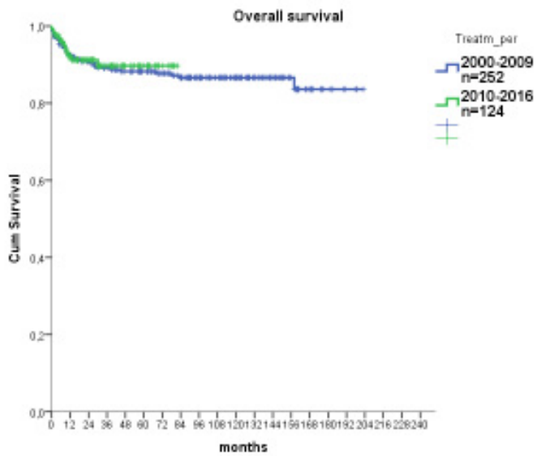
Distribution of patients according to year of diagnosis



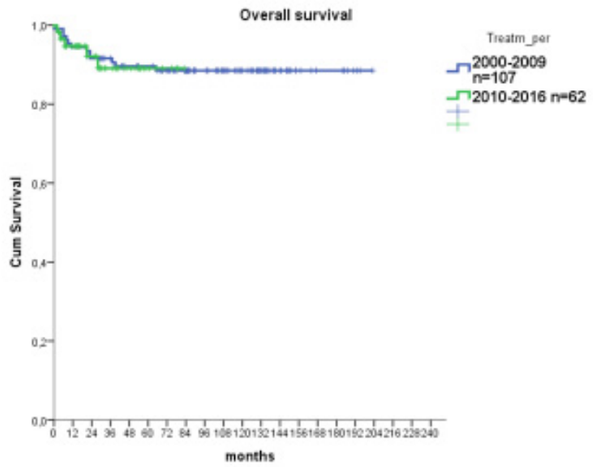
Survey of NHL-patients diagnosed 2000-2017

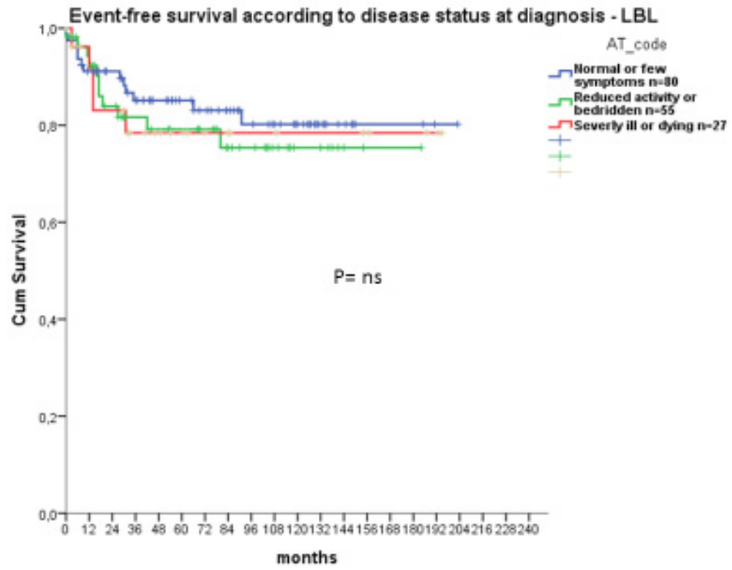


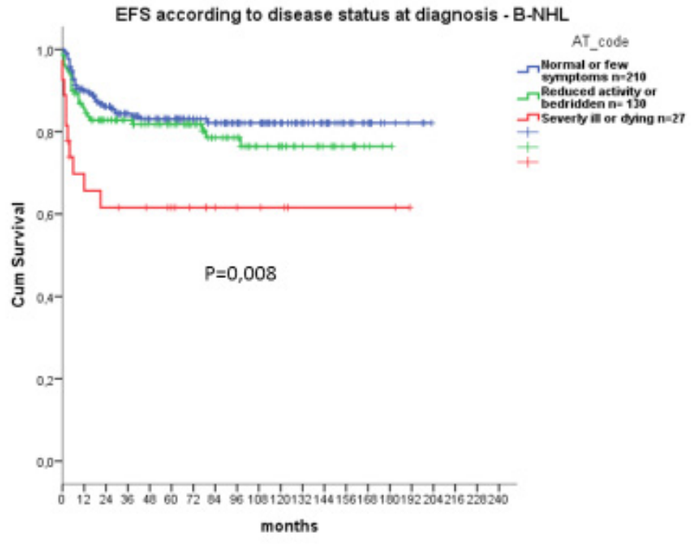
Survival B-NHL according to treatment period (PTLD excluded)



Survival LBL according to treatment period







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 (data not shown). 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 conclusion

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. For some NHL subtypes there is clearly need of new protocols.

Lisa Lyngsie Hjalgrim, Chair, Copenhagen, April 2017
Karin Mellgren, datamanager, Göteborg, April 2017

Leukaemia Working Groups

Leukemia and Lymphoma Committee

Chair	Päivi Lähteenmäki (FI) 2014
Denmark	Peder Skov Wehner, Thomas Frandsen 2014
Finland	Kirsi Jahnukainen (stepping down 2017), Minna Koskenvuo 2017, Mervi Taskinen
Iceland	Ólafur G. Jónsson, Sólveig Hafsteinsdóttir 2013
Lithuania	Ramune Pasauliene 2016
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
ALL Together	Mats Heyman and Mervi Taskinen
ALL Relapse	Johan Arvidson (stepping down 2017), Jochen Büchner
ALL WG	Mats Heyman
Adult-ALL-group	Nina Toft
LL Biology	Linda Fogelstrand, Olli Lohi 2016
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 2015
MDS/JMML	Henrik Hasle
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 2016 were held in Reykjavik (May 27-28) and in Stockholm (November 15). 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.

One important task brought up by the new LL-Biology WG is the importance of pediatric oncologists being present at the meetings as clinical problems for scientific sessions are needed. A new initiative is the reporting of cytogenetic ALL data online at diagnosis from the cytogenetic labs. Prototype registration system is ready for testing. Discussions on the topic “Biobank material and the ethics” started in the May meeting. Conclusions can be found in the minutes of November LLC meeting.

In the May meeting, ALL2016 PI-group was changed to the ALLTogether group where the NOPHO-representatives are Mats Heyman and Mervi Taskinen. LLC has supported the group going on with

preparations for ALLTogether protocol.

"Nordic Study Day" was organized with several Nordic authorities in January 2016 by the Secretary General, and chairs of Scientific Committee, LLC and Biobank as well as NOPHO registry in order to find out how NOPHO with its member countries having different laws for data protection and research issues could continue collecting data on cancer patients, and also share its data with other international study groups. A summary of the discussions is attached to the LLC minutes from Reykjavik in the NOPHO website. One important action point was that NOPHO should design a long term study in order to collect new epidemiological data and store the registry data after the end of the protocols. A study proposal, "NOPHO-CARE" was developed and accepted by the relevant NOPHO-bodies during the year 2016. Most urgent matter in this context will be to finalize the contracts between each NOPHO-center and Stockholm NOPHO-Registry.

LLC chair position has to be checked after two year periods. In May meeting, it was decided that Päivi Lähteenmäki continues as the LLC chair up to May 2018. Norway will take over then.

LLC chair represents NOPHO at the I-BFM board. In the Athens meeting, two practical issues were brought up. Young active people should be introduced to the I-BFM network, and the best way to do this is to encourage people to contact the I-BFM WG chairs and get positions there. Also the structure of I-BFM meetings will change in the future: Martin Schrappe is the new chair of the SIOPE and he continues with planning a new meeting format where separate days for Leukemia/lymphoma, brain tumors and solid tumors will be organized within the SIOPE-meeting concept.

Importantly, I-BFM AML group has now its chair from NOPHO (professor Henrik Hasle), and NOPHO has the big task of organizing the I-BFM meeting and Childhood Leukemia Symposium (CLS) in 2018. The schedule will be: 18.5.2018 closed meetings, 19.-20.5. I-BFM Annual meeting, and 21-22.5. CLS. The venue is the Marina Congress Center in Helsinki. Jukka Kanerva will chair the organizing committee that includes representation from NOPHO countries.

Finally, the 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.

Turku, March 2017
Päivi Lähteenmäki

ALL Working Group

Coordinator	Mats Heyman
Denmark	Thomas Frandsen
	Birgitte Klug Albertsen
Finland	Päivi Lähteenmäki
	Mervi Taskinen
Iceland	Olafur Gislí Jonsson
Norway	Inga Maria Rinvoll Johannsdottir
	Trond Flaegstad
	Bendik Lund
Sweden	Jonas Abrahamsson
	Anders Castor
	Johan Malmros
Lithuania	Goda Vaitkeviciene
Representative from other Baltic countries (Estonia)	
	Mari Punab
Adult representatives	
Denmark	Nina Toft
Finland	Ulla Wartiovaara-Kautto
Norway	Petter Quist-Paulsen, Geir Tjönnfjord
Sweden	Helene Hallböök
Lithuania	Laimonas Griskevicius
Estonia	Katrin Palk, Kristi Lepik
Chair of the	
Leukemia and Lymphoma group	Päivi Lähteenmäki
ALL 2008 protocol committee	Kjeld Schmiegelow
Event group	Thomas Frandsen
Infant ALL	Birgitte Lausen
Relapse of ALL	Johan Arvidson
Ph+ ALL/CML	Anders Castor
MRD group	Hanne Marquart
Cytogenetic group	Ulrika Noren-Nyström, Bertil Johansson
Pharmacology group	Goda Vaitkeviciene
A representative from	
NOPHO registry	Mats Heyman
Young NOPHO	Adam Alexandersson, Nikolas Herold
General secretary	Mervi Taskinen

The ALL group meets twice yearly, the day after the Leukaemia & Lymphoma Committee meetings. The meetings during the year from the last report have been held at Kastrup, Copenhagen (September 13th of September 2016) and in Helsinki (8th of March 2017). 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 1964 patients from 1.7.2008 to 31.12.2016. Out of those 1655 were children 1-17.99 years from the Nordic and Baltic countries, 309 adults (age 18-45) from the Nordic and Baltic adults. The protocol is now also recruiting adults up to 45 years in Finland. 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: 0.86 , adults: 0.70.
- pOS at five years: overall: children: 0.92, adults: 0.75.
- 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).
  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 ongoing with definitions of protocol patients and risk-groups.
- The randomised parts (R1: treatment with or without 6MP increments during consolidation for SR and IR-patients; R2: 2-weekly vs 6-weekly PEG-Asp during post-consolidation therapy for SR and IR-patients) are now being compiled for publication and the comparison of outcome between adults and children has been submitted for publication. The third randomization exploring the addition of Depocyte to high-risk patients in Maintenance has already been published. A large number of additional publications 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.
- To prepare for publication, quality-control measures are currently taken – scrutinized "final" critical MRD-values are under compilation by the MRD-group.

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 is now planned to be extended to the Baltic countries.
The database, which has been managed for many years by Erik Forestier will be stored in a MySQL database together with the rest of the NOPHO ALL-data in Stockholm. The database will also have a web-based access, so that genetic labs can enter data directly into the database and central review can be performed on-line.

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. Several meetings have been conducted and working-groups with representatives from the different study-groups have prepared consensus documents for a long list of pre-defined toxicities. The efforts are planned to result in a consensus-paper. The first collaborative paper on Pancreatitis on the way to be published and CNS-toxicity and Osteonecrosis have been chosen as second in line for consensus papers compiling clinical data and biologic material for GWAS-analysis.

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 matured. The initial motivation was primarily the difficulties asking meaningful study-questions in smaller study-groups, due to the very good overall results, particularly for the lower-risk patients. There is also a wish to collaborate on research issues making use of the expertise in the different groups. The participating study groups are currently: NOPHO, UKALL, DCOG and COALL and has since the last report been amended with the Belgian group (BSPHO) and Portugal (SHOP). Mats Heyman, Kjeld Schmiegelow and Mervi Taskinen are the NOPHO representatives and in a meeting in April 2016 Mats Heyman was appointed coordinator of the common effort.

- The NOPHO ALL-2016 group has thus been re-vamped into the NOPHO "ALLTogether"-group to support the NOPHO representatives and make sure that the protocol work is firmly based in the NOPHO membership. Because of the multitude of meetings throughout NOPHO, most of the work within the NOPHO ALLTogether-group is ongoing within the framework of the ALLTogether working-groups with representation from all study-groups in the consortium. A considerable amount of updating and discussion also takes place in the ALL working-group and in the LLC.

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, 2017
Mats Heyman

Leukemia - ALL Registration Working Group

Coordinator	Mats Heyman
Denmark	Niels Clausen
Finland	Kim Vettenranta
Iceland	Olafur Gisli Jonsson
Norway	Inga Maria Johannsdottir
Sweden	Jonas Abrahamsson, Mats Heyman

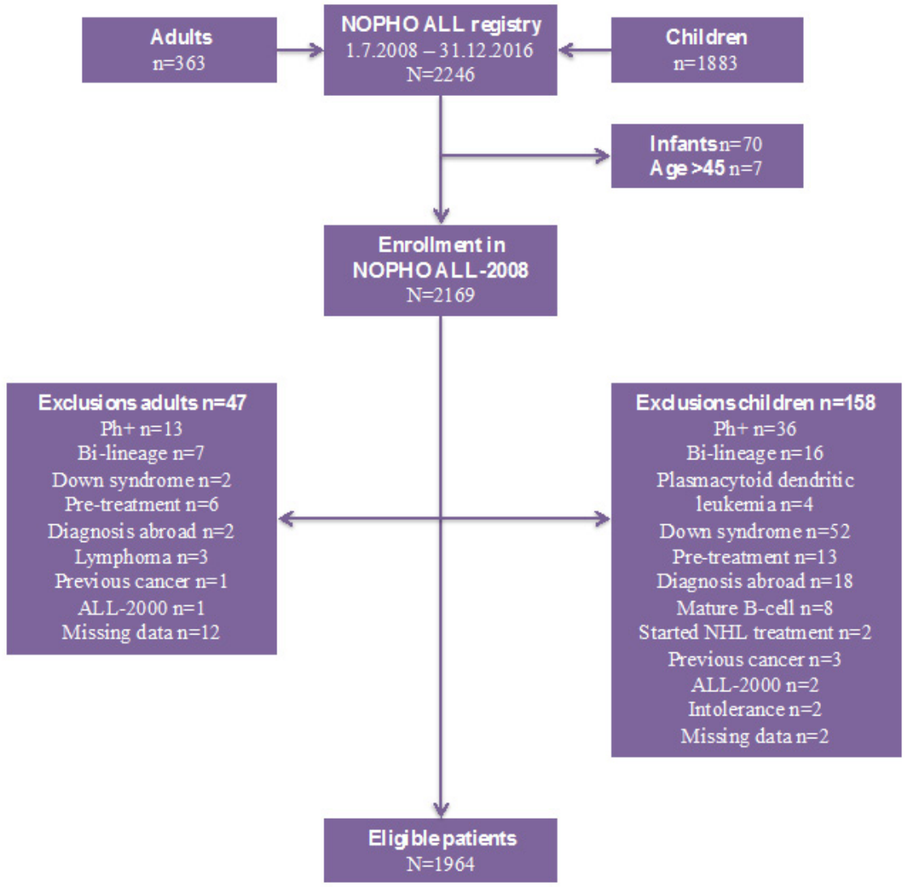
Data management group Stockholm
Mats Heyman
Trausti Óskarsson
Matteo Bottai
Göran Gustafsson
Kristian Lindström
Lili Zheng
Mats Nordström

Data checks Copenhagen (NOPHO ALL-08)
Kjeld Schmiegelow (PI, NOPHO ALL-08)
Thomas Frandsen
Louise Rold Helt
Kirsten Kørup Rasmussen
Nina Toft

Introduction

The randomized parts of the NOPHO ALL-2008 protocol was closed 1.3.2016 but the protocol is still open for the population-based cohort as best available treatment. From the beginning of the trial 1.7.2008 to 31.12.2016, 2246 patients have been diagnosed with ALL in the NOPHO countries (including Estonia and Lithuania) and entered in the NOPHO ALL registry. Patients <1years (n=70) and >45 years (n=7) were excluded from the NOPHO ALL-2008 study recruitment. In addition, 205 patients, 158 children (1-17 years) and 47 adults (18-45 years), were excluded since they did not meet the study eligibility criteria (Figure 1). The total number of patients analyzed in this annual report is 1964 patients, 246 more than last year´s report. The follow-up time is getting longer, allowing a better capture of late events such as SMN and late relapses.

Figure 1. NOPHO ALL-2008 trial enrollment and exclusions



Patient characteristics and risk stratification

The characteristics of patients eligible for the NOPHO ALL-2008 trial are described in Table 1.

Table 1. Baseline characteristics, by age groups.

Characteristics	All patients n (%)	1-17 years n (%)	18-45 years n (%)
Overall	1964	1655	309
Gender			
Boys	1106 (56.3)	914 (55.2)	192 (62.1)
Girls	858 (43.7)	741 (44.8)	117 (37.9)
WBC at diagnosis (highest value)			
<100 x 10^9/l	1699 (86.5)	1443 (87.2)	256 (82.8)
≥100 x 10^9/l	265 (13.3)	212 (12.8)	53 (17.2)
Immunophenotype			
Pre-B ALL	1661 (84.6)	1446 (87.4)	215 (69.6)
T-cell ALL	303 (15.4)	209 (12.6)	94 (30.4)
CNS involvement			
CNS1	1718 (87.5)	1437 (86.8)	281 (90.9)
CNS2	157 (8.0)	140 (8.5)	17 (5.5)
CNS3	80 (4.1)	73 (4.4)	7 (2.3)
Missing data	9 (0.5)	5 (0.3)	4 (1.3)
Cytogenetics[1]			
Unfavorable cytogenetics	90 (4.6)	65 (3.9)	25 (8.1)
Intermediate cytogenetics	115 (5.9)	102 (6.2)	13 (4.2)
Favorable cytogenetics	889 (45.3)	854 (51.6)	35 (11.3)
Other	464 (23.6)	351 (21.2)	113 (36.6)
Normal	327 (16.6)	231 (14.0)	96 (31.1)
Missing data	79 (4.0)	52 (3.1)	27 (8.7)
Final risk group			
Standard risk	884 (45.1)	817 (49.4)	67 (21.7)
Intermediate risk	700 (35.6)	572 (34.6)	128 (41.1)
High risk chemo	225 (11.5)	162 (9.8)	63 (20.4)
High risk HSCT	134 (6.8)	86 (5.2)	48 (15.5)
No risk group assigned[2]	2 (0.2)	2 (0.1)	0
Induction Failure	19 (0.9)	16 (1.0)	3 (1.0)

[1]*Unfavorable cytogenetics:* MLL rearrangement and hypodiploidy, *Intermediate cytogenetics:* t(1;19), dic(9;20) and iAMP21, *Favorable cytogenetics:* t(12;21) and high hyperdiploidy.

[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.

The decision on the final risk group of patients was made on an "intention-to-treat" basis (Figure 2). All cases undergo central review for the final risk group and MRD response. Cytogenetics results were reviewed centrally for all patients from 2008-2015 whereas results from 2016 have not been reviewed yet. The patients diagnosed last year were assigned a cytogenetic group based on the reported cytogenetic results from the clinics. Two patients could not be assigned a risk group since there was insufficient data for risk stratification. Nineteen patients died during induction and could therefore not be assigned a risk group. Table 2 describes the relationship between the risk stratification at diagnosis and the final risk stratification.

