Past Successes. Future Challenges in Paediatric Oncology

Sverre O Lie: Practical needs of treatment
NOPHO - history

1981    First meeting in Sweden. Start of ALL-registry

1983    Formally established

1984    First common protocol (AML)

1991    First common ALL protocols

From 1995 ⇒ Most children on NOPHO or international protocols

Lie, 2005
Survival by 5-year time periods 1985-1999
All children < 15 years of age, solid tumours (n=7372)

0.81 1995-99 (n=2491)  0.77 1990-94 (n=2512)  0.71 1985-89 (n=2369)

P<0.0001
Fig. 2g) Survival by diagnostic groups 1985-2004
Subgroups II-VI

Lymphomas: 0.88 +/- 0.02 (5yr) n=1664
CNS tumours: 0.75 +/- 0.01 (5yr) n=3937
Neuroblastoma: 0.62 +/- 0.03 (5yr) n= 816
Retinoblastoma: 0.96 +/- 0.02 (5yr) n= 356
Wilms' tumour: 0.89 +/- 0.02 (5yr) n=760

p<0.001
Fig. 2c) Survival by 5-year time periods 1985-2004
Non-Hodgkin’s lymphoma

1985-89: 0.77 +/- 0.07 (5yr) n=163
1990-94: 0.76 +/- 0.06 (5yr) n=181
1995-99: 0.88 +/- 0.04 (5yr) n=233
2000-04: 0.89 +/- 0.05 (5yr) n=187
Fig. 2d) Survival by 5-year time periods 1985-2004
Neuroblastoma – infants (<1 years of age)

1985-89: 0.71 +/- 0.10 (5yr) n=78
1990-94: 0.82 +/- 0.09 (5yr) n=77
1995-99: 0.91 +/- 0.07 (5yr) n=76
2000-04: 0.91 +/- 0.07 (5yr) n=72

p=0.003
NOPHO ALL 1992 (92-2003), Non-B cell ALL 1-<15 years at diagnosis (infants excluded). Overall results by country (n=1656).

**EFS**

- 0.77 (10yr) n=18, 3 events (Iceland)
- 0.75 (10yr) n=437, 89 events (Denmark)
- 0.74 (10yr) n=392, 80 events (Norway)
- 0.74 (10yr) n=468, 101 events (Finland)
- 0.73 (10yr) n=759, 160 events (Sweden)

NOPHO ALL 1992 (92-2003), Non-B cell ALL 1-<15 years at diagnosis (infants excluded). Overall survival by country (n=1656).

**pSurv**

- 0.86 (10yr) n=759, 81 dead (Sweden)
- 0.85 (10yr) n=468, 55 dead (Finland)
- 0.84 (10yr) n=166, 2 dead (Iceland)
- 0.83 (10yr) n=392, 50 dead (Norway)
- 0.81 (10yr) n=437, 62 dead (Denmark)
NOPHO-AML-TRIALS 7/1984-12/2003
Protocol patients. Down excluded (n=507)

p-Survival

N-84 vs. N-88  n.s.
N-84 vs. N-93  p<0.01
N-84 vs. N-93  p<0.01

0.64 +/- 0.03 (n=303) NOPHO-93 (3)
0.42 +/- 0.05 (n=108) NOPHO-88 (2)
0.35 +/- 0.05 (n=96) NOPHO-84 (1)
EFS NOPHO-AML 2004 vs. 1993 protocol
2007-10-30

pEFS 2 years
2004: 0.63
1993: 0.57
Childhood cancer survival in Europe

G. Gatta*, I. Corazziari†, C. Magnani‡, R. Peris-Bonet‡, P. Roazzi‡, C. Stiller¸ and the EUROCARE Working Group†

Background: EUROCARE-3 collected data from 35 population-based cancer registries in 30 countries on 24 520 European children aged from 0 to 14 years diagnosed with malignancy in the period 1990-1994.

Methods: Five-year survival between countries was compared for all malignancies and for the major diagnostic categories, adjusting for age, and estimated average European survival weighting for differences in childhood populations.

