Autologous Stem Cell Transplantation in NEUROBLASTOMA

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S² IRP – Children’s Cancer Research Institute
Studies and Statistics for Integrated Research and Projects

SIOPEN International Society of Paediatric Oncology – Europe Neuroblastoma Group
Neuroblastoma
EBMT Data

- Lessons learned
EBMT PWP-Solid Tumors

>8000 Patients with Autologous SCT
Selected Data

Neuroblastoma (n=3425)
Ewing Tumours (n=1489)
CNS tumours (n=909)
Soft tissue sarcoma (n=856)
Wilms tumours (n=333)
Germ cell tumours (n=267)
Osteosarcomas (n=215)
others (n=1671)
EBMT Neuroblastoma DATA
Age and Survival

Relative hazard rate (vs. < 1)

5-years pSU
EBMT Neuroblastoma - Age

3350 pts. with autologous SCT

<table>
<thead>
<tr>
<th>Age Group</th>
<th>n</th>
<th>5-yrs.pSU ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 year</td>
<td>32</td>
<td>0.66 ± 0.09</td>
</tr>
<tr>
<td>1 - 2 years</td>
<td>406</td>
<td>0.60 ± 0.03</td>
</tr>
<tr>
<td>2 – 14 years</td>
<td>2781</td>
<td>0.34 ± 0.01</td>
</tr>
<tr>
<td>14 - 18 years</td>
<td>59</td>
<td>0.23 ± 0.07</td>
</tr>
<tr>
<td>&gt; 18 years</td>
<td>72</td>
<td>0.25 ± 0.08</td>
</tr>
</tbody>
</table>
EBMT- Neuroblastoma
First Line Treatments 2741 pts

CR1  n=1200  5-yrs.pSU=0.43±0.02
PR, VGPR  1416  0.36±0.02
SD  53  0.30±0.07
PRD  72  0.19±0.08

p<0.001
EBMT Neuroblastoma

2333 Patients HDT Regimens/autologous SCT

![Graph showing survival probabilities with error bars for different regimens: Busulfan/Melphalan without CYC/TTP (n=343), 5-yrs.pSU=0.48±0.03, Busulfan/Melphalan with CYC/TTP (n=90), 0.40±0.05, Melphalan alone (n=234), 0.34±0.03, Melphalan+ (n=287), 0.34±0.04, TBI (n=322), 0.34±0.03, others (n=125), 0.41±0.05. The p-value is less than 0.001.](image)
EBMT- Neuroblastoma
Auto vs Allo SCT

Autologous SCT: n=3754, 5-yrs. pSU=0.37±0.01
Allogeneic SCT: n=81, 0.24±0.05

p=0.0023
## EBMT Neuroblastoma DATA

**MVA 3421 Patients**

<table>
<thead>
<tr>
<th>Status prior HDT (vs. CR1)</th>
<th>pvalue</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR, VGPR</td>
<td>0.001</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>SD</td>
<td>0.018</td>
<td>1.5</td>
<td>1.1</td>
</tr>
<tr>
<td>PRD</td>
<td>&lt;0.001</td>
<td>2.5</td>
<td>1.9</td>
</tr>
<tr>
<td>CR2</td>
<td>0.350</td>
<td>1.1</td>
<td>0.9</td>
</tr>
<tr>
<td>sens. Relapse</td>
<td>&lt;0.001</td>
<td>2.1</td>
<td>1.7</td>
</tr>
<tr>
<td>res. Relapse</td>
<td>&lt;0.001</td>
<td>3.2</td>
<td>2.3</td>
</tr>
<tr>
<td>RU</td>
<td>&lt;0.001</td>
<td>4.2</td>
<td>2.6</td>
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<table>
<thead>
<tr>
<th>Source</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td>SC allogen vs. autologous</td>
<td>0.031</td>
<td>1.4</td>
<td>1.0</td>
</tr>
<tr>
<td>Stem cells (BM vs. PSC)</td>
<td>0.014</td>
<td>1.1</td>
<td>1.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HDT Regimens vs. BUMEL</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Busulfan/Melphalan+CYC-TTP</td>
<td>0.458</td>
<td>1.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Melphalan</td>
<td>0.003</td>
<td>1.4</td>
<td>1.1</td>
</tr>
<tr>
<td>Melphalan±</td>
<td>0.025</td>
<td>1.3</td>
<td>1.0</td>
</tr>
<tr>
<td>TBI</td>
<td>&lt;0.001</td>
<td>1.5</td>
<td>1.2</td>
</tr>
<tr>
<td>Others</td>
<td>0.514</td>
<td>1.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Sequentiell</td>
<td>0.020</td>
<td>1.3</td>
<td>1.0</td>
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</table>