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

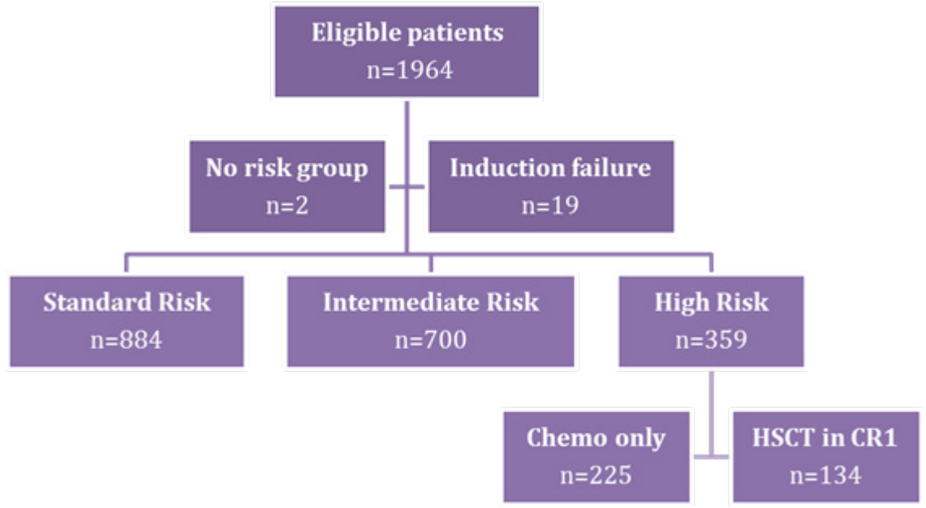


Table 2. The relationship between the stratification at diagnosis and the final risk stratification.

Final risk group	Non-HR induction	HR induction
SR	884	0
IR	484	214
HR chemo	48	117
HR HSCT	95	39
Induction failure	10	9
No risk group	2	0
Total	**1525**	**439**

Treatment

Induction treatment

The majority of patients (1525, 77.6%) were stratified to the non-HR arm (B-lineage ALL and WBC <100 x 109/l at diagnosis) induction therapy and 439 patients (22.4%) to the HR-induction (T-ALL and/or WBC ≥100x109/l at diagnosis).

In the protocol amendment released in November 2009 it was recommended that patients with B-lineage ALL and WBC ≥100.000 x109/l at diagnosis that started HR-induction would 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 study randomizations and would be stratified to the IR-arm if the MRD-result did not exceed 5% day 29, in which case they would be stratified to HR-SCT. In total, 19 patients switched from HR-induction to non-HR-induction when t(12;21) was confirmed. All of these were l-17.9 years and all are alive in CR1 (Table 3). In addition, five patients had the same characteristics but were not switched to non-HR induction since they were diagnosed before the amendment was published. Among these five patients, one died during induction, one died in CR1, one experienced an isolated CNS relapse and two are currently in CR1. Two of the patients had d29 MRD >0.1% and <5%, but were treated according to the HR chemo arm instead of the IR arm.

Table 3. Characteristics of patients with B-lineage ALL, hyperleukocytosis and t(12;21) that were switched from dexamethasone to prednisolone.

Characteristics	Number of patients
Overall	19
Age	
Children	19
Adults	0
Gender	
Boys	7
Girls	12
Risk group	
SR	NA
IR	19
HR	0
Primary events	
CR1	19
Induction failure	0
DCR1	0
Relapse	0
SMN	0

Response day 15

The first response evaluation after the start of the induction phase was performed at day 15. 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. Of the 1964 patients, 48 (2.4%) were switched to block therapy based on poor MRD response day 15 (Table 4). In these cases the decision was based on the MRD results without being reviewed centrally. For patients with T-ALL flow cytometry was the method of choice since it is considered a more reliable method than PCR for high MRD values. Three of the patients that were switched to block therapy were reviewed centrally as having MRD <25% (all adults). Three patients received non-HR induction; one with MLL rearrangement, one with hypodiploidy and one had non-stratifying cytogenetics but was still switched directly to block therapy. The outcome of patients that were switched directly to block therapy was very poor, 5-year OS 45.1 ± 9.4% and 5-year EFS 40.3 ± 9.5%. The outcome was very similar between patients that underwent HSCT in CR1 and those that did not. Only two of the 11 patients that relapsed are currently alive in ≥2nd CR.

Table 4. Characteristics of patients that received block therapy directly after day 15.

Characteristics	Number of patients
Overall	48
Age	
Children	28
Adults	20
Gender	
Boys	36
Girls	12
WBC at primary diagnosis	
<100 x 10^9/l	24
≥100 x 10^9/l	24
Immunophenotype	
Pre-B ALL	16
T-cell ALL	32
Cytogenetics	
Unfavorable	10
Intermediate	0
Favorable	2
Normal	9
Other	24
Missing	3
Induction treatment	
High risk	25
Non-high risk	3
MLL, n=1	
Hypodiploidy, n=1	
Other cytogenetics, n=1	
HSCT in CR1	
Yes	25
No	23
Primary events	
CR1	27
Induction failure	NA
DCR1	7
Relapse	13
SMN	1
Survival	
5-year overall survival ± s.e.	45.1 ± 9.4%
5-year event-free survival ± s.e.	40.3 ± 9.5%

Response day 29

The second response evaluation in NOPHO ALL-2008 was performed at the end of the induction phase, day 29 (Table 5). Flow cytometry was the method of choice for measuring MRD in B-lineage ALL and PCR in T-ALL (except for high MRD values, ≥5%). If d29 MRD was ≥5%, HSCT in CR1 was recommended. In total 105 patients had MRD values ≥5% at day 29, 26 with MRD ≥ 25% and 79 with MRD ≥5% but <25%, respectively.

Table 5. Treatment response at day 29. Centrally reviewed MRD values.

MRD day 29	All patients n (%)	1-17 years n (%)	18-45 years n (%)
≥25%	26 (1.3)	19 (1.1)	7 (2.3)
≥5% - <25%	79 (4.0)	48 (2.9)	31 (10.0)
≥0.1% - <5%	478 (24.3)	382 (23.1)	96 (31.1)
<0.1%	612 (31.2)	533 (32.2)	79 (25.6)
<0.1% negative	693 (35.3)	624 (37.7)	69 (22.3)
Block therapy directly after d15	48 (2.4)	28 (1.7)	20 (6.5)
Death before d29 MRD	18 (0.9)	15 (0.9)	3 (1.0)
No marker found	6 (0.3)	3 (0.2)	3 (1.0)
Missing data	4 (0.2)	3 (0.2)	1 (0.3)

Table 6 describes patient characteristics by treatment response at day 29 between three MRD groups. In general, treatment response was worse for adults compared to children. Event-free survival and overall survival correlated well with the MRD response.

Table 6. Characteristics of patients at day 29 by MRD values

MRD day 29	MRD<0.1% n (%)	MRD ≥0.1-<5% n (%)	MRD≥5%[1] n (%)
Overall	1305	478	105
Age			
Children	1157 (88.7)	382 (79.9)	67 (63.8)
Adults	148 (11.3)	96 (20.1)	38 (36.2)
Gender			
Boys	732 (56.1)	267 (55.9)	61 (58.1)
Girls	573 (43.9)	211 (44.1)	44 (41.9)
WBC at diagnosis			
<100 x 10^9/l	1170 (89.7)	400 (83.7)	86 (81.9)
≥100 x 10^9/l	135 (10.3)	78 (16.3)	19 (18.1)
Immunophenotype			
Pre-B ALL	1149 (88.0)	396 (82.8)	76 (72.4)
T-cell ALL	156 (12.0)	82 (17.2)	29 (27.6)
Cytogenetics			
Unfavorable	52 (4.0)	18 (3.8)	5 (4.8)
Intermediate	96 (7.4)	15 (3.1)	4 (3.8)
Favorable	634 (48.6)	227 (47.5)	18 (17.1)
Normal	204 (15.6)	81 (16.9)	28 (26.7)
Other	273 (20.9)	119 (24.9)	42 (40.0)
Missing	46 (3.5)	18 (3.8)	8 (7.6)
Induction treatment			
Non-high risk	1073 (82.3)	359 (75.1)	70 (66.3)
High risk	323 (17.8)	119 (24.9)	35 (33.3)
Risk group[2]			
Standard risk	882 (67.5)	-	-
Intermediate risk	363 (27.8)	332 (69.5)	1 (1.0)
High risk chemo	57 (4.4)	112 (25.5)	19 (17.1)
Pre-B	*55*	*41*	*1*
T-ALL	*2*	*81*	*18*
High risk HSCT	3 (0.2)	23 (4.8)	86 (82.0)
HSCT in CR1			
Yes	10 (0.8)	28 (5.9)	78 (74.3)
No	1295 (99.2)	450 (94.1)	27 (25.7)
Primary events			
CR1	1205 (92.3)	396 (82.8)	77 (73.3)
Induction failure	-	-	1 (1.0)
DCR1	22 (1.7)	20 (4.2)	11 (10.5)
Relapse	67 (5.1)	61 (12.8)	16 (15.2)
SMN	11 (0.8)	1 (0.2)	-
Survival			
5-year OS ± s.e.	94.7 ± 0.7%	86.4 ± 1.8%	70.5 ± 5.4%
5-year EFS ± s.e.	90.0 ± 1.0%	77.9 ± 2.3%	66.4 ± 5.4%

[1]All MRD values over 5%, [2]One patient with MRD <0.1% was not assigned a risk group

Protocol adherence

Not all patients were treated according to their assigned risk-group. Protocol adherence was high during the induction phase (Tables 7 and 8) but slightly lower for the treatment used after the final risk stratification, 97.1% for children compared to 91.8% for adults (Tables 9 and 11). The most common reasons for non-adherence were discrepancies in the interpretation of MRD and cytogenetics between the clinics and the central review (Tables 10 and 12). 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 7. Protocol adherence – Induction treatment (patients 1-17 years).

Admin\RG	RG=non-HR	RG=HR	Total
Admin=non-HR	1327	4[1]	1338
Admin=HR	4[2]	317	314
Other[3]	2	1	3
Total	1196	459	1655

[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]Received 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): 1327+317+4 (included since recommended in the protocol amendment)/1655 **(99.6%).**

Table 8. Protocol adherence – Induction treatment. (patients 18-45 years)

Admin\RG	RG=non-HR	RG=HR	Total
Admin=non-HR	189	2[1]	191
Admin=HR	3	115	118
Total	192	117	309

[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): 189+115/309 **(98.4%).**

Table 9. Protocol adherence - Final risk-group (patients 1-17 years)

Admin\RG	RG=SR	RG=IR	RG=HR-chemo	RG=HR-SCT	Total
Admin=SR	797	7	0	0	804
Admin=IR	14	553	2	6	575
Admin=HR	2	8	160	79	249
Other	4	4	0	1	9
Total	817	572	162	86	1637[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): 797+553+160+79/1637 (97.1%).

Table 10. Non-adherence (patients 1-17 years)

Non-adherence	Total	Toxicity	MRD	Cytogenetics	Other
RG SR					
Admin IR	14	3	4	1	6
Admin HR	2	0	0	2	0
Other	4	3	0	0	1
RG IR					
Admin SR	7	0	3	2	2
Admin HR	8	1	4	2	1
Other	4	1	2	0	1
RG HR chemo					
Admin IR	2	0	2	0	0
RG HR HSCT					
Admin IR	6	0	6	0	0
Other	1	0	0	0	1
Total non-adherence	**48**	**8**	**21**	**7**	**12**

Table 11. Protocol adherence - Final risk-group (patients 18-45 years)

Admin\RG	RG=SR	RG=IR	RG=HR-chemo	RG=HR-SCT	Total
Admin=SR	60	5	0	0	65
Admin=IR	6	113	0	1	120
Admin=HR	0	6	63	45	114
Other	1	4	0	2	7
Total	67	128	63	48	306[1]

[1]Three patients died during induction

Protocol adherence: RG = Adm: 60+113+63+45/306 **(91.8%).**

Table 12. Non-adherence (patients 18-45 years)

Non-adherence	Total	Toxicity	MRD	Cytogenetics	Other
RG SR					
Admin IR	6	0	1	2	3
Other	1	1	0	0	0
RG IR					
Admin SR	5	1	0	1	3
Admin HR	6	0	5	0	1
Other	4	2	0	0	2
RG HR HSCT					
Admin IR	1	0	1	0	0
Other	2	1	0	0	1
Total non-adherence	**25**	**5**	**7**	**3**	**10**

Primary events - children

Table 13. NOPHO ALL-2008 - treatment-results – all events. Patients 1-17 years treated in Nordic and Baltic centres.

Event	BCP WBC<100 n=1333		BCP WBC>100 n=113	T-cell n=209	Total n=1655
Non-responders	0		0	0	0
Death in induction	10		3	3	16
CR-reached	**1323**		**110**	**206**	**1639**
Remission %	**99.2**		**97.3**	**98.6**	**99.0**
CR1, no RG d29*	2		0	0	2
	SR n=817	IR n=572	HR-chemo n=162	HR-SCT n=86	n=1637 (1639)**
Death in CR1	8	12	19	7	46
Relapses	28	37	31	8	104 (106)**
BM	14	18	23	7	52 (54)**
CNS	5	10	4	0	19
Testis	0	0	1	0	1
BM+CNS	4	7	3	0	10
BM+testis	2	0	0	0	2
BM+CNS+testis	2	1	0	0	3
BM+Other site	1	1	0	1	3
SMN	10	1	1	0	12
All events	46	50	51	15	162 (180)**
CCR number	771	522	111	71	1475 (1475)**
CCR %	94.4	91.3	68.5	82.6	90.1 (89.1)**
CR>/=2 (n)	27	32	19	5	83 (84)**
CR2 %****	96.4	86.5	61.3	62.5	79.8 (79.2) **
pDFS (60 mo)	0.95 (0.01)	0.91 (0.02)	0.77 (0.04)	0.85 (0.05)	0.91(0.01)***
pEFS (60 mo)	-	-	-	-	0.86 (0.01)
All dead	18	26	43	13	100 (118)**
All alive	799	546	119	73	1537 (1537)**
alive %	97.8	95.5	73.5	84.9	93.9 (92.9)**
pOS (60 mo)	0.97 (0.01)	0.95 (0.01)	0.70 (0.04)	0.82 (0.05)	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.

****The proportion of patients that reached second remission, CR2 rate.

Follow-up time for surviving patients: median 1465 days (48.1 months), range 19-3144 days).

More events have occurred in the HR-chemo group. The 5-year DFS is now 77% (±4%) but the 5-year OS is only 70% (±4%). The reason for an OS lower than the DFS is the high frequency of deaths in CR1 (11.7%) and a very poor OS after relapse, only eight (25.6%) of 31 patients with relapse are currently alive. Nine of the nineteen patients that died in CR1 had unfavorable cytogenetics. Forty-seven patients in the HR-chemo group had d29 MRD <0.1% but the HR stratification was based on unfavorable cytogenetics. Three of these patients experienced a relapse, three died in CR1 and one developed a SMN.

Events since the last survey

Induction failures

There were two reported induction deaths:
A 12-year old boy with BCP and WBC 142 x 109/l at diagnosis. The patient received one dose of prednisolone and one dose of rasburicase but died the same day of septicemia, enterocolitis and massive hematemesis. Cytogenetic aberrations were not analyzed.

A 2-year old girl with BCP, CNS2 and WBC <10 x 109/l at diagnosis. No stratifying cytogenetic aberrations. The patient received non-HR induction but died 40 days after diagnosis of intestinal gangrenous necrosis.

Table 14. Post-induction Events by risk-group (final stratification)

Event	SR	IR	HR-chemo	HR-SCT	Total
Relapse	5	7	5	1	18
DCR1	0	1	5	1	7
SMN	0	0	1	0	1
Total	5	8	11	2	28

Table 15. Relapses by site and risk-group (final stratification)

Rel site	SR	IR	HR-chemo	HR-SCT	Total
BM	2	3	4	1	10
CNS	0	1	0	0	1
Testis	0	0	1	0	1
BM+CNS	1	3	0	0	4
BM+T	1	0	0	0	1
BM+CNS+T	1	0	0	0	1
Total	5	7	5	1	18

Deaths in CR1 (n=7)

IR-group: 1 case
An 8-year old girl at diagnosis with BCP. CNS1 and no stratifying cytogenetic aberrations. She received non-HR induction but MRD d29 was >0.1% and she was therefore treated according to the IR arm. The patient died 51 days after diagnosis of hemorrhagic acute pancreatitis.

HR-chemo-group: 5 cases
Patients aged 1-10 years, four girls and one boy. Three patients with T-ALL and WBC >100 x 109/l at diagnosis, one with T-ALL and WBC <100 x 109/l at diagnosis and two with BCP and WBC >100 x 109/l at diagnosis. All patients received HR-induction. One patient had MRD>25% at d15 and received block therapy directly and four patients had d29 MRD between 0.1% to 5%. One died of CMV pneumonitis, one of severe adenvirus pneumonia, one of combined CMV and fungal infection, one of ESBL sepsis

but information regarding the cause of death is missing in the ALL registry for one patient (previously diagnosed with an invasive aspergillus infection).

HR-SCT group: 1 case
An 8-year old girl at diagnosis with BCP, CNS1, no stratifying cytogenetic aberrations. She received non-HR induction but although MRD d15 was >25% she completed the induction phase. Day 29 MRD was >5% and she was therefore stratified to the HR HSCT-group. She received an adapted AML block due the appearance of sub-clones expressing myeloid markers. She responded well with MRD <0.1% before starting an A-block. The patient died following the first A-block, 103 days after diagnosis.

SMNs (n=1)
HR-chemo-group: 1 case
A 13-year old girl at diagnosis with BCP. She received non-HR induction and d29 MRD response was good, <0.1%. Since she had a hypodiploid clone she continued treatment according to the HR arm. She developed AML during HR maintenance 1 and died six months later.

Primary events – Adults

Table 16. 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=192		BCP WBC>100 n=23	T-cell n=94	Total n=309
Non-responders	0		0	0	0
Death in induction	0		2	1	3
CR-reached	**192**		**22**	**93**	**306**
Remission %	**100**		**95.7**	**98.9**	**99.0**
	SR n=67	IR n=128	HR-chemo n=63	HR-SCT n=48	n=306
Death in CR1	1	6	6	2	15
Relapses	6	19	12	15	52
BM	4	10	7	11	32
CNS	0	5	1	0	6
Testis	2	1	0	0	3
BM+CNS	0	0	1	1	2
BM+other site	0	1	0	1	2
Other site	0	2	3	2	7
SMN	0	0	1	0	1
All events	7	25	19	17	68 (71)*
CCR number	60	103	44	31	238 (238)*
CCR %	89.6	80.5	69.8	64.6	77.8 (77.0)*
CR>/=2 (n)	3	16	7	11	36
CR2 %***	50.0	84.2	58.3	73.3	71.2
pDFS (60 mo)	0.82 (0.07)	0.80 (0.05)	0.74 (0.07)	0.56 (0.09)	0.75 (0.03)**
pEFS (60 mo)	-	-	-	-	0.70 (0.03)
All dead	4	19	19	13	58 (61) *
All alive	63	109	44	35	251 (251)*
alive %	94.0	85.2	69.8	72.9	82.0 (81.2)
pOS (60 mo)	0.90 (0.06)	0.81 (0.04)	0.63 (0.07)	0.64(0.08)	0.76 (0.03)
Overall pOS (60 Mo)	-	-	-	-	0.75 (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.
***The proportion of patients that reached second remission, CR2 rate.

Follow-up time for surviving patients: median 1072 days (35.2 months), range 29-2992 days.

Events since the last survey

Induction failures

None of the adult patients died during induction in 2016.