Results: For all cancers combined, survival variation was large (45% in Estonia to 90% in Iceland), and was generally low (60-70%) in eastern Europe and high (75%) in Switzerland, Germany and the Nordic countries (except Denmark). The Nordic countries had the highest survival for four of the seven major tumor types: nephroblastoma (92%), acute lymphoid leukemia (85%), CNS tumors (73%) and acute non-lymphocytic leukemia (62%). The eastern countries had lowest survival: 80% for Hodgkin’s disease, 71% for nephroblastoma, 68% for acute lymphoid leukemia, 61% for non-Hodgkin’s lymphomas, 57% for central nervous system (CNS) tumors and 24% for acute non-lymphocytic leukemia.

Conclusions: The Nordic countries represent a survival gold standard to which other countries can aspire. Since most childhood cancers respond well to treatment, survival differences are attributable to differences in access (including treatment and follow-up) and to differences in the selection of patients for treatment. Most differences are due to access and application of standard treatments which probably vary markedly with country.

Key words: childhood tumours; Europe; population-based study; survival variation

"The Nordic countries represent a survival gold standard to which other countries can aspire"
DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 4 April 2001
on the approximation of the laws, regulations and administrative provisions of the Member States
relating to the implementation of good clinical practice in the conduct of clinical trials on
medicinal products for human use

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE
EUROPEAN UNION,

Having regard to the Treaty establishing the European
Community, and in particular Article 95 thereof;

Having regard to the proposal from the Commission (1);

Having regard to the opinion of the Economic and Social
Committee (2),

Acting in accordance with the procedure laid down in Article
251 of the Treaty (3),

(3) Persons who are incapable of giving legal consent to
clinical trials should be given special protection. It is
incumbent on the Member States to lay down rules to
this effect. Such persons may not be included in clinical
trials if the same results can be obtained using persons
capable of giving consent. Normally these persons
should be included in clinical trials only when there are
grounds for expecting that the administering of the
medicinal product would be of direct benefit to the
patient, thereby outweighing the risks. However, there is
a need for clinical trials involving children to improve
the treatment available to them. Children represent a
vulnerable population with developmental, physiological
and psychological differences from adults, which make
age- and development- related research important for
their benefit. Medicinal products, including vaccines, for
children need to be tested scientifically before wide-
The EU Clinical Trials Directive: 3 years on

The EU clinical trials directive came into force in May, 2004, with the aim of simplifying the trial application process and providing a common set of regulations for member states. But some believe the directive has badly misfired, increasing costs and bureaucracy. Richard Hoey reports.

Lars Welzing will think hard before setting up another drug trial. Welzing, a specialist in paediatric intensive care at the University of Cologne, Germany, has just spent close to 3 years getting a modest, 20-patient study off the ground, and right now, he cannot face going through that grind all over again. His problem has been the EU Clinical Trials Directive, which was designed to streamline the trial application process and harmonise by rigorous new insurance policies, which are reportedly more expensive than those that had been previously required.

Supporters of the directive claim it has been successful at driving up standards and point to the benefits of a single set of trial application procedures across the EU. A spokesperson for the UK’s Medicines and Healthcare Products Regulatory Agency (MHRA) insists that the aim of the directive was of red tape has increased. Another promise was harmonisation, but I am not sure this has been achieved. And I am not sure there have been many positive effects for safety [although] there have been some."

A key concern is that although the directive was supposed to introduce a single set of regulations, in practice EU states have implemented it in various of ways, some more rigidly than others. Countries differ in their

Richard Hoey The Lancet 369: 1777-78
Frequency of the Prescription of Drugs in a Children's Hospital during a Five-Week Period, According to Whether Use of the Drug Was Unapproved, Off Label, or Approved

't Jong, G W et al, NEJM 343: 1125, 2000
Off-label Drug Use in Hospitalized Children

Samir S. Shah, MD; Matthew Hall, PhD; Denise M. Goodman, MD, MS; Pamela Feuer, MD; Vidya Sharma, MBBS, MPH; Crayton Fargason, Jr, MD; Daniel Hyman, MD, MMM; Kathy Jenkins, MD, MPH; Marjorie L. White, MD; Fiona H. Levy, MD; James E. Levin, MD, PhD; David Bertoch, MHA; Anthony D. Slonim, MD, DrPH


31 tertiary care hospitals – data from Jan 1 to Dec 31, 2004

Off-label use of at least one drug: 78.7% of 355,409 patient

Representing 270 mill USD (40.5%) of total dollars spent on drugs
Medicines for children

A brighter future
for child health

The EU Paediatric Regulation


The objective of the Paediatric Regulation is to improve the health of children in Europe by:

- facilitating the development and availability of medicines for children aged 0 to 17 years,
- ensuring that medicines for use in children are of high quality, ethically researched, and authorised appropriately,
- improving the availability of information on the use of medicines for children,

without:

- subjecting children to unnecessary trials,
- or delaying the authorisation of medicines for use in adults.