**Statistics:** Ulrike Pötschger
### NEUROBLASTOMA & Auto SCT

**Proven Indication:**
3 Randomized Studies in First Line Treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Author</th>
<th>Question</th>
<th>No Pts</th>
<th>5 yrs EFS</th>
<th>5 yrs OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENSG1</td>
<td>Ped.B &amp; C Pritchard 2005</td>
<td>Mel (R1) vs. Non (R2) (unpurged BM)</td>
<td>R1: 24 R2: 24</td>
<td>38 % 17 %</td>
<td>46 % 21 %</td>
</tr>
<tr>
<td>CCG</td>
<td>N Engl J Med Matthay 1999</td>
<td>CEM –TBI(R1) vs. cCHT (R2) +/- 13 cis RA (purged BM)</td>
<td>R1:189 R2:190</td>
<td>34 % 22 %</td>
<td>43 % 44 %</td>
</tr>
<tr>
<td>GPOH</td>
<td>Lancet Oncol Berthold 2005</td>
<td>MEC (R1) vs. Maintenance (R2) (ASCR) +/- Immunotherapy</td>
<td>R1:149 R2:146</td>
<td>53 % 30 %</td>
<td>68 % 53 %</td>
</tr>
</tbody>
</table>
High Dose Melphalan in the Treatment of Advanced Neuroblastoma: Results of a Randomised Trial (ENSG-1) by the European Neuroblastoma Study Group

Jon Pritchard, FRCP, FRCPCH, Simon J. Cotterill, BA, Shirley M. Germond, John Imeson, PhD, Jan de Kraker, MD, PhD, and David R. Jones, PhD

C. Event-Free survival by treatment arm in patients age > 1 yr with stage 4 disease (n=48)

D. Survival by treatment arm in patients age > 1 yr with stage 4 disease (n=48)
CCG 3891 Treatment Schema

TREATMENT OF HIGH-RISK NEUROBLASTOMA WITH INTENSIVE CHEMOTHERAPY, RADIOThERAPY, AUTOLOGOUS BONE MARROW TRANSPLANTATION, AND 13-CIS-RETINOIC ACID

Katherine K. Matthay, M.D., Judith G. Villablanca, M.D., Robert C. Seeger, M.D., Daniel O. Stram, Ph.D., Richard E. Harris, M.D., Norma K. Ramsay, M.D., Patrick Swift, M.D., Hiroyuki Shimada, M.D., C. Thomas Black, M.D., Garrett M. Brodeur, M.D., Robert B. Gerbing, M.A., and C. Patrick Reynolds, M.D., Ph.D., for the Children’s Cancer Group®

Myeloablative megatherapy with autologous stem-cell rescue versus oral maintenance chemotherapy as consolidation treatment in patients with high-risk neuroblastoma: a randomised controlled trial

Frank Berthold, Joachim Boos, Stefan Burdach, Rudolf Erttmann, Günter Henze, Johann Herrmann, Thomas Klingebiel, Bernhard Kremens, Freimut H Schilling, Martin Schrappe, Thorsten Simon, Barbara Hero
Neuroblastoma- High Risk?  
Black or White?
GOAL: To develop a uniform classification system for pre-treatment risk stratification that can be compared internationally.
INRG Staging System

