Introduction to Pediatric Neoplasms

Program Outline

- Introduction
- Types of Pediatric Neoplasms
- Signs and Symptoms
- Causes and Risk Factors
- MPH Rules – Solid Tumors
- MPH Rules – Heme/Lymph Neoplasms
- Staging Pediatric Tumors
- Collaborative Stage Data Collection System
- Treatment Options
- Future Webcasts
- Q&A

Introduction


Introduction

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Building on 50 Years of Cooperative Research

<table>
<thead>
<tr>
<th>PEDiATRIC CliNICAL TRIAL ENROLLMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 and younger</td>
</tr>
<tr>
<td>10 and younger</td>
</tr>
<tr>
<td>10 to 15</td>
</tr>
<tr>
<td>Adolescents aged 15 to 19</td>
</tr>
</tbody>
</table>
**Introduction**

**Building on 50 Years of Cooperative Research**

**1940s**
- Remission achieved in pediatric leukemia patients using an antifolate drug, aminopterin

**1950s**
- 6-mercaptopurine treats pediatric acute lymphoblastic leukemia
- Combination chemotherapy introduced by NCI researchers
- NCI begins funding pediatric cooperative clinical trials

**1960s**
- Dactinomycin first used to treat Wilms tumor
- National Wilms Tumor Study Group formed and multi-modality therapy first used in pediatric patients (surgery, radiation, chemos)
- Prophylaxis of occult central nervous system leukemia markedly improves outcome for children with ALL
- Laminar airflow technology creates "sterile rooms" for chemotherapy patients

**1970s**
- Intergroup Rhabdomyosarcoma Study Group Committee pioneers repetitive-course, multi-agent chemotherapy for advanced rhabdomyosarcoma
- First successful bone marrow transplant (BMT) for leukemia
- Knudson describes the 2-hit hypothesis for retinoblastoma to describe genetics and heredity of cancer

**1980s**
- First tumor-suppressor gene, in retinoblastoma, is cloned
- MYCN identified as a target of genomic amplification in neuroblastoma
- Adjuvant chemotherapy improves relapse-free survival for pediatric osteosarcoma
- Different treatment for lymphoblastic lymphoma vs other lymphomas are realized
- Platinum-based chemo improves response rates in pediatric germ cell tumors
- National Marrow Donor Program begins

**1990s**
- Autologous BMT and 13-cis-retinoic acid improve survival for neuroblastoma
- Characteristic fusion genes identified for pediatric solid tumors
- Combined ifosfamide and etoposide improve outcomes for Ewing sarcoma
- Long-term survival rates of 80-90% achieved for advanced Burkitt lymphoma
- Genetic test for thyroid cancer enables prophylactic thyroidectomy before age 2
- NCI-funded Childhood Cancer Survivors Study begins
Introduction

Building on 50 Years of Cooperative Research

2000s

- Four legacy research groups merge as the Children’s Oncology Group (COG)
- COG publishes long-term follow-up guidelines for pediatric cancer survivors
- Imatinib added to intensive chemotherapy improves early outcomes for Ph+ ALL
- 5-year survival rates for children with cancer (age 0-14 years) approach 80%

Pediatric Cancer Research

Pediatric Cancer Registries

Children’s Oncology Group

http://cancer.gov/

Childhood Cancer Survivor Study

- Diagnosis 1970-1986
- 20,000 person cohort
- Survival at least 5 years
- Chance for long-term effects increase over time
- > 70% at least 1 chronic illness related to treatment
- > 25% have 3 or more chronic illnesses related to tx

http://cancer.gov/

Children’s Oncology Group

- The world’s childhood cancer experts

http://cancer.gov/

Childhood Cancer Survivor Study

- Kidney Disease
- Second Cancers
- Cognitive Dysfunction
- Cardiovascular Disease
- Endocrine Abnormalities
- Musculoskeletal Conditions

Long-Term Active Follow-Up is CRITICAL...
**Childhood Cancer Survivor Study**

<table>
<thead>
<tr>
<th>Health Effects</th>
<th>Childhood Cancer Survivor Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioral</td>
<td>- Any modification in patient's behavior or development potential in adulthood.</td>
</tr>
<tr>
<td>Physiological</td>
<td>- Any change in patient's physiology or body function.</td>
</tr>
<tr>
<td>Psychological</td>
<td>- Any change in patient's psychological or emotional well-being.</td>
</tr>
</tbody>
</table>