Table 17. Post-induction Events by risk-group (final stratification)

Event	SR	IR	HR-chemo	HR-SCT	Total
Relapse	3	7	3	0	15
DCR1	0	0	1	0	1
Total	3	6	9	1	16

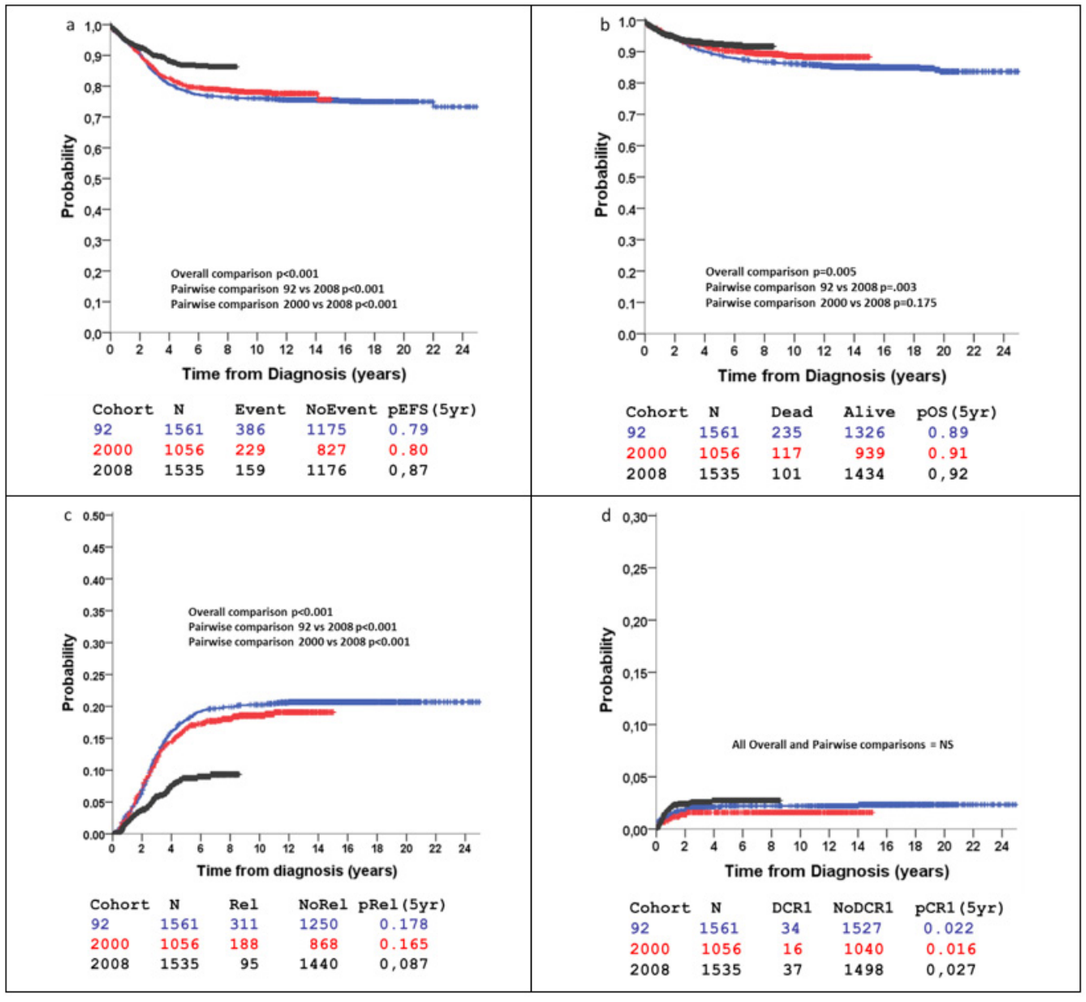
Table 18. Relapses by site and risk-group (final stratification)

Rel site	SR	IR	HR-chemo	HR-SCT	Total
BM	3	3	2	1	9
CNS	0	2	0	0	2
BM+other	0	1	0	0	1
Other	0	1	1	1	3
Total	3	7	3	2	15

Deaths in CR1 (n=1)

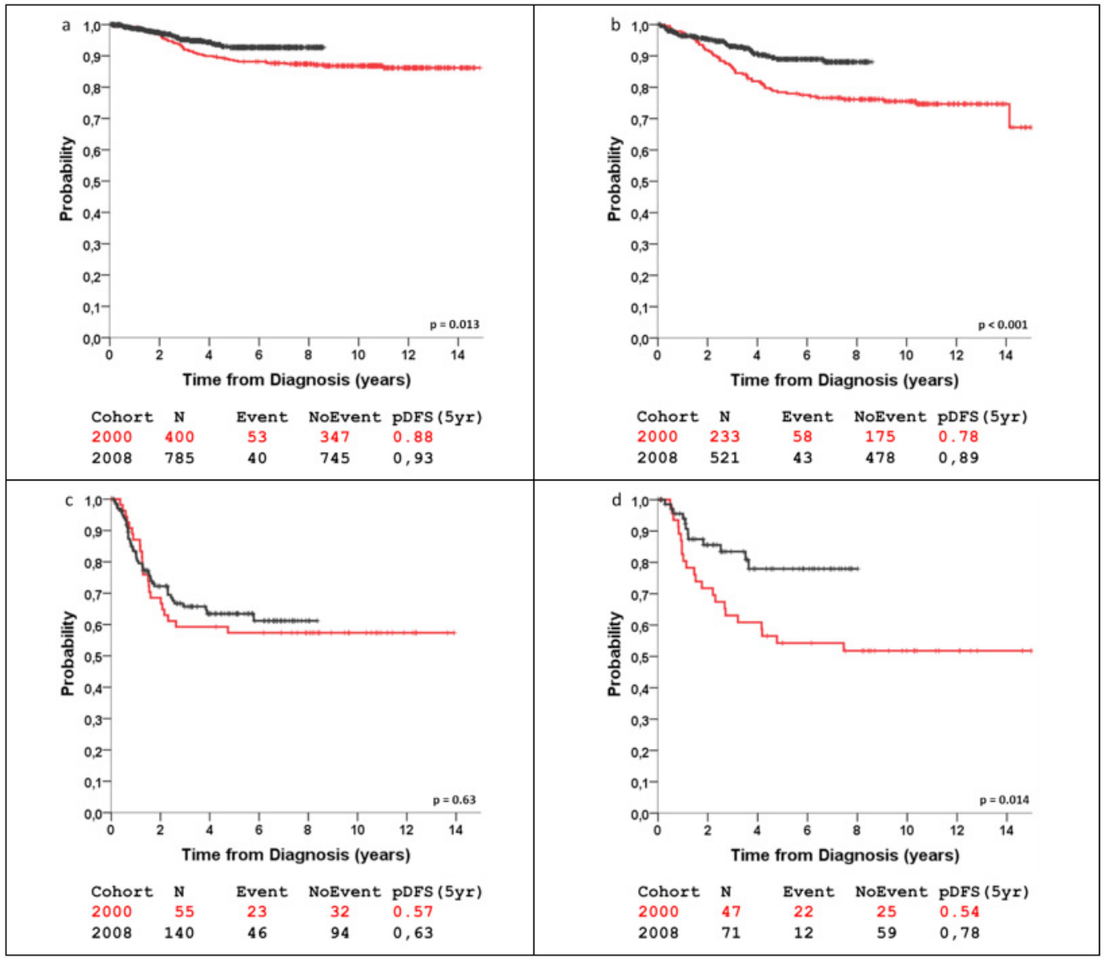
HR-chemo-group: 1 case
Female with T-ALL, WBC <10 x109/l at diagnosis and d29 MRD >0.1%. She died of multiorgan failure following severe and prolonged neutropenia after the first A-block.

Figure 3. 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.



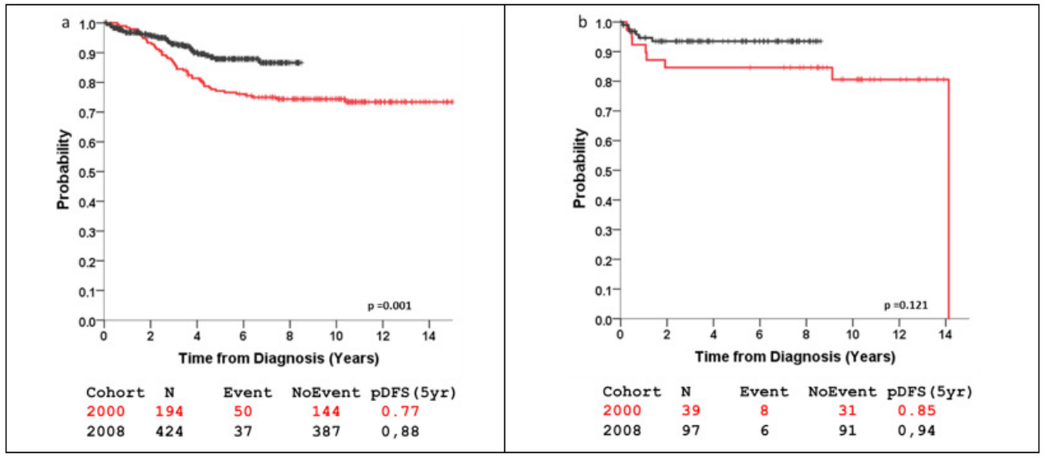
Results are stable and with longer follow-up time differences are starting to show also in overall survival. The toxic death rate has dropped over time, but there was a backlash in the high-risk group with six toxic deaths in 2016. The analyses below try to identify the patients that have benefited the most.

Figure 4. NOPHO ALL-2000 and NOPHO ALL-2008, Non-B cell ALL 1-<15 years at diagnosis. DFS-Analysis by risk-group (a) SR, (b) IR, (c) HR-chemo, (d) HR-SCT.



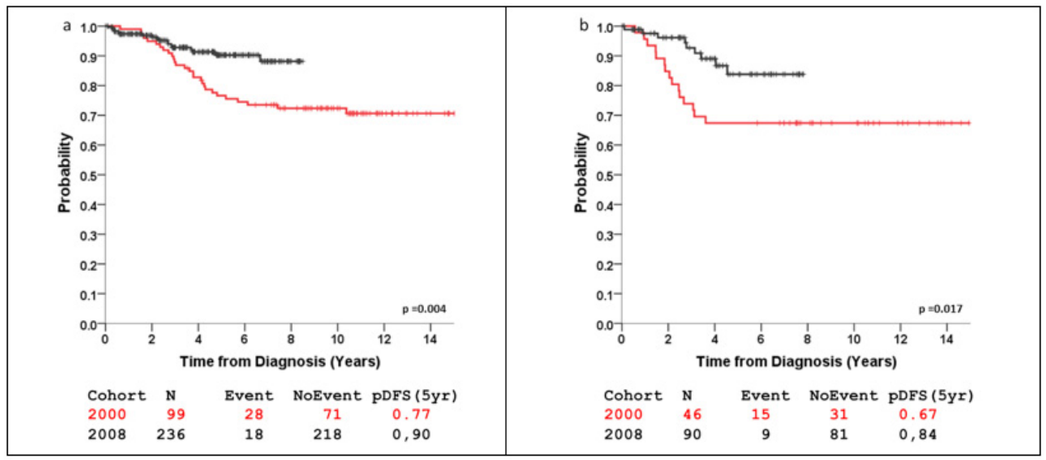
Only patients from the 2000-cohort, who had MRD-values recorded and who could thus be assigned risk-group in the NOPHO ALL-2008 stratification system, are included. The improvement is clear in the IR and HR-SCT groups, but is now starting to show also in the SR-group. Only the HR-chemo patients have a disappointing outlook both in overall results and compared with previous results, which have not really approved at all.

Figure 5. NOPHO ALL-2000 and NOPHO ALL-2008, Non-B cell ALL 1-<15 years at diagnosis. IR-stratification according to the NOPHO ALL-2008 protocol. DFS-Analysis by immunophenotype (a) BCP, (b) T-cell.



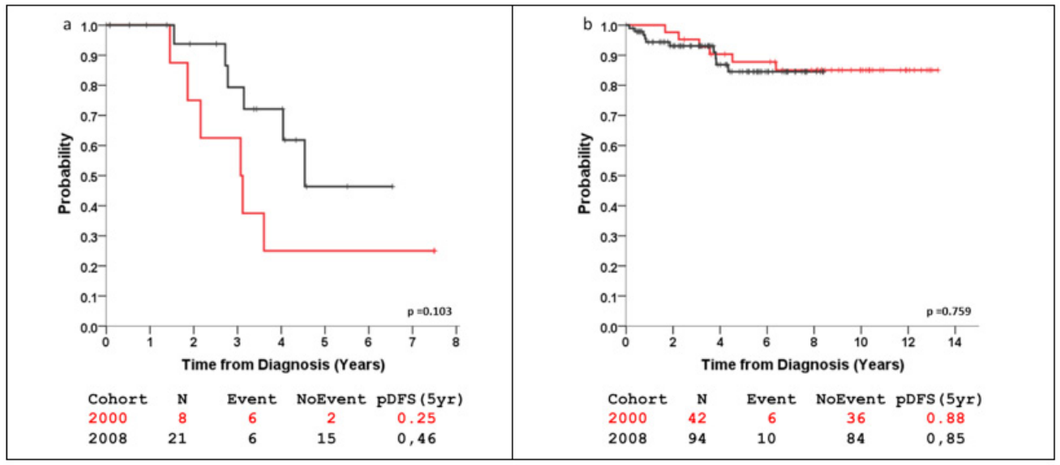
Within the IR-group, both immunophenotype-groups have improved, but the improvement is more pronounced for the BCP-group. All T-cell patients were previously in the HR-group, but the 2008 IR-therapy is probably more intensive regarding some aspects and clearly sufficient for well responding T-cell patients.

Figure 6. Analysis of IR-subgroups by genetic subtype (a), Favourable (HeH/t(12;21) (b) IR-stratifying (iAMP21, dic(9;20), t(1;19)).



Within the BCP-group the favorable and IR-stratifying groups have improved significantly. The improvement is greater for HeH-patients than for t(12;21)-cases (not shown). In the IR-stratifying group the difference is pronounced for t(1;19) and dic(9;20), which have excellent results (5-year pDFS of 0.97 and 0.90 respectively) with the NOPHO ALL-2008 protocol. The situation is different for the iAMP21-group, which pulls the overall results in this sub-group down (see below).

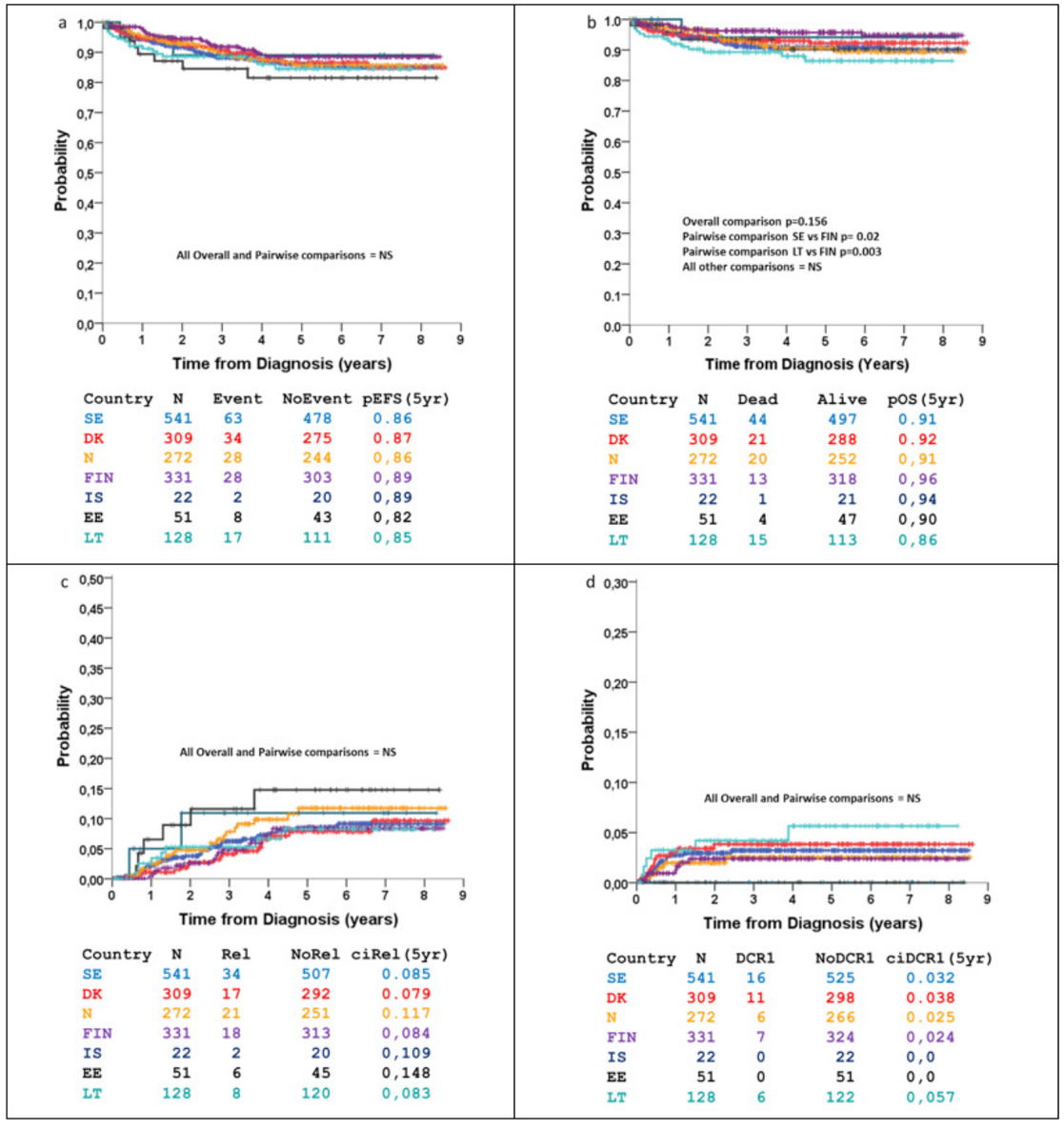
Figure 7. Analysis of IR-subgroups by genetic subtype (a), iAMP21 (b) B-other/normal.



Not only is the iAMP21-group not improving very much, it also singles itself out as the real failure of the IR-group. It seems completely logical to put iAMP21 in the category of high-risk genetics in the next protocol. There are few patients with this abnormality – particularly in the ALL-2000 group. Because the diagnostics have picked up rather late, there is also a shorter follow-up time even for the patients from the 2000-protocol.

Somewhat surprisingly, the B-other/normal group has not improved at all between the protocols. The overall outcome of this heterogeneous group is slightly below the average for the IR-group, probably because of the contribution of genetic entities such as IKZF1-deletion and "poor risk copy-number alterations", which will be explored in the next protocol and used to further sub-divide it.