- **INRG Stage L1**: Locoregional tumor without IDRFs
- **INRG Stage L2**: Locoregional tumor with one or more IDRFs
- **INRG Stage M**: Distant metastatic disease (except Ms)
- **INRG Stage Ms**: INRG Stage L1 or L2 tumor with metastatic disease confined to skin and/or liver and/or bone marrow
LNESG1 Chair Jean Michon
Localised Resectable Neuroblastoma

- **Aims**
  - Evaluation of benefit of surgical risk factors (SRF)
  - Collect clinical, histological and biological data on NBL stage 2 without MYCn amplification
  - Collect data on other subsets of localised NBL without MYCN amplification

- LNESG1-study showed that primary surgery in the presence of surgical risk factors associated with
  - lower complete excision rate
  - greater risk of surgery-related complications
  - **Cecchetto et al J Clin Oncol 2005;23:8483-9:**
    Unresectable tumours have an inferior prognosis to resectable tumours 92% vs. 87% 5year RFS
<table>
<thead>
<tr>
<th>INRG Stage</th>
<th>Age</th>
<th>Diagnostic Category Tumor Grade</th>
<th>MYCN</th>
<th>Unb 11q aberration</th>
<th>Ploidy</th>
<th>Pre-treatment Risk Group</th>
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<tbody>
<tr>
<td>L1</td>
<td></td>
<td>GN maturing GNB intermixed</td>
<td>NA</td>
<td></td>
<td></td>
<td>A Very Low</td>
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<tr>
<td></td>
<td></td>
<td>Any, except GN maturing or GNB intermixed</td>
<td>NA</td>
<td></td>
<td></td>
<td>B Very Low</td>
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<tr>
<td></td>
<td></td>
<td>Amp</td>
<td></td>
<td></td>
<td></td>
<td>H Intermediate</td>
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<tr>
<td>L2</td>
<td>&lt;18m</td>
<td>GN maturing GNB intermixed</td>
<td>NA</td>
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<td>A Very Low</td>
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<tr>
<td></td>
<td></td>
<td>Any, except GN maturing or GNB intermixed</td>
<td>NA</td>
<td>No</td>
<td></td>
<td>D Low</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
<td></td>
<td>I Intermediate</td>
</tr>
<tr>
<td></td>
<td>&gt;18m</td>
<td>GNB nodular, differentiating NB, differentiating</td>
<td>NA</td>
<td></td>
<td></td>
<td>E Low</td>
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<tr>
<td></td>
<td></td>
<td>GNB nodular, poorly differentiated or undifferentiated</td>
<td>NA</td>
<td>Yes</td>
<td></td>
<td>J Intermediate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NB, poorly differentiated or undifferentiated</td>
<td>NA</td>
<td>(Any)</td>
<td></td>
<td>J Intermediate</td>
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<td></td>
<td>(Any)</td>
<td>Amp</td>
<td></td>
<td></td>
<td></td>
<td>N High</td>
</tr>
<tr>
<td>M</td>
<td>&lt;18m</td>
<td>NA</td>
<td>Hyperdiploid</td>
<td>F Low</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Diploid</td>
<td>G Low</td>
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<td></td>
<td>Amp</td>
<td>O High</td>
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<td></td>
<td>&gt;18m</td>
<td>Amp</td>
<td></td>
<td></td>
<td></td>
<td>P High</td>
</tr>
<tr>
<td>MS</td>
<td>&lt;18m</td>
<td>NA</td>
<td>No</td>
<td>C Very Low</td>
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<td></td>
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<td></td>
<td>Yes</td>
<td>K Intermediate</td>
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<td></td>
<td></td>
<td>Amp</td>
<td></td>
<td></td>
<td></td>
<td>Q High</td>
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</table>
## INRG Pre-treatment Groups

<table>
<thead>
<tr>
<th>Pre-treatment Group</th>
<th>5-year EFS</th>
<th>Proportion of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low</td>
<td>&gt; 85%</td>
<td>28.2</td>
</tr>
<tr>
<td>Low</td>
<td>75-%&lt;85%</td>
<td>26.8</td>
</tr>
<tr>
<td>Intermediate</td>
<td>50-%&lt;75%</td>
<td>9.0</td>
</tr>
<tr>
<td>High</td>
<td>&lt;50%</td>
<td>36.1</td>
</tr>
</tbody>
</table>
INRG Publications

☐ Cohn SL et al

☐ Monclair T et al
The International Neuroblastoma Risk Group (INRG) staging system: an INRG Task Force report.