**Pediatric Cancer Registries**

- COG – Childhood Cancer Research Network
- CDC NPCR – National Childhood Cancer Registry
- FAPTP – Florida Consortia Pediatric Cancer Registry
- Cancer Site/Type Specific Registries
- Bone Marrow Donor Registries
- National Children’s Study
- Other

**Florida Association of Pediatric Tumor Programs**

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**Types of Pediatric Neoplasms**

- Hematopoietic: leukemia, lymphoma
- Neuroblastoma
- Wilms tumor
- Retinoblastoma
- Nephroblastoma
- Neurofibromatosis
- Leukemia
- Lymphoma
- Brain tumors
- Soft tissue tumors
- Bone tumors
- Breast cancer
- Gastrointestinal tumors
- Gynecological tumors
- Thyroid cancer
- Endocrine tumors
- Renal cell carcinoma
- Hepatobiliary tumors
- Pancreatic cancer
- Kidney cancer
- Bladder cancer
- Uterine cancer
- Testicular cancer
- Ovarian cancer
- Prostate cancer
- Breast cancer
- Gastrointestinal tumors
- Gynecological tumors
- Thyroid cancer
- Endocrine tumors
- Renal cell carcinoma
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http://cancer.gov/
Major Types of Pediatric Neoplasms

Childhood Cancer Incidence Rates (SEER) by ICCC Group 2001-2004 – All Sex, All Race

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Rate per 1,000,000 Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>44.2</td>
</tr>
<tr>
<td>Brain/CNS</td>
<td>27.4</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>23.2</td>
</tr>
<tr>
<td>Soft Tissue</td>
<td>12.0</td>
</tr>
<tr>
<td>Germ Cell</td>
<td>11.8</td>
</tr>
<tr>
<td>Bone</td>
<td>8.9</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>7.6</td>
</tr>
<tr>
<td>Renal</td>
<td>6.0</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Note: Rates are per 1,000,000 population

http://cancer.gov/

Major Types of Pediatric Neoplasms

Lymphoid Neoplasms
- Hodgkin Lymphoma
- Non-Hodgkin Lymphoma
- Acute Lymphocytic Leukemia

Myeloid Neoplasms
- Myeloid Leukemia Associated with Down Syndrome
- Chronic Myeloid Leukemia
- Acute Myeloid Leukemia

http://cancer.gov/

Major Types of Pediatric Neoplasms

Brain and CNS – Non-Germ Cell Tumors
- Astrocytoma
- Glioblastoma
- Ependymoma
- Medulloblastoma
- PNET – Primitive Neuroectodermal Tumor

Brain and CNS – Germ Cell Tumors
- Atypical Teratoid/Rhabdoid Tumor
- Mixed Germ Cell Tumor
- Embryonal Tumor

http://cancer.gov/

Source: The Simpsons – Homer Brain X-Ray

http://www.montekids.org/services/neurosurgery/neurologicaldisorders/brain_tumor/

Source: http://www.vivo.colostate.edu/hbooks/pathphys/endocrine/hypopit/anatomy.html

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Major Types of Pediatric Neoplasms

<table>
<thead>
<tr>
<th>Pediatric Sarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarcoma – Bone</td>
</tr>
<tr>
<td>Ewing Sarcoma – Undifferentiated pPNET</td>
</tr>
<tr>
<td>Soft Tissue</td>
</tr>
<tr>
<td>Brain/CNS</td>
</tr>
<tr>
<td>pPNET – pPNET with Neural Differentiation</td>
</tr>
<tr>
<td>Soft Tissue</td>
</tr>
</tbody>
</table>

Ewing Family of Tumors

- 9473/3 Ewing Sarcoma – Bone
- 9364/3 pPNET – pPNET with Neural Differentiation
- 9365/3 Askin Tumor – Soft Tissue
- 9360/3 Ewing Sarcoma – Soft Tissue
- 9260/3 Ewing Sarcoma – Extra Osseous
- pPNET – pPNET
- pPNET – Soft Tissue
- Soft Tissue
- Bone