The Paediatric Regulation dramatically changes the regulatory environment for paediatric medicines in Europe. The leaflet on the right provides a brief overview of the key aspects of the changes in which the European Medicines Agency has a role to play.
New rewards, incentives and obligations for pharmaceutical companies

For unauthorised medicinal products

As of July 2008, marketing-authorisation applications for new products not authorised in the EU prior to 26 January 2007 will have to include the results of studies conducted in the paediatric population, in compliance with an agreed PIP, unless the EMEA has granted a deferral or waiver for their provision. Waivers may be granted for medicines intended to treat conditions that occur only in adults (a list of such conditions has been agreed by the PDCO), and for medicines that may be unsafe or ineffective, or do not offer significant therapeutic benefit and/or fulfill a therapeutic need in children.

Once authorisation is obtained in all EU Member States and study results are included in the product information, the medicine is eligible for six months’ patent extension.

Orphan-designated medicinal products are subject to the same requirements as above, and benefit from two years of market exclusivity in addition to the 10-year exclusivity awarded under the EU Orphan Regulation.

Some medicines, such as generics, are exempt from these requirements.

For authorised, patented medicinal products

As of 26 January 2009, the requirements described above also apply to applications to vary a marketing authorisation to add a new indication (including paediatric), a new pharmaceutical form, or a new route of administration. In these cases, the PIP or waiver must cover all existing and new indications, formulations and routes of administration.

Paediatric-use marketing authorisation (PUMA)

Off-patent medicines developed specifically for paediatric use and with an appropriate formulation can benefit from a new marketing authorisation — the paediatric-use marketing authorisation. Provided the product development follows an agreed PIP, the company will benefit from 10 years of data protection.

A new Paediatric Regulation entered into force in the EU on 26 January 2007.

The objective of the Paediatric Regulation is to improve the health of children in Europe by:

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- ensuring that medicines for use in children are of high quality, ethically researched, and authorised appropriately,

- improving the availability of information on the use of medicines for children without:

- subjecting children to unnecessary trials,

- or delaying the authorisation of medicinal products for use in adults.


Better medicines for children

Overview of the European Medicines Agency’s role in the European regulatory environment for paediatric medicines

Need more information?

Visit the ‘Medicines for children’ section of the EMEA website.

Questions on paediatric issues may be submitted by e-mail to: paediatrics@emea.europa.eu

Website: www.ema.europa.eu


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Medicines for children

Introduction
The EU Paediatric Regulation
Paediatric Committee
Guidance for applicants
Scientific advice
Paediatric investigation plans (PIPs), waivers and modifications
Pedestrianised marketing authorisations (PUMAs)
Compliance
Submission of paediatric studies
Opinions and decisions on PIP applications
Background
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Paediatric clinical trials
Priority list of off-patient medicines
Scientific guidance
Presentations
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Priority list of off-patient medicines

Thanks to the Paediatric Regulation, funding of studies into off-patient medicinal products (i.e. those not covered by a patent or supplementary protection certificate) is available. This funding, provided through the EU Framework Programmes, should cover the development of off-patient medicinal products with a view to the submission of an application for a paediatric use marketing authorisation.

In order to ensure that funds are directed into research of medicinal products with the highest need in the paediatric population, the EMEA and the Paediatric Working Party (PWP), in consultation with paediatric learned societies, have drawn up the following priority list of off-patient products for which studies are required:

- Priority list for studies into off-patient paediatric medicinal products (updated 14/06/07) (EMEA/1979/2/2007)

For further information on when and how to apply to the 7th Framework Programme for off-patient medicines developed for children, please refer to:

- FP7 Cooperation Work Programme: Health (on the Cordis website).

The second call for proposals has a deadline of 18 September 2007. See page 52 of the abovementioned document for details on this call for proposals.

A workshop on the funding through FP7 of studies into off-patient medicines developed for children was hosted at the EMEA on 6 June 2007. Further information can be found under 'Workshops'.