Figure 8. 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	N	Event	NoEvent	pEFS(5yr)
SE	541	63	478	0.86
DK	309	34	275	0.87
N	272	28	244	0,86
FIN	331	28	303	0,89
IS	22	2	20	0,89
EE	51	8	43	0,82
LT	128	17	111	0,85

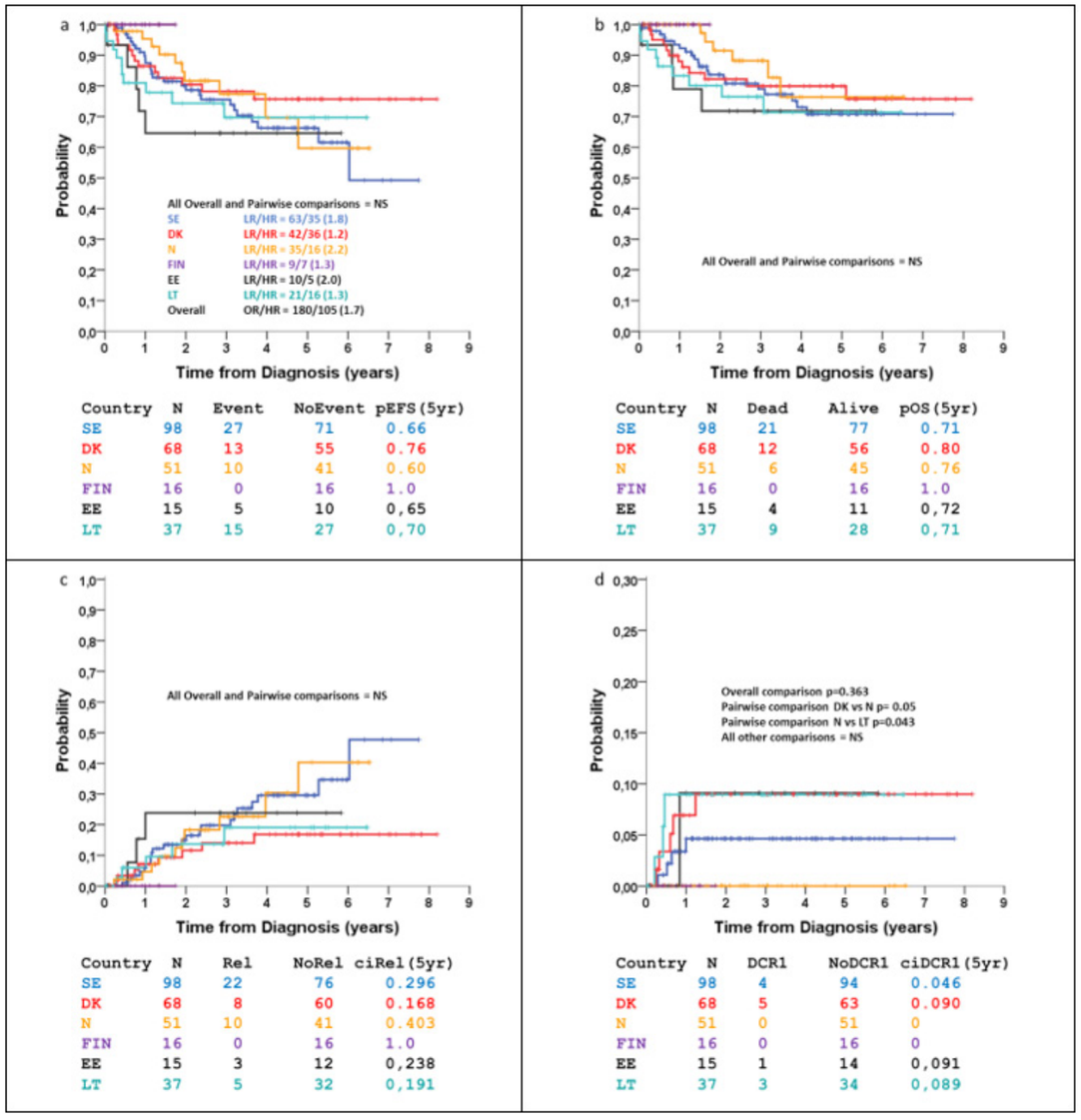
Country	N	Dead	Alive	pOS(5yr)
SE	541	44	497	0.91
DK	309	21	288	0.92
N	272	20	252	0,91
FIN	331	13	318	0,96
IS	22	1	21	0,94
EE	51	4	47	0,90
LT	128	15	113	0,86

Country	N	Rel	NoRel	ciRel(5yr)
SE	541	34	507	0.085
DK	309	17	292	0.079
N	272	21	251	0.117
FIN	331	18	313	0,084
IS	22	2	20	0,109
EE	51	6	45	0,148
LT	128	8	120	0,083

Country	N	DCR1	NoDCR1	ciDCR1(5yr)
SE	541	16	525	0.032
DK	309	11	298	0.038
N	272	6	266	0.025
FIN	331	7	324	0,024
IS	22	0	22	0,0
EE	51	0	51	0,0
LT	128	6	122	0,057

The differences in OS are mostly driven by differences in treatment-related mortality. Norway Estonia and Iceland compensate for a higher relapse-rate with lower TRM. Finland has a combination of low relapse- and, despite a few deaths in CR1 in 2016, still low TRM-rates resulting in a very high OS.

Figure 9. 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	N	Event	NoEvent	pEFS(5yr)
SE	98	27	71	0.66
DK	68	13	55	0.76
N	51	10	41	0.60
FIN	16	0	16	1.0
EE	15	5	10	0,65
LT	37	15	27	0,70

Country	N	Dead	Alive	pOS(5yr)
SE	98	21	77	0.71
DK	68	12	56	0.80
N	51	6	45	0.76
FIN	16	0	16	1.0
EE	15	4	11	0,72
LT	37	9	28	0,71

Country	N	Rel	NoRel	ciRel(5yr)
SE	98	22	76	0.296
DK	68	8	60	0.168
N	51	10	41	0.403
FIN	16	0	16	1.0
EE	15	3	12	0,238
LT	37	5	32	0,191

Country	N	DCR1	NoDCR1	ciDCR1(5yr)
SE	98	4	94	0.046
DK	68	5	63	0.090
N	51	0	51	0
FIN	16	0	16	0
EE	15	1	14	0,091
LT	37	3	34	0,089

The spread of results is more pronounced for the adult group, but the comparisons show no significant differences. Countries with a higher LR/HR index (a higher proportion of lower-risk patients) have perhaps done slightly worse than countries with more high-risk patients, indicating that the adults fare relatively slightly worse with the lower risk therapy.

Concluding remarks

We are now quite familiar with the results of the NOPHO ALL-2008 protocol. We note improvements compared with previous therapy – particularly for adults, but also some problem areas, that we have addressed over the years that the protocol has been running.

Despite our amendments tempering the HR-therapy, we again have an unwanted cluster of deaths in CR1 during block-therapy reminding us that this intensive therapy is toxic and should be reserved for the worst risk patients. It seems completely logical to assign this type of intensive therapy to a smaller fraction of patients in the upcoming ALLTogether protocol (the estimate is 4-5% of all patients compared with 15% presently). Some of these patients may also be eligible for experimental immunotherapy.

It also seems completely logical that the iAMP21-group is considered a high-risk genetic aberration in the next protocol. This group is the only distinct group, where we have not managed to correctly risk-stratify the patients.

The HR-chemo-group can be seen as a disappointment on the whole, but it is a very heterogeneous group. Results from other study-groups indicate that some of these patients may be treated by a more continuous approach with at least as good results. Hopefully, new diagnostics will also help stratify these patients in a better way and select the higher risk patients for experimental intensifications.

We have improved the relapse-rate, but the results after relapse have to some extent compensated for that loss. This is important, when we consider how to design therapy in the future. Also from this perspective, we have probably reached a limit where further intensification will not improve the results.

As we take stock of what has been by publishing all the results of the NOPHO ALL-2008 protocol, we should make sure that the fruitful discussions and research-ideas that have flourished during this era is carried forward in new studies on local-, national-, NOPHO- and consortium (ALLTogether)-level as we move towards the new era.

Even if many things will change with the advent of the new protocol, we still need the dedication and hard work of all the people who work with the patients clinically as well as those recording the data in the NOPHO-registry. Our gratitude goes out to all of you involved in both aspects of care for and of our patients.

All the best to all of you – and most welcome to the NOPHO-meeting in Stockholm.

Stockholm, springtime 2017

Mats Heyman & Trausti Oskarsson

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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

1766 patients diagnosed before March 1st 2016 (when randomisations were closed) comprise the study cohort that forms the basis for publications. Excluded patients include Down and other predisposition, previous cancer, mixed phenotype ALL, pre-treatment etc. (7.4% of all patients treated according to ALL2008 and diagnosed before March 1st 2016).

Baltic countries

Outcome has improved significantly during the last 5 years. pEFS is stable above 95% (study target) and is now very similar for the Nordic and Baltic Pediatric centers (see elsewhere in the annual report). Lithuania became full NOPHO member in 2015. No decision has been taken re Estonia.

Adults

Finnish adult hematology centers now use the ALL2008 protocol, and patients are entered into the database. Nina Toft (DK, adult hematologist in training) continues as coordinator for the adult ALL activities. 296 of the 1766 study patients have been treated at adult hematology centers. This is beyond the target of 200+ patients ≥18 years in the ALL2008 protocol.

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 650 to Rx2. Rx1 and Rx2 publication are expected to be submitted for publication by mid 2017. 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).

Risk grouping

For patients <15 years, the risk group stratification has been close to what was anticipated, although with somewhat more HR patients. Even with identical therapy and risk grouping criteria, older patients are heavily skewed towards higher risk groups. This has been analysed in detail and published (Toft, Eur J Haematol 2013).

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. The toxicity profiles for children and adults have been published (Toft, Eur J Haematol 2016). Scrutinization of patient files have 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). 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 burdened by toxic death. The toxic death rate for SR and IR patients is acceptable, but was as high as 20% following block therapy. 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 publishedand 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).

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

Publications

Much of the work done as part of the preparation for the protocol has been published, submitted for publication, or is in the writing phase:

Published studies important for the ALL2008 protocol:

1. **Schmiegelow K, Forestier E, Kristinsson J, Söderhäll S, Vettenranta K, Weinshilboum R, Wesenberg F.** *Thiopurine methyltransferase activity is related to the risk of relapse of childhood acute lymphoblastic leukemia - results from the NOPHO ALL-92 study.* Leukemia 2009; 23: 557-64.
2. **Schmiegelow K, Al-Modhawi I, Andersen MK, Berendtz M, Forestier E, Hasle H, Heyman M, Kristinsson J, Nersting J, Nygaard R, Svendsen AL, Vettenranta K, Weinshilboum R.** *Methotrexate/6-mercaptopurine maintenance therapy influences the risk of a second malignant neoplasm after childhood acute lymphoblastic leukemia - results from the NOPHO ALL-92 study.* Blood 2009; 113: 1077-84.
3. **Bjorklund E, Matinlauri I, Tierens A, Axelsson S, Forestier E, Jacobsson S, et al.** *Quality control of flow cytometry data analysis for evaluation of minimal residual disease in bone marrow from acute leukemia patients during treatment.* J Pediatr Hematol Oncol 2009; 31:406-1.
4. **Schmiegelow K, Heyman M, Kristinsson J, Mogensen UB, Rosthøj S, Vettenranta K, Wesenberg F, Saarinen-Pihkala U.** *Oral methotrexate/6-mercaptopurine may be superior to a multi-drug LSA2L2 maintenance therapy for higher risk childhood acute lymphoblastic leukemia.* J Ped Hematol Oncol 2009; 31:385-92.
5. **Schmiegelow K, Forestier E, Hellebostad M, Heyman M, Kristinsson J, Söderhäll S, Taskinen M; Nordic Society of Paediatric Haematology and Oncology.** *Long-term results of NOPHO ALL-92 and ALL-2000 studies of childhood acute lymphoblastic leukemia.* Leukemia. 2010; 24:345-54.
6. **Schmiegelow K, Heyman M, Gustafsson G, Lausen B, Wesenberg F, Kristinsson J, Vettenranta K, Schroeder H, Forestier E, Rosthoej S.** *The degree of myelosuppression during maintenance therapy of adolescents with B-lineage intermediate risk acute lymphoblastic leukemia predicts risk of relapse.* Leukemia 2010; 24: 715-20.
7. **Brüggemann M, Schrauder A; Raff T, Pfeifer H, Dworzak M, Ottmann OG, Asnafi V, Baruchel A, Bassan R; Benoit Y, Biondi A, Cavé H, Dombret H, Fielding AK, Foa R, Gökbuget N, Goldstone AH, Goulden N, Henze G, Hoelzer D, Janka-Schaub G, Macintyre EA, Pieters R, Rambaldi A, Ribera JM, Schmiegelow K, Spinelli O, Stary J, von Stackelberg A, Kneba M, Schrappe M, van Dongen JJM, also on behalf of the European Working Group for Adult Acute Lymphoblastic Leukemia (EWALL) and the International Berlin-Frankfurt-Münster Study Group (I-BFM-SG).** *Standardized MRDquantification in European ALL trials – proceedings of the second international symposium on MRD assessment in Kiel, Germany, 18-20 September 2008.* Leukemia 2010; 24:521-35.
8. **Vaitkevciene G, Forestier E, Hellebostad M, Heyman M, Jonsson OG, Lähteenmäki PM, Rosthoej S, Söderhäll S, Schmiegelow K. On behalf of the Nordic Society of Paediatric Haematology and Oncology (NOPHO).** *Should white blood cell count at diagnosis of childhood acute lymphoblastic leukaemia be included in risk stratification in contemporary treatment protocols? Results from the NOPHO ALL-92 and ALL-2000 studies.* Eur J Haematol 2011; 86:38-46.
9. **Lund B, Åsberg A, Heyman M, Kanerva J, Harila-Saari A, Hasle H, Söderhäll S, Jonsson OG, Lydersen S, Schmiegelow K. On behalf of the Nordic Society of Paediatric Haematology and Oncology (NOPHO).** *Risk factors for treatment related mortality in childhood acute lymphoblastic leukaemia.* Ped Blood Cancer 2011; 56: 551-9.
10. **Relling MV, Gardner EE, Sandborn WJ, Schmiegelow K, Pui CH, Yee SW, Stein CM, Carrillo M, Evans WE, Klein TE.** *Clinical pharmacogenetics implementation consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing.* Clin Pharmacol Ther. 2011, 89:387-91.
11. **Toft N, Schmiegelow K, Klausen TW, Birgens H.** *A national population-based retrospective study on acute lymphoblastic leukaemia in Denmark 1998-2008.* Br J Med 2012; 175: 87-104.
12. **Levinsen M, Shabaneh D, Bohnstedt C, Harila-Saari A, Jonsson OG, Kanerva J, Lindblom A, Lund B, Andersen EW, Schmiegelow K - for the Nordic Society of Paediatric Haematology and**

Oncology (NOPHO). *Pneumocystis jiroveci pneumonia prophylaxis during maintenance therapy influences methotrexate/6-mercaptopurine dosing but not event-free survival for childhood acute lymphoblastic leukaemia.* Eur J Haematol 2012; 88: 78-86.

13. **Bohnstedt C, Levinsen M, Rosthøj S, Zeller B, Taskinen M, Hafsteinsdottir S, Björgvinsdóttir H, Heyman M, Schmiegelow K.** *Physicians Compliance during Maintenance Therapy in Children with Down Syndrome and Acute Lymphoblastic Leukemia.* Leukemia 1013: 27:866-70.
14. **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.
15. **Levinsen M. Taskinen M, Abrahamsson J, Forestier E, Frandsen TL, Harila-Saari A, Heyman M, Jonsson OG, Lähteenmäki PM, Lausen B, Vaitkevičienė G, Åsberg A, Schmiegelow K,** *Central nervous system involvement in childhood acute lymphoblastic leukemia at diagnosis: Clinical features and early treatment response.* Ped Blood Cancer 2014; 61:1416-21.
16. **Taskinen M, Oskarsson T, Levinsen M, Bottai M, Hellebostad M, Jonsson OG, Lähteenmäki P, Schmiegelow K, Heyman M.** *The effect of central nervous system involvement and irradiation in childhood ALL: Lessons from the NOPHO ALL-92 and ALL-2000 protocols.* Ped Blood Cancer 2017 (In press).

Publications critical for the randomized or add-on targeted ALL2008 projects:

1. **R1: Frandsen TL, Abrahamsson J, Lausen B, Vettenranta K, Heyman M, Behrentz M, Castor A, Wehner PS, Frost B-M, Andersen EW, Schmiegelow K.** *Individualized toxicity-titrated 6-mercaptopurine increments during high-dose methotrexate consolidation treatment of lower risk childhood acute lymphoblastic lymphoma.* A NOPHO pilot study. Br J Haematol 2011;155:244-7.
2. **Host genomics: Wesolowska A, Dalgaard MD, Borst L, Gautier L, Bak M, Weinhold N, Nielsen BF, Helt LR, Audouze K, Nersting J, Tommerup N, Brunak S, Ponten TS, Leffers H, Schmiegelow K, Gupta R.** *Cost-effective multiplexing before capture allows screening of 25,000 clinical relevant SNPs in childhood acute lymphoblastic leukemia.* Leukemia 2011; 25: 1001-6.
3. **Host genomics: Wesołowska-Andersen A, Borst L, Dalgaard MD, Yadav R, Rasmussen KK, Wehner PS, Rasmussen M, Ørntoft TF, Nordentoft I, Koehler R, Bartram CR, Schrappe M, Sicheritz-Ponten T, Gautier L, Marquart H, Madsen HO, Brunak S, Stanulla M, Gupta R, Schmiegelow K.** *Genomic profiling of thousands of candidate polymorphisms predicts risk of relapse in 778 Danish and German childhood acute lymphoblastic leukemia patients.* Leukemia 2015; 29:297-303.
4. **Maintenance therapy: Jacobsen JH, Schmiegelow K, Nersting J.** *Liquid chromatography-tandem mass spectrometry quantification of 6-thioguanine in DNA using endogenous guanine as internal standard.* J Chromatogr B 2012; 15: 881-2.
5. **Maintenance therapy: Schmiegelow K, Levinsen M, Attarbaschi A, Baruchel A, Devidas M, Escherich G, Gibson B, Heydrich C, Horibe K, Ishida Y, Liang D-C, Locatelli F, Michel G, Pieters T, Piette C, Pui C-H, Raimondi S, Silverman L, Stanulla M, Stark B, Winick N, Valsecchi MG.** *Second Neoplasms after Treatment of Childhood Acute Lymphoblastic Leukemia.* J Clin Oncol 2013; 31: 2468-76.
6. **Maintenance therapy: Schmiegelow K, Nielsen SN, Frandsen TL, Nersting J.** *Mercaptopurine/Methotrexate maintenance therapy of childhood acute lymphoblastic leukemia: clinical facts and fiction.* J Pediatr Hematol Oncol 2014; 36:503-17.