Signs and Symptoms

- Continued, unexplained weight loss
- Headaches, often with early morning vomiting
- Increased swelling or persistent pain in bones, joints, back, or legs
- Lump or mass, especially in the abdomen, neck, chest, pelvis, or armpits
- Development of excessive bruising, bleeding, or rash
- Constant infections
- A whitish color behind the pupil
- Nausea which persists or vomiting without nausea
- Constant tiredness or noticeable paleness
- Eye or vision changes which occur suddenly and persist
- Recurrent or persistent fevers of unknown origin

Causes and Risk Factors

- Genetic Abnormalities
- Ionizing Radiation Exposure
- History of Chemotherapy and/or Radiation Therapy
- Infectious Agents Including Prenatal Infection
  - HIV
- Environmental Including Parental Exposure
  - Toxins
  - Solvents
  - Pesticides
  - Magnetic Fields
- Cancer Predisposition Syndromes
  - Down Syndrome
  - Li-Fraumeni Syndrome
  - Neurofibromatosis
  - Gerlin Syndrome
**Causes and Risk Factors**

- Environmental factors
- Genetic factors
- Hormonal changes
- Infectious agents
- Radiation exposure

**MPH Rules – The Basics**

1. Is the condition reportable?
2. How many cases do I abstract?
3. How do I code the primary site?
4. How do I code the histology?
5. How do I code the grade?

**MPH Rules – Solid Tumors**

- Identify the Primary Site
- Use Multiple Primary Rules
  - General Rules
  - Site-Specific Rules
    - Brain – Malignant
    - Brain – Benign/Borderline
    - Melanoma
    - Kidney
    - N/A – breast, colon, head & neck, lung, urinary system

**MPH Rules – Solid Tumors**

- Histology Coding Rules
- What Drives Treatment Decisions?
- Pediatric Pathology – Characteristics and Terminology
- Tumor Characteristic Testing
- Tumor Marker Testing
- Genetic Testing
- Profile

**MPH Rules – Heme/Lymph Neoplasms**

- Hodgkin Lymphoma
- Non-Hodgkin Lymphoma
- Acute Lymphoblastic Leukemia
- Acute Myeloid Leukemia
- Chronic Myeloid Leukemia
- Myeloid Leukemia Associated with Down Syndrome
- Langerhans Cell Histiocytosis – solitary/multifocal

**MPH Rules – Heme/Lymph Neoplasms**

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Staging Pediatric Tumors

- Wilms Tumor Study Group Staging
- International Neuroblastoma Staging System
- Children’s Oncology Group Neuroblastoma Risk Grouping
- Intergroup Rhabdomyosarcoma Study Staging System
- Soft Tissue Sarcoma Tumor Pathological Grading System
- FNCLCC Grading System
- TNM Staging System

Collaborative Stage Data Collection System

CS Core Data Items and Site Specific Factors Used to Derive
- AJCC Cancer Stage
- TNM 6th edition
- Clinical Stage
- Pathologic Stage
- Best Combined Stage
- T, N, and M Core Elements
- Anatomic/Prognostic Stage Group
- SEER Summary Stage 1977
- SEER Summary Stage 2000

NO Pediatric-Specific Staging Schema or SSFs
Staging is often Site/Type Specific or Clinical Trial-Specific

Solid Tumor Staging

Source: SEER Summary Staging Manual 2000

Solid Tumor Staging - Example

- Wilms Tumor
  - Stage I – 45%
    - Tumor is limited to the kidney
    - Tumor is completely resected.
    - The renal capsule is intact.
    - Tumor is not ruptured or biopsied prior to removal.
    - No involvement of renal sinus vessels.
  - Stage II – 20%
    - Tumor is completely resected.
    - The tumor extends beyond the kidney as evidenced by any one of the following:
      - There is regional extension of the tumor (i.e., penetration of the renal sinus capsule).
      - Blood vessels in the nephrectomy specimen outside the renal parenchyma with tumor
  - Stage III – 21%
    - Renal or non-hematogenous tumor present following surgery confined to the abdomen
  - Stage IV – 11%
    - Hematogenous metastases (lung, liver, bone, brain).
    - Lymph node metastases outside the abdomen-pelvic region are present
  - Stage V – 5%
    - Bilateral involvement by tumor is present at diagnosis
**Brain Tumor Staging**