☐ Bagatell R et al
Significance of MYCN amplification in international neuroblastoma staging system stage 1 and 2 neuroblastoma: a report from the International Neuroblastoma Risk Group database.
Neuroblastoma
Current Definition of Neuroblastoma High Risk Disease

- Stage 4: > 18 months
- Stage 4: 12 – 18 months
  - Intensity based on biological risk
  - Discussion: MycNA only or unfavourable by newer definitions (Structural abnormalities – CGH, MLPA; unfavourable gene expression signatures)
- Myc N amplified tumours:
  - Any age and consensus for stages 2 to 4
- AYA population: > 12 yrs including adult age
Current Milestones
in High Risk Stage 4 NBL Therapy

- Induction
  - COG (Kushner N7-modified, Topo - Cyc)
  - Rapid Cojec
  - GPOH (N5/N6/N7)
  - Surgery

- MAT
  - CEM (MEC)
  - BUMEL
  - Tandem MAT

- Radiotherapy (miBG)
  - 21 Gy – 36gy (primary / others sites ?)
  - miBG
    - HD- mIBG (+/- Topotecan or Irinotecan), 1-2 x SCR
    - 2 weeks prior MAT as above

- MRD Treatments
  - 13 cis RA
  - Anti GD2 mABs (+/- Il2 a/o +/- GM- CSF)
NEUROBLASTOMA

High Risk Disease
Current Approaches & Questions

Trials of National & International Groups
- COG
- SIOPEN
- GPOH
A3973 High-Risk Disease Trial
Chair: Kreissman

- Closed to accrual 02/10/06 (N=453)
- Primary Objective: Purging of PBSCs will result in improved EFS
- Results presented ASCO 2007

**Diagram:**
- Purged (N=225) vs. Unpurged (N=228) PBSC
- NS

**Processes:**
- Harvest
- Surgery
- Local Radiation
- CEM + PBSC
- ANBL0032
High-Risk Neuroblastoma Treated With Tandem Autologous Peripheral-Blood Stem Cell–Supported Transplantation: Long-Term Survival Update

Schema of induction and high-dose therapy before autologous stem-cell rescue

Results

George, R. E. et al.
J Clin Oncol; 24:2891-2896 2006

- 97 patients with high-risk neuroblastoma
- 1994 to 2002
- 5 yr PFS (A) 47% (95% CI, 36% to 56%)
- 5 yr OS (B) 60% (95% CI, 48% to 69%)
ANBL0052: Randomized comparison of single versus tandem myeloablative consolidation

Chair: J. Park
Vice-Chairs: L. Diller and S. Grupp

AT#1
CTX
Topo
Cisplatin
VP16
CTX
VCR
DOX

AT#2
CEM

On-Study

PBSC
Harvest

Surgery

Randomization
Time point

XRT*

*Increased dose for <VGPR (local)

ANBL0032
Neuroblastom & $^{131}$I-MiBG
Radiolabeled metaiodobenzylguanidine for the treatment of neuroblastoma

Steven G. DuBois, Katherine K. Matthay*

Department of Pediatrics, UCSF School of Medicine, Box 0106, San Francisco, CA 94143-0106, USA

Received 15 April 2008; received in revised form 1 May 2008; accepted 6 May 2008
## HD-mIBG and Auto-SCT