Publications emerging from the ALL2008 protocol data:

1. **Raja 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.** I*ncorporation 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.
7. **Raja RA, Schmiegelow K, Albertsen BK, Prunsild K, Zeller B, Vaitkeviciene G, Abrahamsson J, Heyman M, Taskinen M, Harila-Saari A, Kanerva J, Frandsen TL.** *Asparaginase associated Pancreatitis in Children with Acute Lymphoblastic Leukaemia in the NOPHO ALL2008 Protocol.* Br J Haematol 2014; 165: 126-33.
8. **Levinsen M, Taskinen M, Abrahamsson J, Forestier E, Frandsen TL, Harila-Saari A, Heyman M, Jonsson OG, Lähteenmäki PM, Lausen B, Vaitkevičienė G, Asberg A, Schmiegelow K; Nordic Society of Paediatric Haematology and Oncology (NOPHO).** *Central nervous system involvement in childhood acute lymphoblastic leukemia at diagnosis: Clinical features and early treatment response.* Pediatr Blood Cancer. 2014; 61:1416-21.
9. **Vaitkevičienė G, Matuzevičienė R, Stoškus M, Žvirblis T, Ragelienė L, Schmiegelow K.** *Cure rates of childhood acute lymphoblastic leukemia in Lithuania and the benefit of joining international treatment protocol.* Medicina (Kaunas). 2014;50(1):28-36.
10. **Henriksen LT, Nersting J, Raja RA, Frandsen TL, Rosthøj S, Schrøder H, Albertsen BK; Nordic Society of Paediatric Haematology and Oncology (NOPHO) group.** *Cerebrospinal fluid asparagine depletion during pegylated asparaginase therapy in children with acute lymphoblastic leukaemia.* Br J Haematol. 2014;166: 213-20.
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19. **Levinsen M, Marquart HV, Groth-Pedersen L, Abrahamsson J, Albertsen BK, Andersen MK, Frandsen TL, Harila-Saari A, Pronk C, Ulvmoen A, Vaitkevičienė G, Lähteenmäki PM, Niinimäki R, Taskinen M, Jeppesen M, Schmiegelow K - for the Nordic Society of Pediatric Hematology and Oncology (NOPHO).** *Leukemic blasts are present at low levels in spinal fluid in one third of childhood acute lymphoblastic leukemia cases.* Ped Blood Cancer 2016; 63:1935-1942.
20. **Nielsen SN, Grell K, Nersting J, Frandsen TL, Hjalgrim LL, Schmiegelow K.** *Measures of 6-mercaptopurine and methotrexate maintenance therapy intensity in childhood acute lymphoblastic leukemia.* Cancer Chemother Pharmacol 2016; 78:983-94.
21. **Ranta S, Palomäki M, Levinsen M, Taskinen M, Abrahamsson J, Mellgren K, Niinimäki R, Schmiegelow K, Heyman M, Harila-Saari A.** *Role of neuroimaging in children with acute lymphoblastic leukemia and central nervous system involvement at diagnosis.* Ped Blood Cancer 2017; 64:64-70.
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23. **Wolthers BO, Frandsen T, Abrahamsson J, Albertsen B, Helt L, Heyman M, Jonsson O, Kõrgvee L-T, Lund B, Raja B, Rasmussen K, Taskinen M, Tulstrup M, Vaitkeviciene G, Yadav R, Gupta R, Schmiegelow K.** *Asparaginase-associated pancreatitis A study on pheno- and genotype in the NOPHO ALL2008 protocol.* Leukemia 2017;31:325-332.
24. **Taskinen M, Oskarsson T, Levinsen M, Bottai M, Hellebostad M, Jonsson OG, Lähteenmäki P, Schmiegelow K, Heyman M.** *The effect of central nervous system involvement and irradiation in childhood ALL: Lessons from the NOPHO ALL-92 and ALL-2000 protocols.* Ped Blood Cancer 2017 (In press).
25. **Svahn T, Mellgren K, Harila-Saari A, Åsberg A, Kanerva J, Jónsson O, Vaitkeviciene G, Mikkelssen TS, Schmiegelow K, Heldrup J.** *Delayed elimination of high dose methotrexate and use of Carboxypeptidase G2 in pediatric patients during treatment for acute lymphoblastic leukemia.* Ped Blood Cancer 2017 (in press).
26. **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).
27. **Nielsen SN, Grell K, Nersting J, Abrahamson J, Lund B, Kanerva J, Jónsson OG, Vaitkeviciene G, Pruunsild K, Hjalgrim LL, Schmiegelow K.** *Population-based, prospective analysis of dna thioguanine nucleotide levels during maintenance therapy of childhood acute lymphoblastic leukemia.* Lancet Oncol 2017 (In press).

ALL Relapse Working Group

Members 2016

Sweden	Johan Arvidson	Coordinator
	Mats Heyman	Registration, PI SR Sweden
	Petter Svenberg	PI HR Sweden
	Trausti Óskarsson	Young NOPHO
	Stefan Söderhäll	Retired during the year
Denmark	Thomas Frandsen	PI SR, HR Denmark
	Peder Skov Wehner	
Finland	Päivi Lähteenmäki	PI SR, HR Finland
	Kim Vettenranta	SCT
	Laura Korhonen	Young NOPHO
Iceland	Olafur G. Jónsson	
Lithuania	Goda Vaitkeviciene	PI Lithuania
Norway	Jochen Büchner	SCT, PI HR Norway
	Inga Maria Johansdottir	PI SR Norway
	Marit Hellebostad	Retired during the year
	Dorota Malgorzata-Wojcik	
	Finn Wesenberg	
On the mailing list:		
	Jonas Abrahamsson	Sweden
	Henrik Hasle	Denmark
	Mervi Taskinen	Finland

NOPHO relapse group had had four telephone meetings and one regular meeting during the last year:

160314	Telephone meeting
160527	Reykjavik
160926	Telephone meeting
161107	Telephone meeting
170213	Telephone meeting

Minutes are posted on the working group site at NOPHO.org.

Events during the year

IntReALL SR

The protocol for SR patients is recruiting patients in Norway, Denmark and Finland but still not in Sweden. Around 15 patients are registered. No protocol specific difficulties so far. Randomisation procedures are working. The study has to go on for about 3 more years to reach the estimated number of patients needed to draw conclusions.

IntReALL HR

The protocol for HR patients has been finalized, and the Nordic HR PIs have finalized the national parts of the paper work, and are awaiting legal paperwork from study center in Berlin.

PIs for Denmark and Finland will be the same as for SR study. For Norway, Jochen Büchner, Oslo will be the PI and for Sweden Petter Svenberg, Stockholm.

Lithuania report

In 2014 Goda V asked study center if Lithuania could register the patient with ALL relapse, use the standard arm in the protocol but not enter randomisations. No decision taken.

FORUM study

All Nordic countries have joined the study and more than 30 Nordic patients are registered. Interim safety analyses has been done and the study goes on.

CAR-T study

Novartis Global Trial was presented by Jochen Büchner at EBMT, Marseille. Oslo will open an expanded protocol based on this study during spring 2017.

Manuscript

Relapsed childhood acute lymphoblastic leukemia in the Nordic countries: prognostic factors, treatment and outcome. *Oskarsson T, Söderhäll S, Arvidson J, Forestier E, Montgomery S, Bottai M, Lausen B, Carlsen N, Hellebostad M, Lähteenmäki P, Saarinen-Pihkala UM, Jónsson ÓG, Heyman M; Nordic Society of Paediatric Haematology and Oncology (NOPHO) ALL relapse working group.* Haematologica. 2016 Jan;101(1):68-76.

Meetings

Most PIs attended BFM interim meeting "Resistant disease group", Hexham, Feb 10-12 2017.

I-BFM group annual meeting will be held in Jerusalem on May 10-12 2017.

LLC: Friday the 19 May 2017, 13.00-18.00 and Saturday 20 May 2017, 9.00-12.00 in Stockholm.

Next NOPHO relapse group meeting 19 May 2017 at 10-12 at the NOPHO Annual meeting venue in Stockholm - Room Deluxe 2.

New Chairperson for the NOPHO ALL relapse group: retiring Johan Arvidson will announce Jochen Büchner, Oslo, as the next chairman at the NOPHO board meeting in Stockholm.

Uppsala 170409
For the working group

Johan Arvidson
Sweden

Events Working Group (EWG)

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Ruta Tuckuviene (Thrombosis study)		ruta@dadlnet.dk

Since last annual report the NOPHO Events group has met 2 times. 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 study and as part of The iBFM/PdL toxicity consensus work), relapses, 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 Jerusalem the PdL toxicity working group will be discussing strategies for capturing the next cases from the working group (ON and Neuro-toxicity) as well as the group will be discussing the Pancreatitis phenotypes (submitted) on more than 600 pancreatitis cases collected by MD, PhD student Benjamin Ole Wolthers and as the next work the group will look at GWAS for these cases. DNA is available for SNP/GWAS profiling on more than 300 of these patients and has been analysed. The group will be looking at the findings from this GWAS.

- 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. During the last year this work has matured: DCOG, UKALL, COALL and NOPHO as well as Belgium and Portugal have joined the work. 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 – manuscript has been submitted)
- ON (Signe Mogensen – manuscript in preparation)
- VOD (Thomas Frandsen – manuscript in preparation)
- CNS-leukemia (Mette Levinsen)
- Hyperleukocytosis (Goda Vaitkeviciene)
- Thrombosis (Morten Tulstrup and 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.

Next meeting Sept 18th, 2017 Copenhagen
Copenhagen 23.4.2017 Thomas Frandsen

Events group related Publications 2016-2017

Wolthers BO, Frandsen, TL, Abrahamsson J, Albertsen BK, Helt LR, Heyman M, Jónsson OG, Kõrgvee L, Lund B, Raja RA, Rasmussen KK, Taskinen M, Tulstrup MR, Vaitkevičienė GE, Yadav R, Gupta R and Schmiegelow K. *Asparaginase-associated pancreatitis. A study on pheno - and genotype in the NOPHO ALL2008 protocol.* Leukemia. 2016 Jul 25. doi: 10.1038/leu.2016.203. [Epub ahead of print]

Toksvang LN, Pietri SD, Nygaard 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 leukaemia is associated with continuous asparaginase therapy and mercaptopurine metabolites.* Pediatr Blood Cancer. 2017 Apr 19. doi: 10.1002/pbc.26519. [Epub ahead of print] PubMed PMID: 28423235

Mogensen SL, Schmiegelow K, Grell K, Albertsen BK, Wehner PS, Kampmann P, Frandsen TL. *Hyperlipidaemia is a risk factor for osteonecrosis in children and young adults with acute lymphoblastic leukaemia.* Haematologica. 2017 Feb 16. pii: haematol.2016.160507. doi: 10.3324/haematol.2016.160507. [Epub ahead of print] PubMed PMID: 28209659.

NOPHO ALLTogether Working Group

Coordinators	Mervi Taskinen, Mats Heyman
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	Birgitte Klug Albertsen
	Nina Toft
Finland	Mervi Taskinen
	Olli Lohi
	Päivi Lähteenmäki
	Ulla Wartiovaara-Kautto
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	Trond Flaegstad
	Petter Quist Paulsen
Sweden	Mats Heyman
	Johan Malmros
	Helene Halböök
Estonia	Kristi Lepik
Lithuania	Goda Vaitkeviciene
Adults	Nina Toft (Denmark)
	Helene Hallböök (Sweden)
	Petter Quist-Paulsen (Norway)
	Ulla Wartiovaara-Kautto (Finland)
	Laimonas Griscevicius (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. There have so far been two meetings, 24th of February and and 12th of February 2016. The meetings have been spent defining the NOPHO-representation in the working-groups of the ALLTogether consortium, formulating hopes and fears for the collaboration and to some extent reacting to the protocol work achieved so far.

The group defined the following NOPHO-aims

- to achieve both a comprehensive treatment protocol (essentially including all patients)
- to create a strong scientific framework for treatment-related studies
- to increase power to make it possible for randomised questions to be asked within the protocol
- to enable the introduction of specific therapy for rarer subtypes
- to have a less toxic therapy for at least some of the patients
- to bring both the NOPHO atmosphere of openness, “grass-root involvement” and collaboration but also the NOPHO experience and expertise to the larger context of the ALLTogether collaboration
- to have a dynamic collaboration, making it possible to conduct translational studies without undue bu-reaucracy and with the ability to rise to challenges and setbacks

The group also defined the following fears/potentially negative consequences to be avoided:

- Loss of the NOPHO-experience – that NOPHO’s legacy is not reflected in the protocol
- Loss of NOPHO influence
- Loss of sense of identification with the protocol – with a risk of less stringent adherence
- Loss of dynamic potential making it difficult to start and conduct studies
- Loss of continuous quality control to formal interim analyses
- A less grass-roots oriented structure with less communication between clinicians and study-leadership
- A too large organisation, with difficulties in communication between the different parts of the consortium
- Lack of operational leadership

The group also decided on NOPHO-attitudes towards parts of the protocol suggestions and a plan to integrate the ALLTogether-work into the other working-groups. The conclusion is that NOPHO has a lot to gain from being active in the protocol process, with the potential of gaining influence for the NOPHO-way of doing things by setting examples for the whole consortium.

One example, where the NOPHO initiative has been successful is the incorporation of the adult group in the protocol work. NOPHO has also been granted some kind of recognition by the appointment of a NOPHO-representative as PI for the entire study.

The integration of the protocol work in the working-groups and the progress of the protocol decisions have resulted in constant updates of the protocol work on many working-group meetings and a less obvious role for the ALLTogether working-group as an independent body. For the spring-meetings in March the group was updated before the ALL working-group meeting and invited to the meeting. The group may still need to be consulted separately regarding some issues and have independent meetings, but the work may also be sub-divided and carried out by NOPHO-representatives in the ALLTogether task-forces with the help of working-groups. One alternative is also to integrate the work into the ALL-working-group as has been the case already.

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 2017

Mats Heyman

AML Working Group

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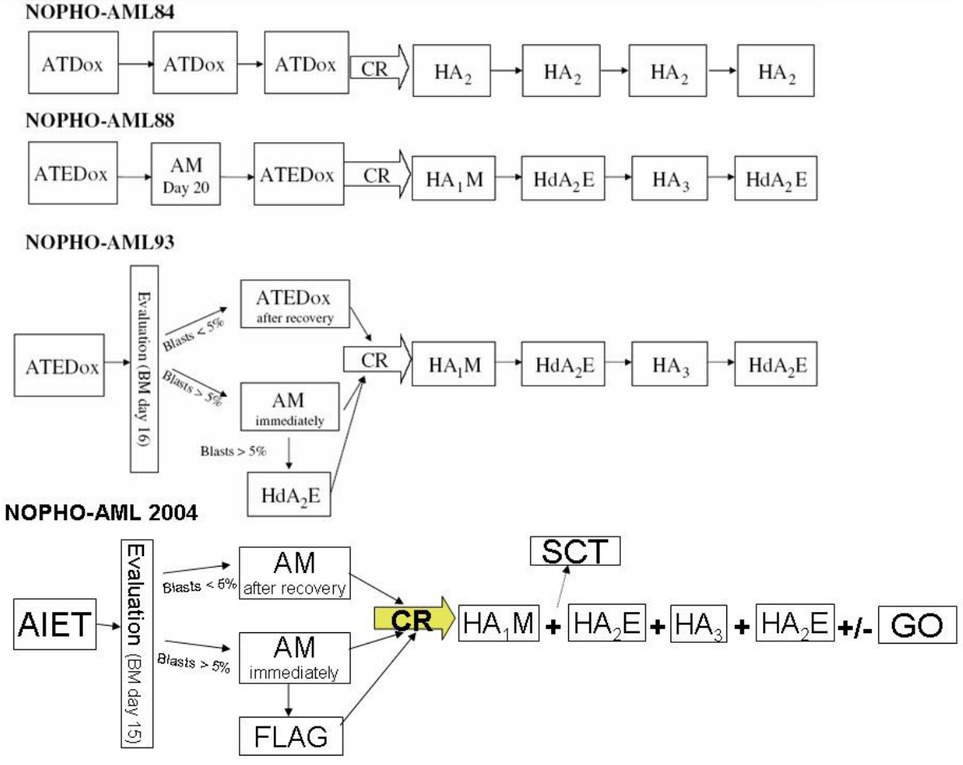

Figure 1. Overview of previous NOPHO treatment protocols from 1984-2012

Organisation

The group has held two meetings during 2016. The main focus of the meetings have been on supervision of the treatment protocol NOPHO-DBH AML2012. There has been a large international interest for the protocol and we have during the year welcomed Nira Arad-Cohen as representative for Israel. Spain is also in the process of joining the AML2012 study and were represented at the November meeting.

We have actively worked, in cooperation with the NOPHO leukemia biology group, to increase the collaboration with preclinical researchers and continue to strengthen the scientific cooperation between NOPHO and the Dutch and Belgian groups.

Several NOPHO AML research projects have been pursued and NOPHO continues to participate in international collaborative scientific studies. 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. 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 EFS_{5y} 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.

During 2016 the main work in the AML group has focused on:

1. Supervising the efficiency, toxicity and logistic framework for the NOPHO-DBH AML2012 protocol.
2. Implementing the new MRD database for NOPHO-DBH AML2012
3. Implementing the NOPHO-DBH AML2012 protocol in Hong Kong and Israel.
4. Increasing the scientific collaboration with preclinical researchers and between NOPHO and the Belgian and Dutch groups.
5. Compiling and publishing data from the NOPHO AML protocols.
6. Planning and participating 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 now mature and extensive work has been done within the group during 2016 to analyze and publish data on outcome, disease biology and toxicity. These efforts will continue during 2017.

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 randomised study had accrued the target number of 120 and therefore was closed for randomisation 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 40% 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 HA_3. 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.

Protocol	N	EFS 5y %
-84	85	28
-88	104	41
-93	298	50
2004	323	47

Protocol	N	OS 5y %
-84	85	38
-88	104	46
-93	298	65
2004	323	69

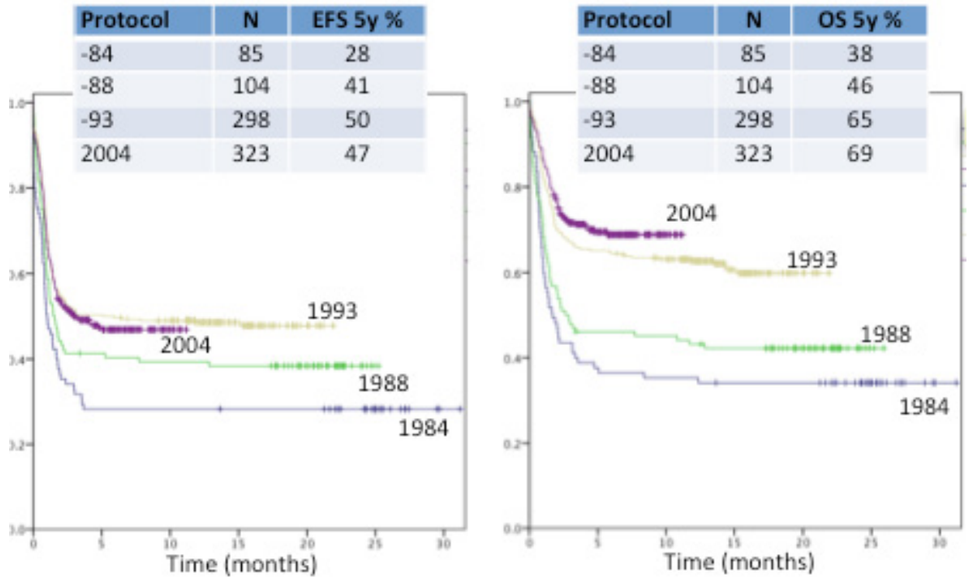

Figure 2. Overall survival (right figure) and event-free survival (right figure) in NOPHO-AML2004 (purple), NOPHO-AML93 (beige), NOPHO-AML88 (green) and NOPHO-AML84 (blue).

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.

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. A major achievement during the year has been the finalization and startup of the new MRD database.

The study was 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.

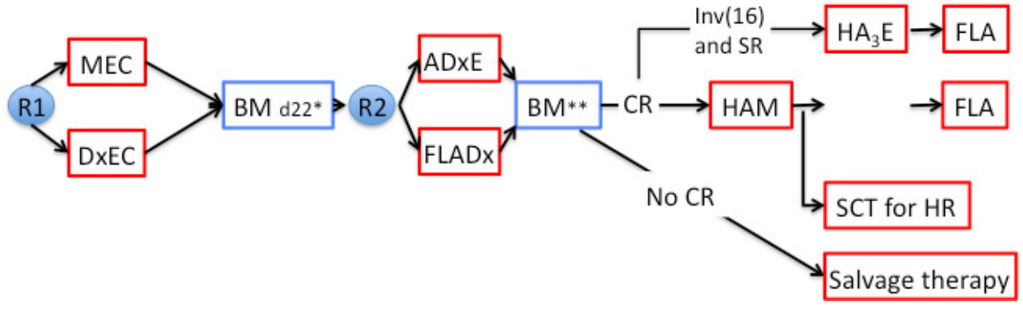

Figure 3. Overview of NOPHO-DBH AML 2012. Evaluation of therapy response is performed on day 22 after the first course and immediately before consolidation.

