Long-term outcomes in survivors of neuroblastoma

Paul Nathan, MD, MSc
Director, AfterCare Program
Division of Hematology/Oncology
Objectives

- Describe the long-term health of NBL survivors
- Explain the importance of risk-based screening in NBL survivors
- Introduce a new study assessing outcomes in survivors of high-risk NBL
Excellent outcomes for low and intermediate risk disease

Pediatric Blood and Cancer, 2012
The high-risk neuroblastoma success story

- Laboratory discoveries
- Clinical trials:
  - Stem cell transplant
  - Biologic agents (e.g. retinoic acid)
  - Immunotherapy
  - Supportive care

What are late effects?

- Chronic health problems following cancer and cancer therapy
- Often do not become clinically apparent until years or decades after the cancer
- Can be physical or psychological
- Can impact quality of life, psychosocial outcomes (school, jobs, relationships)
Physical Late Effects

- Organ dysfunction (heart, lungs etc.)
- Growth & development
- Second cancers
- Fertility
Psychosocial Late Effects

- Mental health
- Body image issues
- Chronic symptoms
- Social Interaction
What Causes Late Effects?

- Location
- Metastases

Tumor

- Age at diagnosis
- Sex
- Genetics

Treatment

- Chemotherapy
- Radiation
- Surgery

Child’s attributes

Lifestyle and health behaviors

SickKids
A first look at NBL survivors’ health: Childhood Cancer Survivor Study (CCSS)

- 954 NBL survivors treated b/w 1970-86
- No risk stratification or staging information
- Medical records, surveys of survivors and siblings
- Average age at questionnaire: 17 years

Laverdière et al. JNCI 2009
CCSS: Chronic health problems and new cancers

At 20 years after NBL diagnosis:
  - Any chronic health problem: 41%
  - Sensory deficit: 9%
  - Endocrine condition: 8%
  - Musculoskeletal complication: 8%

At 25 years after NBL diagnosis
  - 3.5% had developed a new cancer

Laverdière et al. JNCI 2009
Low & intermediate risk NBL

High cure rates but frequent late effects → changes in upfront therapies

Success of “reduction of therapy” trials:

• Avoidance of radiotherapy, surgery
• Reduction in cumulative chemotherapy doses
• Based on exposures → small late effects risk
High-risk NB

What are the long-term outcomes in survivors of high-risk NBL treated with modern therapy?

- Retinoic acid
- Immunotherapy
- Tandem transplants
- Antibody therapy
- MIBG
Current treatment strategy for high-risk NBL

**Induction**
- Surgery
- Chemotherapy
  - Stem-cell harvest

**Consolidation**
- Myeloablative chemotherapy
  - XRT
  - Stem-cell infusion

**Post-Consolidation**
- Immunotherapy and cytokines plus isotretinoin

**Induction Chemotherapy Agents**
- **Cisplatin**
- Cyclophosphamide
- Doxorubicin
- Etoposide
- Topotecan
- Vincristine

**Myeloablative regimens**
- Cisplatin/etoposide/melphalan
- Busulfan/melphalan
- Thiotepa/cyclophosphamide plus cisplatin/etoposide/melphalan

**Immunotherapy Regimens**
- ch 14.18 mAB + subq GM-CSF / ch 14.18 mAB + IV IL-2
- ch 14.18/CHO mAB + subq IL-2
Current treatment strategy for high-risk NBL

<table>
<thead>
<tr>
<th>Induction</th>
<th>Consolidation</th>
<th>Post-Consolidation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>Myeloablative chemotherapy</td>
<td>Immunotherapy and cytokines plus isotretinoin</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>XRT</td>
<td></td>
</tr>
<tr>
<td>Stem-cell harvest</td>
<td>Stem-cell infusion</td>
<td></td>
</tr>
</tbody>
</table>

**Induction Chemotherapy Agents**
- Cisplatin
- Cyclophosphamide
- Doxorubicin
- Etoposide
- Topotecan
- Vincristine

**Myeloablative regimens**
- Cisplatin/etoposide/melphalan
- Busulfan/melphalan
- Thiotepa/cyclophosphamide plus cisplatin/etoposide/melphalan

**Immunotherapy Regimens**
- ch 14.18 mAB + subq GM-CSF / ch 14.18 mAB + IV IL-2
- ch 14.18/CHO mAB + subq IL-2
Current treatment strategy for high-risk NBL