### Relapsed or Refractory Neuroblastoma

<table>
<thead>
<tr>
<th>Reference(s)</th>
<th>Number of patients</th>
<th>$^{131}$I-MIBG Activity per cycle</th>
<th>Combination regimen</th>
<th>Response rate</th>
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<tbody>
<tr>
<td><strong>Nonmyeloablative approaches</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[75,76]</td>
<td>5</td>
<td>100 mCi × 2 doses, 1 week apart</td>
<td>Cisplatin 1 day prior to $^{131}$I-MIBG</td>
<td>80%</td>
</tr>
<tr>
<td>[77]</td>
<td>16</td>
<td>200 mCi on Day 10</td>
<td>Cisplatin and cyclophosphamide on Days 1–4 with or without vincristine and etoposide</td>
<td>75%</td>
</tr>
<tr>
<td>[78]</td>
<td>8</td>
<td>12 mCi/kg on Days 1 and 15</td>
<td>Topotecan on Days 1–5 and 15–19</td>
<td>NR</td>
</tr>
<tr>
<td>[79]</td>
<td>27</td>
<td>200 mCi</td>
<td>Hyperbaric oxygen for 4–5 days after $^{131}$I-MIBG</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Myeloablative approaches</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>[82]</td>
<td>5</td>
<td>300 mCi on Day 0</td>
<td>Carboplatin and melphalan on Days 7–12 with or without vincristine and etoposide</td>
<td>NR</td>
</tr>
<tr>
<td>[83]</td>
<td>5</td>
<td>To yield 2 Gy whole-body dose</td>
<td>Melphalan and 12.6 Gy total body irradiation on Days 10–15</td>
<td>NR</td>
</tr>
<tr>
<td>[84]</td>
<td>11</td>
<td>Median of 15.7 mCi/kg −1 week prior to chemotherapy</td>
<td>Carboplatin, etoposide and melphalan on Days −8 to −2</td>
<td>36%</td>
</tr>
<tr>
<td>[85]</td>
<td>12</td>
<td>12 mCi/kg on Day −21</td>
<td>Carboplatin, etoposide, melphalan on Days −7 to −4</td>
<td>67%</td>
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<tr>
<td>[86]</td>
<td>17</td>
<td>Median of 7 mCi/kg</td>
<td>Busulfan and melphalan 7–10 days after $^{131}$I-MIBG</td>
<td>47%</td>
</tr>
<tr>
<td>[87]</td>
<td>22</td>
<td>12–18 mCi/kg on Day −21</td>
<td>Carboplatin, etoposide, melphalan on Days −7 to −4</td>
<td>27%</td>
</tr>
</tbody>
</table>

Response rate refers to percent of evaluable patients with at least a partial response to therapy as their best overall response. NR=Not reported.
Fig. 1. (A) Overall (OS) and event-free survival (EFS) of patients with relapsed or refractory neuroblastoma treated on a Phase II study of high-dose \( ^{131}\text{I-MIBG} \) [45]. (B) Overall and EFS of patients with refractory neuroblastoma treated on a Phase I study of high-dose \( ^{131}\text{I-MIBG} \) followed by myeloablative chemotherapy with carboplatin, etoposide and melphalan [87]. (Figures reprinted with permission from the American Society of Clinical Oncology.)

Fig. 2. Increased detection of neuroblastoma metastases on an MIBG scan obtained 5 days following 15 mCi/kg \( ^{131}\text{I-MIBG} \) (B) compared to a routine diagnostic scan obtained 24 h after the administration of 5 mCi \( ^{123}\text{I-MIBG} \) (A). Arrows indicate tumor uptake seen on the post-treatment scan and not definitely seen on the diagnostic scan.
ANBL07P1: $^{131}$I-MIBG for Newly Diagnosed High-Risk Patients
Chair: Weiss

**Eligibility:**
(a) High Risk Neuroblastoma:
(b) MIBG avid disease at diagnosis

**Study design:**
Will parallel ANBL0532, with FOLLOWING modifications:
(a) Addition of $^{131}$I-MIBG into CEM BMT regimen.
(b) Use 3973-like radiation doses for local control
mIBG and topotecan in murine xenografts