The main assumptions, which to a large extent were deducted 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. Thus, besides meeting regularly, all laboratories partake in twinning so that each patients MRD data are 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. 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 October 2016, 176 patients have been treated on the protocol. Of these 79% have been randomized for course 1 and 83% for course 2. The overall randomization frequency has been slightly lower than anticipated but in the Nordic countries it is around 90% which is excellent. The adherence to protocol guidelines, particularly regarding diagnostic evaluations and MRD flow measurements, has been very good. A high proportion of patients, 68%, have had AML-specific cytogenetic aberrations. 12% have CFBB-MYH11 (Inv(16)), which in good responding patients stratifies treatment to only two consolidation blocks, and 13% have FLT3-ITD mutation without NPM1 mutation that stratifies to HR treatment. Response evaluation with MRD flow has been feasible in 94% of patients which is higher than our initial expectations and verifies that our multicenter approach to MRD determination functions very well.

The response to induction therapy has been excellent with only five patients having resistant disease following two courses and an additional ten with between 0.1% and 5% leukemic cells after course 2 (HR criterion). There is an interaction between patients with poor response and FLT3-ITD mutation so at present only 12% of patients are assigned to the HR group.

As expected the toxicity of the protocol has been high and figure 4 shows the time-points for the six toxic deaths that have occurred.

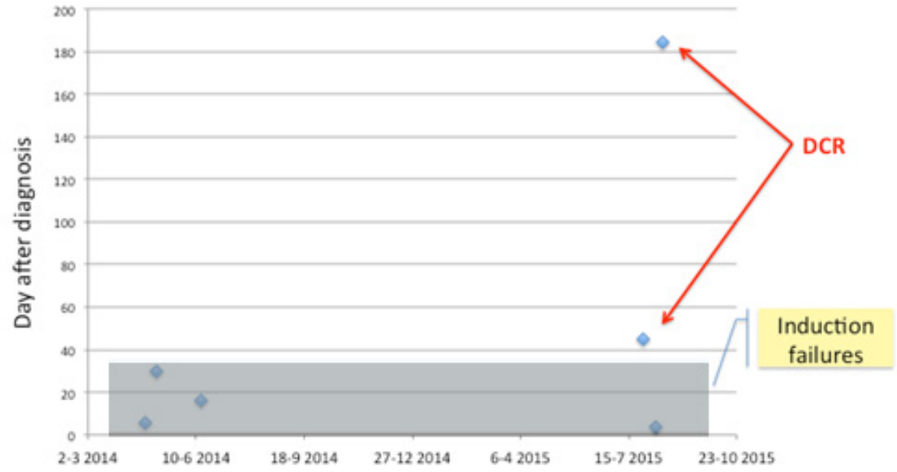

Figure 4. The time-point in treatment of toxic deaths in NOPHO-DBH AML2012 in relation to protocol start. Induction deaths are in the shaded area. DCR – Death in complete remission.

Figure 4 shows that there were three induction deaths in spring 2014. Therefore, the AML group wrote extended guidelines for management of febrile infection which were distributed to all investigators and published on the NOPHO web. No new toxic deaths have occurred since August 2015.

Toxicity registration shows that 60% of patients have documented sepsis after the first course, 13% have typhlitis and 16% require care at ICU. However, induction therapy for AML is very intensive and the toxicity has been manageable and similar to that reported in other protocols. Particularly since new countries are implementing AML2012, continued extreme vigilance is necessary and supportive care must be of the highest standard in these patients. Toxicity registration tends to be delayed for the consolidation courses which is not acceptable in a clinical trial conducted according to good clinical practice. This needs to be improved as does timely reporting of follow-up.

Although the median follow-up still is short, preliminary comparisons of event-free survival between AML2012 and AML2004 can now be performed. While confidence intervals are large, the results, as shown in figure 5, are promising with an estimated EFS at 2.5 years of 65.1% (CI 55.7-76.9) compared to 51.7% (CI 46.5-57.4%) for AML2004. The majority of relapses in AML usually occur within two years from diagnosis but we cannot yet exclude that the relapses are delayed in AML2012.

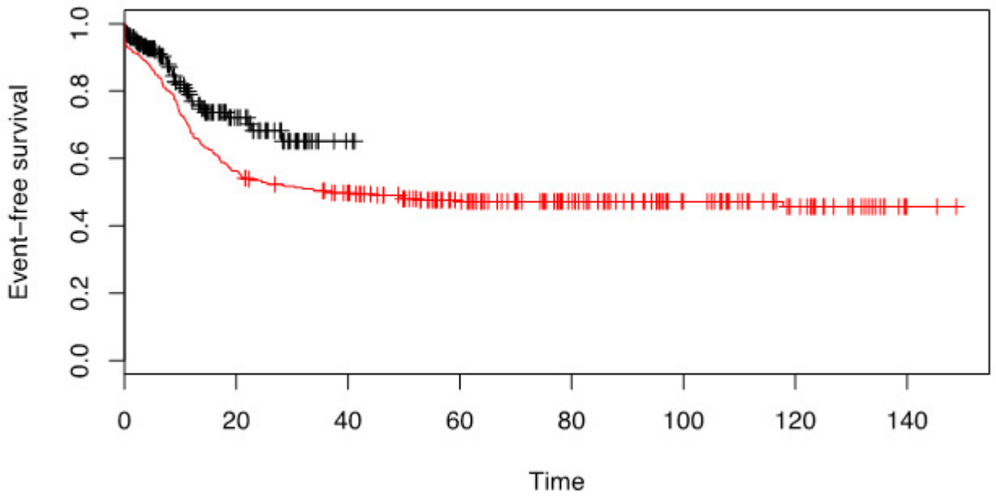

Figure 5. EFS for 176 patients (black curve) treated on NOPHO-DBH AML2012 and 323 patients on NOPHO-AML2004 (red curve). The 2.5 y EFS is 65.1% (CI 55.1-76.9) for AML2012 compared to 51.7% (CI 46.5-57.4) for AML2004 ($P_{Logrank}$ = 0.007). Time is given in months.

The main cause of death in AML is progressive disease following relapse which of course occurs at a later time point than the primary event. Therefore, comparison of survival between the protocols is uncertain for the time being. Figure 6 shows the Kaplan-Meier curves for the AML2012 (black) and AML2004 (red curve) protocol.

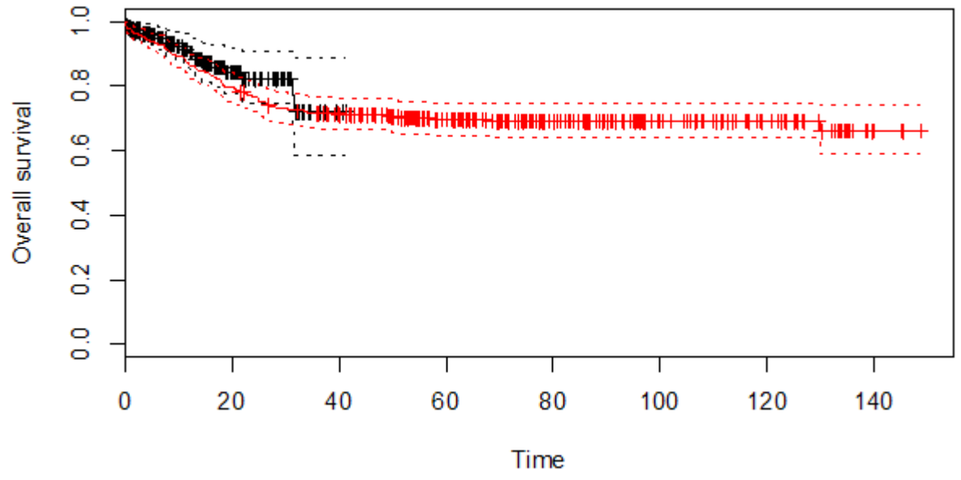

Figure 6. OS for 176 patients (black curve) treated on NOSHED AML2012 and 323 patients on NOPHO-AML2004 (red curve). The OS for AML2012 is 82% (CI 74.7-90.6) at 2.5 years and 72% (CI 58.4-88.7) at 3 years. The survival at three years is burdened by two late treatment-related deaths following relapse treatment. Time is given in months.

In conclusion, the NOPHO-DBH AML2012 protocol has now recruited almost half of the projected patients and accrual is increasing due to the participation of more countries. The protocol logistics are well functioning. The results on treatment efficacy give reason to be optimistic. It will be very interesting to see if the performance of the protocol is similar in the new countries.

Intergroup studies

Myeloid leukemia of Down syndrome

The International DS study ML-DS 2006 reduced the dose in each course and the total number of courses from 6 to 4. 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 now almost finalized. 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. Josefine Palle has been appointed as NOPHO representative in this study.

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 has started and meanwhile NOPHO recommendations for relapse treatment can be found at www.nopho.org.

Common European protocol

During 2012, BFM and DCOG took the initiative to investigate the possibilities to establish a common European de novo AML protocol. The main incentives are to obtain higher patient numbers in order to complete randomizations in a shorter time frame and to achieve power for subgroup analyses. A committee was established and representatives from the NOPHO AML group have taken part of meetings twice yearly and also taken on several tasks. The initial aim was to have a protocol ready in 2019-2020. However, this time frame may be compromised since both the UK and BFM recently have started new treatment studies.

Publications involving the NOPHO AML WG from 2015

- **Damgaard Sandahl J, Kjeldsen E, Abrahamsson J, Ha SY, Heldrup J, Jahnukainen K, Jónsson ÓG, Lausen B, Palle J, Zeller B, Forestier E, Hasle H.** *The applicability of the WHO classification in paediatric AML. A NOPHO-AML study.* Br J Haematol 2015 169(6):859-867.
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- **Zwaan CM, Kolb EA, Reinhardt D, Abrahamsson J, Adachi S, Aplenc R, De Bont ES, De**

Moerloose B, Dworzak M, Gibson BE, Hasle H, Leverger G, Locatelli F, Ragu C, Ribeiro RC, Rizzari C, Rubnitz JE, Smith OP, Sung L, Tomizawa D, van-denHeuvel-Eibrink MM, Creutzig U, Kaspers GJ. *Collaborative Efforts Driving Progress In Pediatric Acute Myeloid Leukemia.* J Clin Oncol 2015 33(27):2949-62.

- **Jarfelt M, Andersen NH, Glosli H, Jahnukainen K, Jónmundsson 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 Haematol 2015:Sep 18.
- **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.
- **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.
- **Juel Adolfsen Løhmann D, 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
- **Støve HK, Damgaard Sandahl J, Abrahamsson J, Asdahl P, Forestier E, Ha SY, Jahnukainen K, Jónsson ÓG, Lausen B, Palle J, Zeller B, Hasle H.** *Extramedullary Leukaemia in Children With Acute Myeloid Leukaemia: A Population-Based Cohort Study From the Nordic Society of Paediatric Haematology and Oncology NOPHO.* Pediatric Blood & Cancer 2017. Mar 23
- **Lene Karlsson, Erik Forestier, Henrik Hasle, Kirsi Jahnukainen, Ólafur Gisli Jónsson, Birgitte Lausen, Ulrika Norén Nyström, Josefine Palle, Anne Tierens, Bernward Zeller, Jonas Abrahamsson.** *Outcome after intensive reinduction therapy and allogeneic stem cell transplant in pediatric relapsed acute myeloid leukemia.* Br J Haematol 2017.
- **Bernward Zeller, Heidi Glosli, Erik Forestier, Shau-Yin Ha, Kirsi Jahnukainen, Olafur Jonsson, Birgitte Lausen, Josefine Palle, Henrik Hasle, Jonas Abrahamsson.** *Hyperleukocytosis in paediatric acute myeloid leukaemia – the challenge of white blood cell counts above 200 x 109/L. The NOPHO experience 1984-2014.* Br J Hematol 2017.

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The Leukemia Cytogenetic group meet once a year divided in two two-day-meetings. All participants with two exceptions are clinical geneticists working at the laboratories responsible for the cytogentic diagnostics in the Nordic countries. The coordinators are both pediatric oncologists and they together with Bertil Johansson participate in both meetings. In May 2016 we met in Umeå and the Swedish leukemia patients diagnosed in 2015 were reviewed during the first meeting. In the second meeting the rest of the Nordic leukemia patients were reviewed. All pediatric AML patients as well as both pediatric and some of the adult ALL patients (the Swedish, Norwegian and Danish) 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 settled, taking into account all diagnostic results we know of for each patient. The cytogentic group defining the patient in the treatment protocol is finally decided by the “worst counts” -principle

Cytogenetic results for NOPHO patients diagnosed with ALL in 2015

In total 178 Nordic children and 40 Nordic adults diagnosed with ALL during 2015 were reviewed. The cytogenetic results for each immunophenotype group are presented below.

Aberrations in BCP-ALL - children	*n*	*%*
MLL/11q23	2	1,3
t(9;22)	2	1,3
Low-hypo (30-39)	1	0,7
Near-haplo (<30)	1	0,7
dic(9;20)	3	2,0
t(1;19)	3	2,0
"other"	32	21,3
Normal	15	10,0
No result	4	2,7
51-67 chr	53	35,3
t(12;21)	34	22,7
iAMP21	0	0
>67 chromosomes	0	0
Total	150	100

Aberrations in T-ALL - children	*n*	*%*
Other	21	77,8
Normal	4	14,8
No result	1	3,7
>67 chromosomes	1	3,7
Total	27	100

Aberrations in Bilineage AL - children	*n*	*%*
iAMP21	1	100
Total	1	100

Aberrations in BCP-ALL - adults	*n*	*%*
MLL/11q23	3	10,3
t(9;22)	2	6,9
Low-hypo (30-39)	1	3,4
"other"	12	41,4
Normal	4	13,8
51-67 chr	5	17,2
t(12;21)	1	3,4
iAMP21	1	3,4
Total	29	100

Aberrations in T-ALL - adults	*n*	*%*
MLL/11q23	1	11,1
"other"	7	77,8
Normal	1	11,1
Total	9	100
Aberrations in Bilineage AL - adults	*n*	*%*
"other"	2	100
Total	2	100

Cytogenetic results for NOPHO children diagnosed with AML in 2015

34 Nordic pediatric patients registered in the NOPHO AML registry diagnosed in 2015 were reviewed. Apart from de novo AML two patients were diagnosed with MDS (other and normal), two with JMML (other and normal) one with t-AML (other) and one patient with Down Syndrome and AML (other). Among the AML patients the molecular analyses for FLT-ITD- and NPM1-mutations were not re-viewed, but checked for in the NOPHO registry. One patient, having a karyotype according to the "other"-group, with FLT-ITD mutation and a concurrent NPM1-wild type, was found . See table below for the cytogenetic results.

Cytogenetic results for NOPHO children diagnosed with AML in 2015

Aberrations in de novo AML children	*n*	*%*
t(8;21)	1	3,6
inv(16)	3	10,7
t(15;17)	2	7,1
"other"	7	25
Monosomy 7	1	3,6
MLL/t(10;11)	2	7,1
MLL/t(9;11)	6	21,4
Other MLL-rearr	1	3,6
MLL/t(11;19)	1	3,6
t(6;9)	1	3,6
Sole +8	1	3,6
Normal	2	7,1
Total	28	100

Future plans

During 2017 the diagnostic genetic laboratories will start to register their results up front in a new part of the NOPHO registry in parallel with the cytogenetic registration from the clinic (just as the MRD results are reported from both sides). This work is ongoing at the NOPHO registry and a proposal for the registration in detail will be discussed in the upcoming cytogenetic review meetings this year in May, and then hopefully implemented.

Umeå 19-04-2017
Ulrika Norén Nyström

Nordic Pediatric Leukemia Biobank Board

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Young NOPHO

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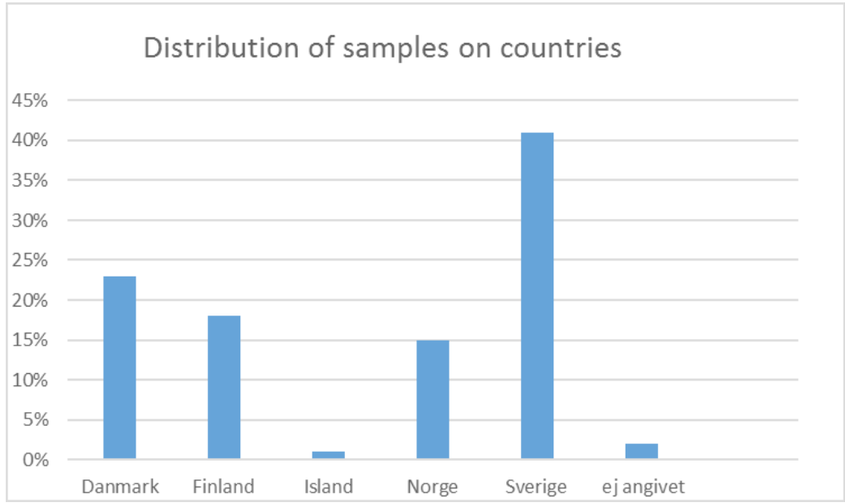
Mats Heyman	*Leukemia registry*
Yanara Mariencevic	*Leukemia Biology*
Sofie Degermann	*Leukemia Biology*

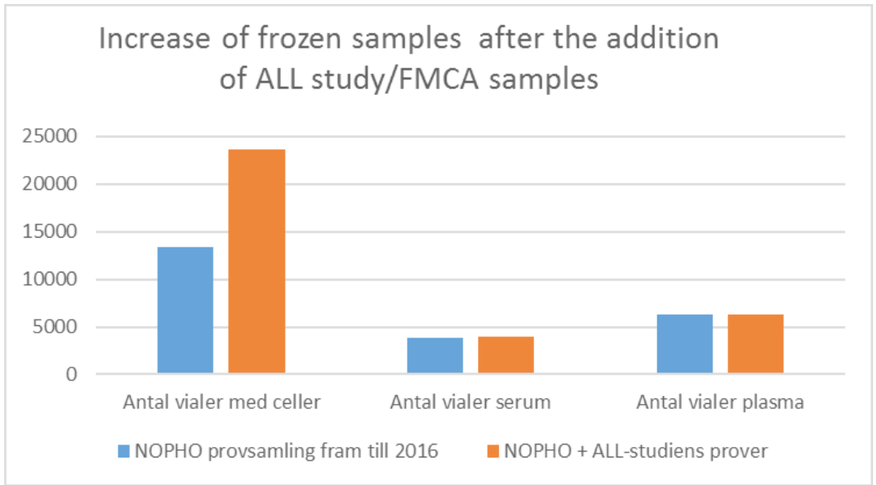


The ALL-study / FMCA (cytotoxic resistance) started in the late nineties. From 2006 samples from the same patients were saved also in the NOPHO biobank and stored at Clinical Pathology in Uppsala. In 2013 the ALL study / FMCA ended, and the practical work with NOPHO biobank continued entirely at Clinical Pathology.

During 2015-2016, the earlier samples from ALL study / FMCA were transferred to NOPHO biobank to be useful in a research context. To incorporate these samples has been quite a complicated job and is not completely finished yet. It has been a lot of work with different data files and change of computer system at the same time. Then some time to correct patient data and double check with CCEG's database (including NOPHO´s clinical leukemia database).