Induction
- Surgery
- Chemotherapy
  - Stem-cell harvest

Induction Chemotherapy Agents
- Cisplatin
- Cyclophosphamide
- Doxorubicin
- Etoposide
- Topotecan
- Vincristine

Consolidation
- Myeloablative chemotherapy
- XRT
  - Stem-cell infusion

Myeloablative regimens
- Cisplatin/etoposide/melphalan
- Busulfan/melphalan
- Thiotope/cyclophosphamide plus cisplatin/etoposide/melphalan

Post-Consolidation
- Immunotherapy and cytokines plus isotretinoin

Immunotherapy Regimens
- ch 14.18 mAb + subq GM-CSF / ch 14.18 mAb + IV IL-2
- ch 14.18/CHO mAb + subq IL-2

Navin R. Pinto et al. JCO 2015;33:3008-3017
Current treatment strategy for high-risk NBL

**Induction**
- Surgery
- Chemotherapy
  - Stem-cell harvest

**Consolidation**
- Myeloablative chemotherapy
  - XRT
- Stem-cell infusion

**Post-Consolidation**
- Immunotherapy and cytokines plus isotretinoin

**Induction Chemotherapy Agents**
- Cisplatin
- Cyclophosphamide
- Doxorubicin
- Etoposide
- Topotecan
- Vincristine

**Myeloablative regimens**
- Cisplatin/etoposide/melphalan
- Busulfan/melphalan
- Thiotepa/cyclophosphamide plus cisplatin/etoposide/melphalan

**Immunotherapy Regimens**
- ch 14.18 mAB + subq GM-CSF / ch 14.18 mAB + IV IL-2
- ch 14.18/CHO mAB + subq IL-2
High-risk NBL survivors have significant endocrine burden

Short stature/growth abnormalities

- Prevalence 7-100%
- Evident even in those not exposed to total body irradiation
- Often not growth hormone responsive
- Premature growth plate closure by 13-cis-retinoic acid? Spine radiation?

Hypothyroidism

- Exposure to therapeutic radiation
- Potential damage from diagnostic exposure to radioactive iodine tracers ($^{131}$I-MIBG)

Delayed/abnormal pubertal development
COG ALTE15N2

Goals:

1. Determine the risk (and risk factors) of organ dysfunction, growth impairment, abnormal pubertal development, neurobehavioral dysfunction and second cancer.

2. Understand how these health problems impact quality of life.

3. Develop a cohort and biobank for future research.
Study Design

• Cross-sectional, non-therapeutic study
  • Target enrollment: N=367

• Full-day clinical evaluation at a COG institution

• Exposures
  • Primary, relapse and second treatments
  • Number of MIBG scans

• Outcomes
  • Health conditions confirmed by health care provider, laboratory and radiologic studies
  • Health-related quality of life and psychological outcomes measured by questionnaires of parents and patients

• Biobank

• St. Baldrick’s Foundation Consortium Award (2015-2020)
Lifelong risk-based follow-up care

AfterCare ensures:

• Health maximized
• Health risks minimized
• Quality of life optimized
Ontario’s Aftercare Network
Goals of Aftercare

- **Education**
  - Treatment received
  - Risks and risk factors

- **Surveillance**
  - Early detection of problems
  - Development of risk profiles
  - Anticipatory guidance
  - Modifiable risk factors
  - Health promotion and maintenance

- **Empowerment/Advocacy**
  - Education
  - Awareness

- **Transitional Needs**
  - Identify adult medical home
  - Provide information to new provider
  - Facilitate transfer of care
  - Assess readiness
Goals for Aftercare

• Education
  • Treatment received
  • Risks and risk factors

• Surveillance
  • Early detection of problems
  • Development of risk profiles
  • Anticipatory guidance
  • Modifiable risk factors
  • Health promotion and maintenance

• Empowerment/Advocacy
  • Education
  • Awareness

• Transitional Needs
  • Identify adult medical home
  • Provide information to new provider
  • Facilitate transfer of care
  • Assess readiness
Goals for Aftercare

- **Education**
  - Treatment received
  - Risks and risk factors

- **Surveillance**
  - Early detection of problems
  - Development of risk profiles
  - Anticipatory guidance
  - Modifiable risk factors
  - Health promotion and maintenance