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Send all queries regarding the Web content to info@emea.europa.eu
Send all queries regarding the Web functionality to EMASEndnavicko
UPDATED PRIORITY LIST - REVISED
FOR STUDIES INTO OFF-PATENT PAEDIATRIC MEDICINAL PRODUCTS

NOTE and DISCLAIMER
The list includes only products considered to be off-patent, i.e. not covered by a patent or a supplementary protection certificate. Information on the off-patent status is not guaranteed by EMEA. It should be noted that information on the authorisation status as well as on available paediatric formulations of medicinal products is very limited and not available for all European Member States. Users of this list are therefore advised to check the patent and authorisation status of the medicinal products of interest.

The methodology used to establish the list was based as much as possible on evidenced based medicine. It is however acknowledged that identification of priorities for research into medicinal products for paediatric use is partly based on subjective criteria and that identified priorities may change over time.
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<thead>
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<th>CONDITION</th>
<th>PRODUCTS</th>
<th>SPECIFIC NEEDS</th>
<th>AGE GROUP</th>
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<tr>
<td>Migraine (prevention of recurrence)</td>
<td>Beta blockers</td>
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<td>Children and adolescents</td>
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<td>Topiramate</td>
<td>Data on PK, efficacy and safety Age appropriate formulation</td>
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<td>Seizure/Epilepsy (generalised and partial seizures)</td>
<td>Clobazam</td>
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<td>Malignant diseases (please note that there may be authorised indications in children licensed for these products)</td>
<td>Actinomycin D</td>
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<td>Cisplatin</td>
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Best Pharmaceuticals for Children Act (BPCA) Activities at NICHD

The Best Pharmaceuticals for Children Act (BPCA) Program is a major activity for the Obstetric and Pediatric Pharmacology Branch (OPPB), a component of the Center for Research for Mothers and Children at the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD).

OPPB is responsible for developing and supporting a comprehensive national research and training effort to increase the knowledge base for understanding how to appropriately treat disease during pregnancy, infancy, and childhood using pharmaceuticals that are appropriately tested within their target populations. NICHD activities related to BPCA are intended to improve pediatric drug therapeutics through preclinical and clinical testing that lead to drug labeling change.
NICHD currently has 4 studies on children with cancer:

• Dactinomycin
• Vincristine
• Methotrexate
• Daunorubicin

Taylor-Zapata & Mattison 2007
 Improving recruitment to clinical trials for cancer in childhood

Prof Kathy Pritchard-Jones FRCPCH, Mary Dixon-Woods DPhil, Marianne Naafs-Wilstra MA and Maria Grazia Valsecchi PhD

Section of Paediatric Oncology/Children's Unit, The Institute of Cancer Research and Royal Marsden NHS Foundation Trust, Sutton, Surrey, UK

Department of Health Sciences, University of Leicester, Leicester, UK

International Confederation of Childhood Cancer Parent Organisations (ICCCPO), Netherlands

Department of Clinical Medicine and Prevention, University of Milano-Bicocca, Milan, Italy


Refers to: Poor accrual of teenagers and young adults into clinical trials in the UK

The Lancet Oncology, Volume 9, Issue 4, April 2008, Pages 306-307

Jeremy S Whelan, Lorna A Fern

PDF (36 K)
TEDDY published the article entitled “Challenges in prescribing drugs for children with cancer”.

Paediatric oncology has achieved high cure rates despite the limited availability of drugs that have been specifically studied for use in children with cancer. Efficacy of these drugs has received more attention than their safety, but permanent side-effects in growing children need to be considered. An absence of pharmacokinetic data, dose-defining studies, schedules defined by age, and appropriate formulations can lead to underdosing or overdosing in specific age groups, resulting in a potential lack of benefit, development of resistance, and increased adverse drug reactions. These major clinical concerns have promoted initiatives in Europe since 2003 regarding the need for a Paediatric Regulation, aimed at improving the risk–benefit ratio of such drugs in children and providing the legal framework to overcome the limitations of the past. However, to undertake the appropriate studies of these drugs in this setting, financial support is essential. Europe is now showing its commitment to overcome the present difficulties of drug prescribing for children with cancer by introducing measures that will encourage new public-private partnerships. All those involved, including researchers, paediatric oncologists, learned societies, regulatory agencies, national agencies, and pharmaceutical companies, need to become more familiar with the opportunities opened up by the new regulation, which is aimed at providing an increased cooperation between researchers and drug developers for the benefit of children.

Friday, 15th February 2006

Target Audience • All
Field • All
Source: [http://www.thelancet.com](http://www.thelancet.com)
Author: TEDDY