In the last few years, samples have been taken from NOPHO biobank to be used in a dozen research projects. According to the law that regulates the sample collections, all leftover material is forced to be returned, which has not happened in all cases. There is still 970 vials of cells sent from Uppsala which are not yet returned. Returned extracted DNA and RNA are also to be brought back to NOPHO biobank.

- The NOPHO sample collection along with the samples received by ALL / FMCA has about 5000 sampling events. That of course includes a number of relapses.
- 11221 vials of cells from bone marrow
- 12367 vials of cells from peripheral blood
- From the cells we have extracted DNA and RNA that is aliquoteted in 2406 vials
- We have over the years also collected plasma from both bone marrow and blood, a total of 6328 vials
- 3973 vials of serum
- 6328 vials of plasma from both bone marrow and peripheral blood



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Organization

Formerly ”ALL Biology” working group was expanded in late 2015 to include AML and lymphoma researchers and clinicians in addition to ALL researchers and clinicans. The group was at the same time renamed as Leukaemia & Lymphoma Biology Working Group (LL Biology WG). Beginning in March 2016, the chairmanship was changed so that Linda Fogelstrand and Olli Lohi were elected as co-chairs. Both of them have a strong background on basic research and furthermore represent either diagnostics (Linda) or clinical (Olli) expertise. The meetings have – as before - been held back-to-back with the ALL-WG meetings. The LL Biology group reports to the LLC, but many of the items are also discussed in the ALL-WG. Meetings have been financed by sponsoring from either the Swedish Barncancerfonden or corporate sponsoring. Travel expenses are covered by the institutions of the participants. In future, the mtgs will be funded by a planning grant received from Swedish Barncancerfonden (3 year funding up till 2019).

Meetings

In 2016, the LL Biology WG held two meetings; in Uppsala in March and Copenhagen in September. Both of them were popular with a lot of enthusiastic participants (58 in Uppsala, 42 in Copenhagen). There is an increasing turnout at the meetings, which are turning into small symposia in their own right. In the Uppsala meeting, the group discussed about the aims of the group and ended up in following themes:

- 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, technolocy/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

During 2016, the structure of the meetings was slightly amended so that a separate ”scientific session” focusing on a timely topic and with outside speakers was introduced. Moreover, meetings have included updates on ongoing NOPHO projects and presentations of newly planned projects with a biology dimension. In addition to increase the chances for collaboration between reserach groups attending the meeting, also other research projects not listed as NOPHO projects have been presented.

Web resources

A web-forum for discussions, postings and suggestions for collaborative projects has been in place since March 2014 and is managed by Vasilios Zachariadis, Stockholm. However, its usage has been very low and there are no plans to revive it. In 2016, a website called eNOPHO was generated by Miikka Voutilainen & Olli Lohi that compiled essential metadata on all genome-wide experiments generated on NOPHO patients and submitted to publicly available repositories. This database would be more helpful if it contained the NOPHO number of cases, but this has encountered ethical and permit issues that are yet unresolved.

Future perspectives

Meetings will continue to be held biannually, in March 2017 in Helsinki and September 2017 in Stockholm. For these meetings, the structure will be as started 2016. There will be more discussion on the optimisation of standardized procedures for preservation of material in the NOPHO biobank, including constitutive samples. We also plan to have a dedicated session for ethical issues related with genome studies. In the future, we plan to increase the collaboration with the ALLTogether consortium to plan for upfront projects that are of interest to the group.

Olli Lohi and Linda Fogelstrand, April 2017

Infant Leukemia Working Group

Coordinator	Birgitte Lausen (DK)
Denmark	Birgitte Lausen
Finland	Olli Lohi
Iceland	Solveig Hafsteinsdottir
Norway	Bem Zeller
Sweden	Anders Castor
	Ulrika Noren Nyström (cytogenetics)
	Mats Heyman (data center)
	Jesper Heldrup (immunophenotyping)
Young NOPHO	Kaisa Vepsäläinen, replaced by Sauli Palmu, Finland, from 2017

The main activity of the NOPHO Infant Leukemia group is to take care of the international Interfant studies. The group had a meeting in January 2016. The annual meeting in the international Interfant group was held in April 2016 during the I-BFM-meeting in Athens.

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. Overall outcome is not different from the Interfant-99 protocol, apart from that SCT in CR1 seems to be successful in high risk patients.

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.

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.
A total of 75 patients are (or have been) treated according to the Interfant-06 protocol, the main part not randomised and thus following the standard arm (December 31st 2016). Seven infant ALL patients have been treated according to the NOPHO ALL2008 protocol in Sweden, and one in Norway. 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 5. All centres are still requested to send samples from MLL-rearranged infant ALL patients from time of diagnosis and Time Point 5 to the MRD-lab. in Copenhagen.
Survival: 5-years OS is 59 % for **MLL+** patients (N=34) treated according to Interfant-06 in the Nordic countries – and 87 % for **MLL-neg** patients (N=27) (December 31st 2015).

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 14th April 2017
Birgitte Lausen
Chair of the NOPHO Infant Leukemia working group

Pharmacology Working Group

Chair	Goda Vaitkeviciene (LT)
Denmark	Birgitte Klug Albertsen
	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 6, 2016 and February 7, 2017.

The group continues working on the projects lasting from previous year and started several new studies. Three pilot studies had just been initiated and have an aim to collect enough data before the ALLTogether 2018 starts.

Maintenance therapy (Kjeld Schmiegelow)

Studies from the NOPHO ALL 92/2000 and 2008 protocols on pharmacokinetics/ -dynamics of MT drugs and their metabolites showed important findings. In the final model only neutrophil count during MT revealed to be a significant risk factor predictive of relapse. An absolute degree of myelosuppression is still unknown. The relapse-specific hazard ratio decreased with increasing DNA-thioguanine, being most pronounced for the patients with measurable residual leukemia day 29. GWAS study on host genome variants detected three additional significant hits in the thiopurine pathway that were associated with DNA-TGN incorporation.

Taking these findings as a background, prospective randomized clinical trial (TEAM - Thiopurine Enhanced ALL Maintenance therapy) has been developed as a pilot before ALLTogether protocol. The study is going to test MTX/6MP/6TG maintenance for non-HR patients as a possibility to reduce the relapse rate and continue exploring pharmacokinetics/ -dynamics of MT. Denmark, Norway and Finland (Helsinki) are joining the study, Germany is planning to join.

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

Another study on MT initiated over the past year with the aim to investigate if addition of allopurinol in patients with wildtype TPMT leads to increase in 6TG and reduction in 6MMP levels without increasing myelosuppression or other untoward side effects. The endpoint of the trial is pharmacological (6TG and 6MMPN levels, hematological parameters, liver function, metabolic function). GCP monitoring. Plan is to recruit 50-75 patients during maintenance-2 phase in ALL2008.
Participating countries: Sweden, Finland (Oulu).

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. Eryaspase is hypothesized to be as a promising alternative option for the patients with exhibited hypersensitivity reactions to maximize the delivery of planned asparaginase therapy. Patients 1 to 45 years old will be included. Participating countries: Denmark, Sweden, Norway, Iceland, Finland and Lithuania; pediatric and adult centers.

Study period: May 2017 to January 2019. Number of patients to be included: 25 children and 5 adults.

The study has already got through the Voluntary Harmonisation Procedure at the Heads of Medicines agencies in Denmark and is now under the process of applications submition to the competent Authorities of participating countries.

Asparaginase TDM (therapeutic dose monitoring) (Birgitte Klug Albertsen)

Asp TDM will be implemented in ALLTogether protocol with targeted trough level 100-250 IU/L. Pilot study for prospective Asp level monitoring at specific time-points for the NOPHO ALL2008 patients commenced in the end of 2016 in order to gather knowledge and experience for Asp TDM in ALLTogether. No dose adjustment except for the patients with serum asparaginase activity below the lower level of quantification for whom participation in the NOR-GRASPALL 2016 pilot study will be suggested. Patients 1 to 45 years old will be included. Participating countries: Denmark, Sweden, Norway, Iceland, Finland, Lithuania and Estonia. Authorities' approvals are covered by the approvals obtained for add-on studies.

HD MTX and Glucarpidase (Kjeld Schmiegelow/Jesper Heldrup/Torben Mikkelsen)

HD MTX guidelines recommendations for ALLTogether protocol prepared by Kjeld Schmiegelow, commented and approved by the Pharmacology group.

Jesper Heldrup took an initiative for an international collaboration with Cincinnati, US to develop a consensus guideline for treatment of delayed MTX clearance and use of Glucarpidase in children. Pharmacology group approved the collaboration.

Danish data on HD MTX toxicity (hematologic, infections, CNS, gastrointestinal, renal) and on 6MP dosing and metabolites level as predictors of toxicity are under analysis.

Pain self-assessment in ALL (Luana Leonora Jensen)

Apps for the smartphones to self-assess pain score/localisation and document measures applied has been developed and tested in Aarhus. Tested by three teenagers and their families. Was evaluated as a useful tool to improve understanding of pain by the patients and their parents, improve dialogue between families and health professionals as well as to individualize pain treatment. Larger study is planned.

NOPHO Pharmacists WG (Magnus Dahlander)

Collaboration with the Pharmacists group continues. Suggestions for future projects discussed. Different kinds of drugs incompatibility is a common phenomenon in pediatric hem/onc and can be related to the risks of changing in effect, embolism, occlusion of catheters etc. Online compatibility database (> 2500 drug combinations) is available in Gothenburg. Access is unavailable outside of VGR.

Pharmacists are not specifically certified as pediatric hem/onc pharmacists within NOPHO. Education programs and certification is needed to provide high quality services in local hospitals.

Publications

1. **Nielsen SN, Grell K, Nersting J, Abrahamsson J, Lund B, Kanerva J, Jónsson ÓG, Vaitkeviciene G, Pruunsild K, Hjalgrim LL, Schmiegelow K.** *DNA-thioguanine nucleotide concentration and relapse-free survival during maintenance therapy of childhood acute lymphoblastic leukaemia (NOPHO ALL2008): a prospective substudy of a phase 3 trial.* Lancet Oncol. 2017 Feb 28.

2. **Svahn T, Mellgren K, Harila-Saari A, Åsberg A, Kanerva J, Jónsson Ó, Vaitkeviciene G, Stamm Mikkelssen T, Schmiegelow K, Heldrup J.** *Delayed elimination of high-dose methotrexate and use of carboxypeptidase G2 in pediatric patients during treatment for acute lymphoblastic leukemia.* Pediatr Blood Cancer. 2016 Dec 14.

3. **Levinsen M, Harila-Saari A, Grell K, Jonsson OG, Taskinen M, Abrahamsson J, Vettenranta K, Åsberg A, Risteli J, Heldrup J, Schmiegelow K.** *Efficacy and Toxicity of Intrathecal Liposomal Cytarabine in First-line Therapy of Childhood Acute Lymphoblastic Leukemia.* J Pediatr Hematol Oncol. 2016 Nov;38(8):602-609.

4. **Nielsen SN, Grell K, Nersting J, Frandsen TL, Hjalgrim LL, Schmiegelow K.** *Measures of 6-mercaptopurine and methotrexate maintenance therapy intensity in childhood acute lymphoblastic leukemia.* Cancer Chemother Pharmacol. 2016 Nov;78(5):983-994.

5. **Henriksen LT, Harila-Saari A, Ruud E, Abrahamsson J, Pruunsild K, Vaitkeviciene G, Jónsson ÓG, Schmiegelow K, Heyman M, Schrøder H, Albertsen BK; Nordic Society of Paediatric Haematology and Oncology (NOPHO) group.** *PEG-asparaginase allergy in children with acute lymphoblastic leukemia in the NOPHO ALL2008 protocol.* Pediatr Blood Cancer. 2015 Mar;62(3):427-33.

6. **Nielsen SN, Frandsen TL, Nersting J, Hjalgrim LL, Schmiegelow K.** *Pharmacokinetics of 6-Thioguanine and 6-Mercaptopurine Combination Maintenance Therapy of Childhood ALL: Hypothesis and Case Report.* J Pediatr Hematol Oncol. 2015 Apr;37(3):e206-9.

7. **Henriksen LT, Nersting J, Raja RA, Frandsen TL, Rosthøj S, Schrøder H, Albertsen BK; Nordic Society of Paediatric Haematology and Oncology (NOPHO) group.** C*erebrospinal fluid asparagine depletion during pegylated asparaginase therapy in children with acute lymphoblastic leukaemia.* Br J Haematol. 2014 Jul;166(2):213-20. doi: 10.1111/bjh.12865. Epub 2014 Apr 5.

Next meeting: Tuesday September 19, 2017 in Copenhagen. The meeting in February, 2018 is planned in Vilnius.

Goda Vaitkevičienė
Chair of the NOPHO Pharmacology WG
April 15, 2017

Other Disease Working Groups

Platelet Working Group

Chair	Mimi Kjærsgaard (DK) 2013
Denmark	Birgitte Lausen
Finland	Samppa Ryhänen
Iceland	Ólafur G. Jónsson
Norway	Anne-Grete Bechensteen
	Bernward Zeller
Sweden	Ulf Tedgård
	Nadine Gretenkort
Young NOPHO	Annika Mårtensson (SE)
Associated members	Tatjana Zaharov
	Steen Rosthøj (DK)
	Minna Koskenvuo (FI) 2016
	Hanna Juntti (FI) 2017

The group met Januar 2017 in Copenhagen and discussed:

1. Recommendation for follow-up, treatment and further investigations in acute and chronic immune thrombocytopenia
2. Medical treatment with the new TPO analogues was discussed
3. Genetics in diagnosis of children suspected for platelet disease was presented by Maria Rossing, Enhed for Genomisk Medicin, Rigshospitalet, Danmark
4. The ideas and options for research projects in platelet diseases were also discussed.

The group has prepared a draft about cases of intracranial hemorrhage in children with immune thrombocytopenia (not yet published).

The discussed recommendations for ITP care will be made available to NOPHO members.

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:	Olafur Gislí Jonsson
Norway:	Ellen Ruud, Jon Helgestad
Lithuania:	Sonata Trakymiene
Sweden:	Susanna Ranta, Ulf Tedgård, Tony Frisk
Young NOPHO:	Nadine Gretenkort Andersson (SE), Kirsten Jarvis (NO)

1. **Meetings:** The Working Group meets twice a year. Last meeting was held in Copenhagen on 24th November 2016. The next meeting is planned in Stockholm on 19th May 2017.

2. **New members:** Marianne Hutchings Hoffmann (DK).

3. **Status on ongoing registration of thromboses.** In total, 150 cases (100 children (1-17,9 years old) and 50 adults (18-45 years old)) with thromboembolism (TE) are registered in NOPHO Registry (November 2016). The collection of detailed information is ongoing and it is completed in all but eight patients. The prevalence of TE is 6.9% in children, and 14 % in adults. Sweden has fewer cases than expected. The WG continues to obtain the detailed information on TE in NOPHO ALL 2008 protocol.

4. **GWAS** among TE patients with ALL is ongoing. GWAS in 54 TE cases resulted in no statistically significant founding. Data is validated in Australian and St. Jude groups, although without significant founding yet. The GWAS analysis of the updated cohort of TE patients is upcoming.

5. **TE in I-BFM.** I-BFM has invited to participate in a survey of thrombotic complications in ALL treatment. A comprehensive questionnaire was send. The aim of the questionnaire was to highlight the diversity within I-BFM and then, with the help of experts within different groups, to gain consensus and formulate a recommendation which everybody can agree on and follow. Thrombosis WG completed the questionnaire about thrombotic complications in children with ALL in NOPHO ALL 2008 protocol.

6. **New studies:**

a) Kirsten Jarvis (NO) started PhD study in autumn 2016 (main supervisor Ellen Ruud). The aims of the study are to examine i) predefined single nucleotide polymorphisms (SNPSs) associated with increased risk of TE in ALL patients with and without thromboses, ii) long-term outcomes in patients with ALL and TE.

b) Cecilie Rank started PhD study entitled "The impact of pharmacokinetics, tumor cyto- and molecular genetics on survival of adult acute lymphoblastic leukemia patients" (main supervisor Nina Toft). The first sub-study in the project has an aim to analyze risk factors for TE in adults with ALL. Cecilie aims also to update the incidence of TE and risk factors to TE in children and adults treated according NOPHO ALL 2008.

c) Erik Svensson and Ulf Tedgård initiated study on blood type as a risk factor for TE.

d) Cecilie Bjerg and Ruta Tuckuviene look in to details of pulmonary embolism in children with ALL.

7. Future plans: Research in TE in setting of the upcoming ALL-Together protocol.

Aalborg, March 2017
Ruta Tuckuviene
Chair of the NOPHO Thrombosis and Haemostasis 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
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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
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 not is opened, the recommended treatment is LCH-III:

1. *Group 1: RISK patients are treated according to the risk protocol, Arm A in LCH-III (the standard arm without methotrexate).*
2. *Group 2: LOW RISK patients receive treatment arm LR12 in LCH-III, with 12 months treatment duration.*
3. *Group 3: Multifocal bone/special site patients are treated as scheduled in LCH-III.*

LCH-IV

Note that for LCH-IV, each country will have separate coordinators.
Denmark: Karsten Nysom (karsten.nysom@regionh.dk)
Sweden: Jan-Inge Henter (jan-inge.henter@ki.se)
Norway: Monica Munthe-Kaas (uxmomu@ous-hf.no)

LCH-IV includes altogether seven interconnected studies ("strata"):
STRATUM I: First-Line Treatment
STRATUM II: Second Line Treatment for non-risk LCH
STRATUM III: Salvage Treatment For Risk LCH
STRATUM IV: Stem Cell Transplantation For Risk LCH (HSCT)
STRATUM V: Monitoring and Treatment of Isolated Tumorous and Neurodegenerative CNS-LCH
STRATUM VI: Natural History and Management of "Other" SS-LCH
STRATUM VII: Long-Term Follow-up

Summary of LCH-III, LCH-Salvage-2005, and LCH-HSCT-2006

LCH-III

The study is closed. For a summary of conclusions, see below. The study was published in 2013: *Gadner*

H, et al. Blood 2013;121:5006-14.

Risk patients: Involvement of the hematopoietic system, the liver, the lungs or the spleen:
- The treatment is prolonged to 12 months.
- A second initial treatment (wk 7 – 12) is administered if intermediate response at 6 weeks.
- A randomized study upfront, with one arm in the risk protocol including methotrexate, whereas the other arm is without methotrexate. After study closure, the arm without mtx is recommended.

Low risk patients:
- PDN and VBL, the treatment duration is randomized between 6 and 12 months. After study closure, the recommended treatment is 12 months.

Multifocal Bone Disease:
- PRD and VBL for 6 months.

Special sites: Single bone lesions with involvement of the facial bones or anterior or middle cranial fossa (temporal, sphenoidal, ethmoidal, zygomatic bone, orbital bones) with intracranial tumor extension, OR soft tissue masses that may lead to spinal cord compression
- PRD and VBL for 6 months.

LCH-Salvage-2005: This is a highly toxic regimen based on 2CdA and ARA-C. Because of the severe toxicity, all patients for whom salvage therapy is considered are suggested to be discussed with the Nordic LCH-study coordinator (Jan-Inge Henter). *The treatment is part of LCH-IV.*

LCH-HSCT-2006: This regimen is based on a reduced intensity regimen (RIC), with Campath, Fludarabine and Melphalan. *The study is part of LCH-IV.*

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, with only minor differences in comparison to the HLH-94 protocol (*Henter JI, et al, Pediatr Blood Cancer 2007;48(2):124-31*).
The formal study was closed in Dec 31, 2011.