- **Empowerment/Advocacy**
  - Education
  - Awareness

- **Transitional Needs**
  - Identify adult medical home
  - Provide information to new provider
  - Facilitate transfer of care
  - Assess readiness
Goals for Aftercare

- Education
  - Treatment received
  - Risks and risk factors

- Surveillance
  - Early detection of problems
  - Development of risk profiles
  - Anticipatory guidance
  - Modifiable risk factors
  - Health promotion and maintenance

- Empowerment/Advocacy
  - Education
  - Awareness

- Transitional Needs
  - Identify adult medical home
  - Provide information to new provider
  - Facilitate transfer of care
  - Assess readiness
Aftercare Multidisciplinary Teams

- Oncologist or Radiation oncologist
- Nurse Coordinator
- Nurse Practitioner
- Endocrinologist
- Neuropsychologist
- Psychologist
- Social Worker
- Dietician
- SAVTI counselor
166 sections detailing exposure-based potential late effects and screening recommendations
Grading of evidence linking exposure to potential late effect
Second (adult) cancer screening recommendations for standard and high risk groups
Health Links for patient education
## Chemotherapy

<table>
<thead>
<tr>
<th>Sec #</th>
<th>Therapeutic Agent(s)</th>
<th>Potential Late Effects</th>
<th>Risk Factors</th>
<th>Highest Risk Factors</th>
<th>Periodic Evaluation</th>
<th>Health Counseling Further Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>Anthracycline Antibiotics</td>
<td>Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mitoxantrone*</td>
<td>Cardiac toxicity, Cardiomyopathy, Arrhythmias, Subclinical left ventricular dysfunction (syndromic dysfunction as assessed by ECHO or MUGA)</td>
<td>Host factors, Female sex, Black or African descent, Younger than age 5 years at time of treatment</td>
<td>History, SO2, DOE, Orthopnea, Chest pain, Palpitations, if under 25 years: Abdominal symptoms (nausea, vomiting), (Yearly)</td>
<td>Health Links, Heart Health, Counseling</td>
</tr>
</tbody>
</table>

*Although Mitoxantrone technically belongs to the anthraconisone class of anti-tumor antibiotics, it is related to the anthracycline family and is included here because of its cardiotoxic potential.

Info Link: Use the following formulas to convert to doxurubicin/doxorubicin li troid equivalents prior to calculating total cumulative anthracycline dose.

- Epirubicin: Multiply total dose x 0.67
- Idarubicin: Multiply total dose x 5
- Mitoxantrone: Multiply total dose x 3.5

Note: There is a paucity of literature to support isosteric dose conversion; however, the above conversion factors may be used for convenience in order to gauge screening frequency. Clinical judgment should ultimately be used to determine indicated screening for individual patients.

### Risk Factors

- Treatment Factors
  - Combined with radiation involving the heart
  - Combined with other cardiotoxic chemotherapy:
    - Cyclophosphamide conditioning for HCT
    - Amphotere

- Medical Conditions
  - Obesity
  - Congenital heart disease
  - Febrile illness
  - Pregnancy

- Health Behaviors
  - Isometric exercise
  - Smoking
  - Drug use (e.g., cocaine, diet pills, phentermine, methamphetamine)

- Chest Radiation
  - ≥ 30 Gy
  - Longer time elapsed since treatment

### Highest Risk Factors

- Host Factors
  - Female sex
  - Black or African descent
  - Younger than age 5 years at time of treatment

- Treatment Factors
  - Higher cumulative anthracycline doses:
    - Patients 18 years or older at time of treatment:
      - ≥ 550 mg/m²
    - Patients younger than 18 years:
      - ≥ 300 mg/m²
    - Any dose in infants

### Periodic Evaluation

- History
  - SO2
  - DOE
  - Orthopnea
  - Chest pain
  - Palpitations
  - If under 25 years:
    - Abdominal symptoms (nausea, vomiting)
    - (Yearly)

Info Link: Electrolyte intolerance is uncommon in young patients (< 25 years). Abdominal symptoms (nausea, emesis) may be observed more frequently than extracellular edema or chest pain in young patients.