Days after tumour implantation

- control
- mIBG alone
- Topotecan alone
- M + T together
- M pre T
- M post T
# Schedule of administration

| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 |
|-----|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| $^{131}$I-mIBG | $\uparrow$ 444 MBq kg$^{-1}$ | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Dosimetry | Measurement of whole body absorbed dose [x Gy] | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Topotecan | $\uparrow\uparrow\uparrow\uparrow\uparrow\uparrow$ 0.7mg m$^2$/ day | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| PBSC | | | | | | | | | | | | | | | | | | | | | | | | $\uparrow$ | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

Activity calculated to give whole body absorbed dose of 4-x Gy

Measurement of whole body absorbed dose [x Gy]

Measurement of whole body absorbed dose
MATIN Pilot Data

- Eligibility
  - primary resistant high-risk neuroblastoma
  - relapsed high-risk neuroblastoma

- Accrual 40 patients (Phase I/II population)
  - 28 relapsed stage 4 disease
  - 12 poor response to induction chemotherapy

- 39 completed treatment as planned
  - 1 toxic death
  - 7/12 proceeded to potentially curative therapy
SI OPEN
SI OP EUROPE Neuroblastoma Group

19 Current Member Countries

- Austria
- Belgium
- Denmark
- France
- Greece
- Hungary
- Israel
- Italy
- Ireland
- Norway
- Portugal
- Poland
- Serbia
- Slovakia
- Spain
- Sweden
- Switzerland
- Czech Republic
- United Kingdom
A randomized Study (R0 / R1/ R2) for High Risk Neuroblastoma

- Stage 4 > 1a
- MycN-Amplification Stages 2 and 3 > 1a
- MycN Amplification < 1a

- Planned recruitment 1400 patients
- 16 European Countries
- https://www.siopen-r-net.org/
HR-NBL 1 / SIOPEN
High Risk Study - 2002

Hypotheses

■ Does the addition of GCSF reduce episodes of febrile neutropaenia in induction therapy?

■ Does carboplatin, etoposide and melphalan as myeloablative therapy result in a superior 3 year event free survival than busulphan melphalan?

■ Does the addition of anti GD2 to 13 cis retinoic acid result in a superior 3 year event free survival than 13 cis retinoic acid alone?
**INDUCTION: Rapid COJEC**

- CBDCA 750 mg/m²
- VP16 175 mg/m²
- VCR 1.5 mg/m²
- CDDP 80 mg/m²
- CYC 1050 mg/m²
- VP16 175 mg/m²
- VCR 1.5 mg/m²

**Staging**
- local MRI / CT /US, mIBG, BM(aspirate/biopsy)
- BM aspirates only / local ultrasound
- local MRI / CT and mIBG post surgery

**Rx**
- **R1**
  - BU 4x150mg/m²/d p.o.
  - L-PAM 140mg/m²/d short i.v.
  - G-CSF 5 µg/kg

**MRD Treatment**
- Ch 14.18 anti GD2 AB iv
  - 20mg/m²/day x 5 days every 4 weeks

- **R2B ACTIVATED**
  - Days after Start of 13 cis RA

**Rx**
- **R2A**
  - 13 cis retinoic acid po
  - 160mg/m²/day x 14 days every 4 weeks
## Accrual numbers by country (2009/03/29)

*Hint:* The table can be sorted by selecting the corresponding table header.

<table>
<thead>
<tr>
<th>Country</th>
<th>Patients registered</th>
<th>Randomised patients</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>R0</td>
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<tr>
<td>National Data Centre UK for HRNBL1</td>
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<td>National Data Centre IT for HRNBL1</td>
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<td>National Data Centre DK for HRNBL1</td>
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<tr>
<td>National Data Centre HU for HRNBL1</td>
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<td>3</td>
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<tr>
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<tr>
<td>National Data Centre CH for HRNBL1</td>
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<td>1</td>
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<tr>
<td><strong>Totals:</strong></td>
<td><strong>1203</strong></td>
<td><strong>239</strong></td>
</tr>
</tbody>
</table>
**HR-NBL1 / SIOPEN**

R0 - Febrile Episodes (CTC2-4)

Mean 0.6 febrile episodes in 8 cycles  \( p = 0.013 \)