NOTE: The Histiocyte Society recommends the HLH-94 protocol as standard of care, since it cannot be shown that HLH-2004 is superior to HLH-94. The HLH-2004 diagnostic criteria (5/8 criteria) are still recommended. HLH-2004 will be open to f-up on enrolled patients until 5 years after start of therapy or 5 years after SCT, but no later than Dec 31, 2017.

You are welcome to contact the Study Center (e-mail: Jan-Inge.Henter@ki.se or Tatiana.Greenwood@ki.se) in case of questions. For pre-treatment sampling of diagnostic value, contact Yenan.Bryceson@ki.se.

Novel Therapy Working Group

Members 2016-2017

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

The working group had a physical meeting during the annual meeting in Reykjavik. Minutes are on the NOPHO web site. This year, a meeting is planned Saturday 20 May 07:30-08:55.

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 12th, 2017
Karsten Nysom

NOPHO novel therapy working group – Overview of ongoing trials – Updated 05 April 2017 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
DC1	Dendritic cell therapy	-	Relapsed high grade glioma	3-39.9y	Stockholm	2	Stefan Holm
ITCC-015	Azacitidine	-	Relapsed MDS or JMML	1-17.9y	Aarhus	1	Henrik Hasle
CREATE EORTC-90101	Crizotinib	-	Locally advanced and/or metastatic inflammatory myofibroblastic tumour	≥15.0y	Oslo	2	Kirsten Sundby-Hall
BI 1200.120	Afatinib	-	Relapsed or refractory intra- and extracranial tumours with confirmed ErbB pathway deregulation, shown in study biomarker pre-screening	2-17.9y	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
AZA-JMML-001	Azacitidine	-	Newly diagnosed JMML	0.1-17.9y	Copenhagen, Gothenburg, Stockholm	2	Karsten Nysom, Jonas Abrahamsson, Karin Belander-Strålin

Late Effects Working Group

Members 2016		
Denmark:	Catherine Rechnitzer	catherine.rechnitzer@regionh.dk
	Niels Clausen	nc@dadlnet.dk
Finland	Riitta Niinimäki (chair)	riitta.niinimaki@oulu.fi
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	Kirsi Jahnukainen	kirsi.jahnukainen@ki.se
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NOPHO solid tumour registry	Finn Wesenberg	finn.wesenberg@rikshospitalet.no
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Meetings

The group had a meeting during the NOPHO Annual meeting, Reykjavik 28 May 2016.

Specific activities

1. The new ALLTogether. Role of late effects group in planning work

ALLTogether group is chaired by Mats Heyman. NOPHOs vision for ALLTogether has been discussed and work with other participating groups is ongoing.

2. Registration of parameters from end of therapy document into the Nordic databases

NOPHO register includes a possibility for an online follow-up registration. Increasing number of Swedish and other Nordic survivor data has been registered into the database. Individualized survivor passport can be printed from database.

3. The Nordic Centre for Fertility Preservation for Boys after Cancer treatment

Cryopreservation and storage of the samples are done in the in the national centres. The research part is centralised in Stockholm.

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.

4. Pancare activities

Pancare had 17th meeting in Lisbon, April 20–22 and 18th meeting in Erice, November 1-3, 2016.

5. Collaboration with NOBOS

Collaboration with NOBOS has started. Nurses from all five Nordic countries joined the meeting in Reykjavik. Vigdís Viggósdottir presented, how the late effect follow-up clinic has been established in Reykjavik. LTFU Resource guide (USA) and NHS, international harmonisation group and SIGN guidelines have been used. The Short Form Health Survey (SF-36) and the ICE questionnaire and psychosocial survivorship screening tool are used.

6. Late effects studies in the Nordic countries

Ongoing Nordic late effects study was presented on LE WG meeting May 2016

- Pernille Mogensen presented her PhD study protocol titled ”Risk of obesity, insulin resistance, type 2 diabetes and associated complications during and after treatment of ALL”.

Oulu, 12th of April, 2017
Riitta Niinimäki
Chair of the NOPHO Late effect working group

Childhood Cancer Etiology Working Group

Denmark	Jesper Brok
	Henrik Hasle
	Henrik Hjalgrim
	Signe Holst
	Torben Stamm Mikkelsen
	Marianne Olsen
	Kjeld Schmiegelow (DK rep)
	Astrid Sehestedt
	Ulrik Stoltze
	Morten Rytter Tulstrup
	Karin Wadt
Finland	Olli Lohi (FI rep)
	Päivi Lähteenmäki
	Atte Nikkila
Iceland	Ólafur Gísli Jónsson
Lithuania	Egle Ramanauskiene
	Jelena Rascon
Norway	Monica Munthe-Kaas (NO rep)
Sweden	Benedicte Bang
	Arja Harila-Saari
	Ann Nordgren (SE rep)
	Fulya Taylan
	Vasilios Zachariadis (chair)

Friends of the working group (mailing list):
DK: Astrid Marie Sehested, Ramneek Gupta, Rachita Yadav
FI: Laura-Maria Madanat-Harjuoja, Tekla Järviaho
IS: Laufey Tryggvadóttir
SE: David Gisselsson Nord, Per Kogner

The past year has been the first full year of this recently formed working group. Two meetings have been held - the latest in-person meeting taking place in August 2016 in Copenhagen. Members now include >20 clinicians and researchers; from pediatric oncology, clinical genetics, epidemiology and genomics.

During the year, discussions and coordinated research efforts have spanned large scale genetic studies within NOPHO - notably the STAGING project launched in Copenhagen - to linking national registry data on exposures for epidemiological studies.

Concerning rare familial and/or syndromic cases of childhood cancer, the group's internal survey, supported by recent data from the I-BFM group (Kratz et al, EJMG 2016), suggests a large proportion of these patients likely go unrecognized in clinical practice.

Short term goals of the group include:

- Continuous coordination, discussion of analytical challenges, and pooling data in prospective germline genetic studies
- Increase detection of suspected syndromic and familial cases of childhood cancer in routine care, through clinical guidelines and/or clinical support algorithms for genetic referral
- Leverage large datasets of germline genetic variation from previous NOPHO-sanctioned studies, linking them to detailed exposure data - a possibility likely unique to the NOPHO countries

The group holds regularly scheduled conference calls, the next of which will take place late spring. The next in-person meeting is expected to take place during fall 2017.

On behalf of the working group,

Vasilios Zachariadis
Stockholm, April 2017

Pharmacists Working Group

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Changes in Group Composition

Ranaa will be on maternity leave from May 2016 to May 2017 and Magnus Dahlander is appointed chair from March 2016 until the end of May 2017.

Meetings

The Pharmacists Working Group has had two physical meetings during 2016.
13th April in Stockholm (Sweden) and 11th November in Helsinki (Finland). In between these meeting we also had 5 short meetings via Skype.

Projects

The main focus of the working group was the competion of an extravasation guideline. A final version has been published on the NOPHO homepage in December 2016.

The group is also working on the following projects:

- Intravenous compatibility – discussion on how to proceed
- Safe prescribing and preparation of chemotherapy – a survey was sent to all NOPHO centers and the results will be presented at the Annual Meeting in Vilnius 2018
- Oral chemotherapy – the project has not been active during the year
- Education plan for pharmacists in pediatric oncology and hematology

Magnus Dahlander
Chair of the NOPHO Pharmacists WG
Gothenburg, April 18, 2016

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
Satu Lehtinen, physician

Iceland
Sigrún Þóroddsdóttir, nurse

Sweden
Cecilia Bartholdson, nurse
Anders Castor, physician
Sara Karlsson, nurse
Pernilla Pergert, nurse (chair)
Jennie Stigmar, nurse
Lisa Törnudd, physician (secretary)

Background

The intention of the WGE is to be a Nordic competence group in clinical ethics that offers ethics support and puts the ethical questions within paediatric oncology on the agenda, by developing and disseminating knowledge and methods. The purpose of clinical ethics support is to assist the healthcare team to deal with ethical issues in clinical practice. Lack of time and resources for ethics undermines the ability to practice ethically good care, indicating a need for clinical ethics support.[1] Healthcare professionals in childhood cancer care have a desire for inter-professional consideration including time and reflection as well as education in order to deal with ethical issues.[2] There is a need for clinical ethics support and especially ethics support provided through training because it will improve the ethical competence and facilitate handling ethical issues in practice.[3]

Training in facilitating ethics case reflection (ECR) sessions

ECR sessions are organised meetings where reflection and dialogue is performed regarding ethical issues in prospective/retrospective cases, and often involves the inter-professional team and a trained and qualified ECR facilitator.[4] ECR enables healthcare professionals to better deal with ethical issues; however, a facilitator is needed to guide the deliberation process. A research group in the Netherlands have developed a training programme, training healthcare professionals to become facilitators of ECR sessions.[4] The training has been found to support the healthcare professionals to become competent, and the programme included practising in the clinic which contributed to implementation and ownership.[4]

Organisation

During 2016 the WGE has had two 2-day meetings; one meeting was originally planned in Finland but was moved to Sweden because mainly Swedish members signed up for the meeting. The upcoming course, arranged by the WGE, will be replacing the meeting during the autumn 2017.

Meetings of the WGE during the last year

3-5 April 2016, Rimbo, Sweden
20-22 November 2016, Sigtuna, Sweden
26-28 Mars 2017, Dragør, Denmark

Upcoming meetings of the WGE

14-16 January, 2018, Lund, Sweden

Upcoming course arranged by the WGE, partly replacing regular meeting

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

Funding

Pergert (co-applicant: Anders Castor) has received grants for the WGE for 2015-2017 (PL2014-0003) from the Swedish Childhood Cancer Foundation.
The Danish Børnecancerfonden funded the 2-day meeting in Dragør.
Pergert (Co-applicants: Anders Castor, Britt-Marie Frost, Bert Molewijk) has received funding (PR2016-0020) from the Swedish Childhood Cancer Foundation for a research project entitled: "Evaluation of ethics support– What is the impact of moral case deliberations on pediatric oncology?"

Activities of the WGE during the last year

During this year the WGE has been involved in common educational and research projects but most of the ethics support is performed locally by the members. The group has continued to work with the Open Space method during meetings. Open space groups have been working on several ideas including:

- An ethics course: guiding ECR sessions, see below
- A Nordic study on communication over language barriers, moral distress and the ethical climate in childhood cancer care, see below
- An article about the experiences of working with ethics support in the clinic
- Plans for future work on genetics/palliation
- Ethics at the NOPHO/NOBOS meeting in Vilnius?

Ethics course: guiding ethics case reflection (ECR) sessions

Members of the WGE have received training to become facilitators of ECR sessions. The training has empowered the implementation of ECR sessions as an integrated part in the clinical setting and the group has found this method to be relevant for ethics support in pediatric cancer care. The training has, since 2003, been developed by the VUmc research team in Amsterdam and is now offered by the WGE in collaboration with Bert Molewijk. A course description and the invitation have been sent out to all centres in Sweden, Norway and Denmark and to WGE members i Finland and Iceland. The course will include the theory of ethics case reflections but is first and foremost a skills course. We will focus on learning by doing. During the course the participants will learn how to handle ethical concerns and they will practice guiding ECR sessions. The first part of the course will be a 3-day introduction (27-29 sept 2017) to guiding ECR sessions followed by a period in which the participants should practice in their clinical setting. The second part of the course is a 2-day follow-up (15-16 march 2018) where participants can fine-tune their knowledge and skills.

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 research project on communication over language barriers, moral distress and the ethical climate in Swedish paediatric oncology. A national cross-sectional survey has been performed with support from the members of the WGE. Healthcare professionals, at all six paediatric oncology centres in Sweden, were invited to answer the questionnaire. In total 279 participants (55 physicians, 157 registered nurses, and 66 nurse assistants) answered the questionnaire (response rate > 80%). The study will now be performed in the other Nordic countries and the Nordic project is approved, as the first study in the field of healthcare science, to be performed in the framework of NOPHO and NOBOS. Members of the WGE are involved in the process of translating and culturally adapting the English translation of a Swedish questionnaire to the Nordic languages.

Clinical ethics support activities

Local clinical ethics support performed by members includes:

- teaching ethics to nursing and medical professionals/students
- performing research projects in clinical ethics
- offering and facilitating ECR sessions in healthcare teams and/or in committees including:
    - ECR sessions on call with healthcare professionals on prospective cases using the Lunda method, Lund, Sweden (Castor, Stigmar)
    - ECR sessions on call with committee members on prospective cases using the Dilemma method, Östergötland, Sweden (Törnudd)
    - Regular ECR sessions (ethics counselling) on themes or cases with healthcare professionals using the Socratic dialogue, Lund, Sweden (Castor)
    - Both regular and on call ECR sessions on prospective/retrospective cases using the Dilemma method and the SME method, Copenhagen, Denmark (Petersen, Sehested)
    - Regular ECR sessions on prospective cases with healthcare professionals using a modified version of the dilemma method, Uppsala Sweden (Karlsson)
- serving as members of national, regional or local clinical ethics committees including:
    - Pediatric regional ethics committee, Östergötland, Sweden (Törnudd)
    - Pediatric ethical committee, Skåne University Hospital, Sweden (Castor, Stigmar)
    - Hospital ethics committee, Skåne University Hospital, Sweden (Castor)
    - Swedish ped assoc, WG for ethics and children's rights, Sweden (Törnudd, Castor)
    - Ethics committee, The Swedish Society of Medicine, Sweden (Castor)
    - Clinical ethics committee, Aarhus University Hospital, Denmark (Wendtland Edslev)
    - Clinical ethics committee of ped. dept. Oulu University Hospital, Finland (Juusola)
    - Clinical ethics committee, Landspitali, Reykjavik, Iceland (Þóroddsdóttir)
    - Clinical ethics committee of paediatrics, Rigshospitalet, Copenhagen, Denmark (Petersen, Sehested)

International meetings on ethics, attended by members in 2016

- International Conference on Clinical Ethics and Consultation (ICCEC), Washington, USA 19-20 May, 2016 (Castor).
- European Clinical Ethics Network (ECEN) 3rd Open Forum Day, Leuven, Belgium, 7 Sept, 2016 (Bartholdson, Pergert, Wendtland Edslev).

Presentations on ethics at international conferences from the group or with group members as co-authors during 2016

- 48th Congress of the International Society of Paediatric Oncology (SIOP), Dublin, Ireland, October 19-22, 2016
    - **Bartholdson, C.** (2016) Ethics case reflection sessions in childhood cancer care –conditions and obstacles. (SIOP Meeting Abstract) *Pediatric Blood & Cancer*, 63, (Suppl. 3), p.S54.
    - **Glosli, H., Bartholdson, C., Broner, T., Hauge, H.F., Karlsson, S., Pergert, P., Poroddsdottir, S., Tornudd, L., Stigmar. J., Petersen G.** (2016) Enhancing nurse/physician collaboration in ethical issues in paediatric oncology. *Pediatric Blood & Cancer*, 63, (Suppl. 3), p.S226.
    - Kienesberger, A (CCI) & **Pergert, P (SIOP Nurses)** Joint Session Parents/Nurses: Full vs selective disclosure –breaking "bad" news to teenagers diagnosed with cancer.
- International Conference on Clinical Ethics and Consultation (ICCEC), Washington, USA 19-22 May, 2016
    - **Castor, A**. The ethics of palliative sedation in children.
- European Clinical Ethics Network (ECEN) 3rd Open Forum Day, Leuven, Belgium, 7 Sept, 2016
    - **Bartholdson, C**. A proposal of a Nordic educational program of facilitating Ethics Case Reflection (ECR) sessions in pediatric cancer care
    - **Pergert, P.** Using open space to better utilize meetings for international cooperation in ethics support – experiences of the Nordic working group on ethics

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

Original articles 2016

- Svedberg, p., Einberg, E-L., Wärnestål, P., **Stigmar, J., Castor, A.**, Enskär, K., & Nygren, JM. (2016) Support from healthcare services during transition to adulthood – Experiences of young adult survivors of pediatric cancer. *European Journal of Oncology Nursing* Apr;21:105-12. DOI: 10.1016/j.ejon.2016.02.008.

Original articles 2017

- af Sandeberg M, **Bartholdson C**, Wenemark M, Lutzen 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, 14. DOI: 10.1186/s12910-017-0176-y
- **Bartholdson, C**., Molewijk, B., Lützén, K., Blomgren, K., & **Pergert, P.** (2017) Enablers and barriers in ethics case reflection sessions in childhood cancer care, *Nursing Ethics*, In press, published online March 21. DOI: 10.1177/0969733017693471

Other publications 2016

- **Törnudd, L**., Price, M., Frost, BM. (2016) Barnets rättigheter i sjukvården kan säkerställas av läkaren. *Läkartidningen* 113:D496. Lakartidningen.se 2016-07-01
- **Castor, A**. (2016) Behovet av etik i barnsjukvården. *Barnläkaren* Nr 6, Tema Etik och barns rättigheter, s.12-13.

On behalf of NOPHO/NOBOS Working Group on Ethics
Pernilla Pergert, Stockholm, April 2017

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2. Bartholdson C, Lutzen K, Blomgren K, Pergert P. Experiences of ethical issues when caring for children with cancer. **Cancer Nurs.** Mar-Apr 2015;38(2):125-132.
3. Kim S, Seo M, Kim DR. Unmet needs for clinical ethics support services in nurse: based on focus group interviews. **Nurs Ethics.** 2016:0969733016654312.
4. Stolper M, Molewijk B, Widdershoven G. Learning by doing. Training health care professionals to become facilitator of moral case deliberation. **HEC Forum**. Mar 2015;27(1):47-59.

Radiotherapy Working Group

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

The NOPHO pediatric radiotherapy working group had its 2nd annual meeting at the annual NOPHO meeting in Reykjavik in 2016. The main discussionpoint was education about pediatric radiation oncology, for radiation oncologists but also for pediatric oncologists. The working group is planning in the future to contact the NOPHO education committee for discussion.

We also discussed the importance of being more involved in other NOPHO working groups like the brain tumour-, solid tumour- and late effect group.

In the frame of the working group meeting we also organised a workshop discussing Craniospinal irradiation. With more conformal techniques from modern radiotherapy a more precise target definition is important as are definition of organs at risk. Different radiotherapy techniques were discussed in detail. Pediatric radiation oncologists, dosimetrists and physicists were present for the workshop.

The Skandion Clinic in Uppsala is running and is routinely treating pediatric patients. For treatment, patients need to be addressed to one of the university hospital for consultation and doseplanning. Also patients from other Nordic countries have been treated at the Skandion Clinic.

For 2017 we are planning a workshop about radiotherapy techniques in nephroblastoma patients at the Stockholm annual meeting.

The main subject for the working group meeting will be to discuss QUARTET, a SIOPE driven initiative for quality assurance in radiotherapy. After the meeting we will give our recommendation to the NOPHO board about the advantages/disadvantages of joining the project.

Yasmin Lassen, for the NOPHO Radiotherapy Working Group

Publications

NOPHO Publications

Publications based on cooperative projects within NOPHO.

1983
Moe PJ. *Combined Nordic Meeting of Pediatric Hematology and Oncology.* Am J Hematol Oncol 1983; 4:438.

1986
Moe PJ, Hertz H, Ludvigsson J, Siimes M, Jonmundsson G. *Feilmedisinering hos barn – profylakse og terapi.* Nordisk Medicin 1986; 101:8-9.

1987
Gustafsson G, Garwicz S, Hertz H, Jonmundsson G, Johanesson G, Moe PJ, Salmi T, Seip M, Siimes MA, Yssing M and Åhström L for NOPHO. *A Population-based study of childhood acute lymphoblastic leukemia diagnosed from July 1981 through June 1985 in the five Nordic countries.* Acta Paediatr Scand 1987; 76: 781-788.

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