### Physical

- Cardiac murmur
- S3, S4
- Increased P2 sound
- Pericardial rub
- Rales
- Wheezes
- Jugular venous distention
- Peripheral edema
- (Yearly)

### Screening

- ECHO or MUGA for evaluation of systolic function
  - Baseline entry to long-term follow-up, then periodically based on age at treatment, history of chest radiation and cumulative anthracycline dose
  - (see table on next page)
- EKG (include evaluation of QTC interval)
  - Baseline entry into long-term follow-up
  - Repeat as clinically indicated

### Considerations for Further Testing and Intervention

Cardiac evaluation in patients with subclinical abnormalities on screening evaluations, left ventricular dysfunction, dysrhythmia, or prolonged QTc interval. Consider excess risk of isometric exercise program in any high-risk patient (defined as needing screening every 1 or 2 years). Females only.

Additional cardiac evaluation in patients who received ≥ 200 mg/m² or ≥ 300 mg/m² plus chest radiation who are pregnant or planning pregnancy. Evaluation to include an echocardiogram before and periodically during pregnancy (especially during third trimester) and monitoring during labor and delivery due to risk of cardiac failure.

### System = Cardiovascular

<table>
<thead>
<tr>
<th>Score</th>
<th>Cardiac failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**COG LTFU Guidelines – Page 33**

**Version 2.0 – March 2006**
<table>
<thead>
<tr>
<th>Age at Treatment*</th>
<th>Radiation with Potential Impact to the Heart§</th>
<th>Anthracycline Dose†</th>
<th>Recommended Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year old</td>
<td>Yes</td>
<td>Any</td>
<td>Every year</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>&lt;200 mg/m²</td>
<td>Every 2 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥200 mg/m²</td>
<td>Every year</td>
</tr>
<tr>
<td>1-4 years old</td>
<td>Yes</td>
<td>Any</td>
<td>Every year</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>&lt;100 mg/m²</td>
<td>Every 5 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥100 to &lt;300 mg/m²</td>
<td>Every 2 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥300 mg/m²</td>
<td>Every year</td>
</tr>
<tr>
<td>≥5 years old</td>
<td>Yes</td>
<td>&lt;300 mg/m²</td>
<td>Every 2 years</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>≥300 mg/m²</td>
<td>Every year</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;200 mg/m²</td>
<td>Every 5 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥200 to &lt;300 mg/m²</td>
<td>Every 2 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥300 mg/m²</td>
<td>Every year</td>
</tr>
<tr>
<td>Any age with decrease in serial function</td>
<td></td>
<td></td>
<td>Every year</td>
</tr>
</tbody>
</table>
## Risks & Surveillance

<table>
<thead>
<tr>
<th>Potential Risk</th>
<th>Exposure</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hearing loss</td>
<td>Cisplatin</td>
<td>Audiograms</td>
</tr>
<tr>
<td>Learning problems</td>
<td>Radiation to head/OMA NBL</td>
<td>School Performance</td>
</tr>
<tr>
<td>Heart problems</td>
<td>Doxorubicin/radiation</td>
<td>Echocardiograms</td>
</tr>
<tr>
<td>Breathing Problems</td>
<td>Radiation to chest</td>
<td>Pulmonary function tests</td>
</tr>
<tr>
<td>Kidney/bladder</td>
<td>Cisplatin/cyclophosphamide/abdominal radiation</td>
<td>Urinalysis</td>
</tr>
<tr>
<td>Hormone abnormalities</td>
<td>Cyclophosphamide/Radiation</td>
<td>Blood work</td>
</tr>
<tr>
<td>Infertility</td>
<td>Cyclophosphamide/Melphalan/Radiation</td>
<td>Discuss semen analysis and oocyte preservation</td>
</tr>
<tr>
<td>Second Cancers</td>
<td>Radiation</td>
<td>Annual exam/Specific screening</td>
</tr>
</tbody>
</table>
Cancer Prevention
Lifestyle Recommendations

Skin cancers:
- Sunscreen for all
- Coverage of XRT sites
- Avoidance of tanning beds & tanning practice

Colon cancer:
- Diet recommendations: fresh fruit & veg, fiber

Breast (& colon):
- Weight maintenance

Lung cancer:
- Smoking cessation & avoidance

Cervical cancer (H&N, rectal):
- HPV vaccination

Liver (Hepatocellular carcinoma):
- Hepatitis B vaccination
POGO Survivor Care Plan

- Personalized treatment summary, exposure-driven risks and follow-up plan
- Late effects and healthy lifestyles
- Emotional health and well-being
- Education and employment
- Survivor links booklet
- Portable *Passport to Health*
Acknowledgements...

- Tara Henderson
- Eleanor Hendershot