<table>
<thead>
<tr>
<th>GCSF-</th>
<th>117</th>
<th>116</th>
<th>115</th>
<th>115</th>
<th>115</th>
<th>114</th>
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<th>110</th>
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<tbody>
<tr>
<td>GCSF+</td>
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<tr>
<th>GCSF-</th>
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<td>116</td>
<td>113</td>
<td>112</td>
<td>111</td>
<td>109</td>
</tr>
</tbody>
</table>
Results R0 - Rapid Cojec

- Recommendations for G-CSF
  - Less febrile episodes
  - Less days in hospital (42 vs. 32)
  - Less days with antibiotics (23 vs. 14)
  - Lower CTC scores for infections and fever (score/cycle)
  - Less hematological toxicity (WBC, ANC)
  - Less gut toxicity (stomatitis, nausea/vomiting, constipation)
  - No adverse effects on stem cell aphaeresis nor on the MAT randomization rate


- Infants with neuroblastoma (stage 2, 3, 4, and 4s) and MYCN gene amplification
  - CBDCA/VP16 – CADO induction
  - delayed surgery,
  - MAT: Bu-Mel conditioning regimen
  - local radiotherapy

- 46 infants / 35 infants were eligible;
  - 97% had metastatic spread
  - 24 infants had stage 4,
  - 10 infants had stage 4s

- 2 OS: 30% (SE, 0.08)
  - Median survival time of 12 months, and 23 deaths due to disease.
  - treatment was well tolerated with no deaths as a result of toxicity or severe toxicity.
  - 30% of the patients experienced disease progression or did not respond to IC
  - 10/16 receiving megatherapy are alive

Overall survival: 30%
SD: 0.08
SEER Data - AYA

Average annual percentage change in relative survival for all invasive cancers
Lower survival rate compared to younger counterparts
EBMT Neuroblastoma
Age cut off 10 yrs

p-value=0.001

<table>
<thead>
<tr>
<th>Age Group</th>
<th>pts</th>
<th>Events</th>
<th>5- yrs. pEFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 10</td>
<td>3517</td>
<td>1920</td>
<td>0.33±0.01</td>
</tr>
<tr>
<td>10-18</td>
<td>205</td>
<td>137</td>
<td>0.10±0.03</td>
</tr>
</tbody>
</table>
SCT for AYA Neuroblastoma

I. Yaniv: WPW Room F4 12:00!

- Above 10 years
- Failure to achieve a complete response
- Slow progression
- Very poor survival in stage 4
- Histology – Ganglioneuroblastoma
- Genetics – Not MYCN amplification, 1p deletion, 11q aberration
- COG-SIOPEN study

NBL Pilot Study for AYA with HR-NB

COG/SIOPEN

Eligible: Age ≥10y with INRG L2 or M disease
Conclusion & Future Challenges

- Despite the improved long-term survival rates seen in patients treated with HDT /autologous SCT more than 50% of children with high-risk disease still are not cured

- Ways for further improvements:
  - New induction strategies – Randomisations needed! (benefits of addition of Topotecan, Irinotecan, Temozolomide, …..) How to integration targeted agents to induction?
  - Dose intensity - MAT strategies (single vs. double- TANDEM HDT/SCT)
  - Incorporation of HD-mIBG strategies
Conclusion & Future Challenges

- Eradication of minimal residual disease

- **Use of differentiating agents**
  - Optimisation of 13 cis retinoic acid
  - Fenretinide – drug formulation & availability

- **Role for Immunotherapy**
  (Anti GD2 ch14.18 (+/- IL2, +/- GM CSF), fusionproteins, vaccination, .....

- **Addition of anti-angiogenics**
  (vinblastine, bevacizumab, small- molecule VEGF inhibitors)

- **Role and availability of inhibitors**
  Mitotic inhibitors (ABT 751), MTOR inhibitors,
  IGF1R inhibitors, Neurotrophin pathway inhibitors (Lestaurtinib),
  Proteosome inhibition (Velcade), HDAC inhibition (SAHA)

- Detection of molecular aberrations by high-throughput approaches needs to be prioritized in an effort to identify new therapeutic targets