**Leukemia Staging**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
</table>
| 100  | Localized disease (Single/multifocal/craniocerebral isolated) May be coded for:  
Mast cell sarcoma (87940)  
Lymphoplasmacytoid lymphoma (79730)  
Lymphoma, unspecified in situ  
Dermatofibrosarcoma protuberans (87980) |
| 800  | Systemic disease (All histologies including those in 100) |
| 999  | Unknown: extension not stated  
Primary tumor cannot be assessed  
Not documented in patient record |

**Lymphoma Staging**

**Treatment**

**Treatment Options – Basic Concepts**

- Surgery
- Chemotherapy
- Radiation Therapy
- Hormonal Therapy
- Combination Therapy
- Continuation Therapy
- Bone Marrow/Stem Cell Transplant
Treatment Options – Basic Concepts

- Risk-Based Treatment – Pre-Induction Risk
  - Patient Characteristics
    - Age at Diagnosis
    - WBC Count at Diagnosis
    - CNS Involvement
    - Gender
  - Neoplasm Characteristics
    - Morphology
    - Immunophenotype
    - Cytogenetics
  - Genetic Characteristics of Neoplasm
    - Philadelphia Chromosome Translocation
    - MLL Translocations
    - CRLF2 and JAK Mutation

Source: [Pediatric Lymphoid Neoplasm NCI PDQ for Health Professionals](http://cancer.gov)

- Risk-Based Treatment – Induction Failure
  - Patients at highest risk of induction failure:
    - T-cell phenotype (especially without a mediastinal mass).
    - B-precursor ALL with very high presenting leukocyte counts.
    - 11q23 rearrangement.
    - Older age.
    - Philadelphia chromosome

- Risk-Based Treatment – ReInduction/Consolidation
  - Re-Induction
  - Intensification
  - Consolidation

- Risk-Based Treatment – Sanctuary Sites

- Risk-Based Treatment – Maintenance Therapy

Source: [Pediatric Lymphoid Neoplasm NCI PDQ for Health Professionals](http://cancer.gov)

Treatment Options – Basic Concepts

- Risk-Based Treatment Assessment
  - Low Risk Disease – Stage I, II – no B symptoms, no bulky disease
  - Intermediate Risk Disease – Stage I, II with B symptoms
  - Intermediate Risk Disease – Stage I, II with bulky disease
  - Intermediate Risk Disease – Stage IIIA, IVA
  - High Risk Disease – Stage IIIB, IVB
  - High Risk Disease – Poor response to initial chemotherapy

Source: [http://cancer.gov](http://cancer.gov)

Images: [http://www.sciencealert.com/science](http://www.sciencealert.com/science) and [http://cancerhelpuk.org](http://cancerhelpuk.org)

Treatment Options – Lymphoid Neoplasms

- Hodgkin Lymphoma
- Non-Hodgkin Lymphoma
- Chronic Lymphocytic Leukemia
- Acute Lymphocytic Leukemia
- Other Lymphoid Neoplasm

Source: [Mosaic Rainbow and Woodland Forest](http://www.etsy.com)

Treatment Options – Lymphoma

Source: [Pediatric Hodgkin Lymphoma NCI PDQ for Health Professionals](http://cancer.gov)
Treatment Options – Lymphoma

Source: [Pediatric Hodgkin Lymphoma NCI PDQ for Health Professionals](http://cancer.gov)

Treatment Options – Myeloid Neoplasms

- Myeloid Leukemia Associated with Down Syndrome
- Chronic Myeloid Leukemia
- Acute Myeloid Leukemia
- Other Myeloid Neoplasm
- MPD/MPS/MDS

Source: [Pediatric Myeloid Neoplasm NCI PDQ for Health Professionals](http://cancer.gov)

Treatment Options – CML/AML

- About 85% of patients are diagnosed in the chronic phase
- The accelerated phase of CML is characterized by 10% - 19% blasts in the WBC of peripheral blood (WHO)
  - Note: There are alternative ways to define the accelerated phase proposed by Sokal et al., the International Bone Marrow Transplant Registry, and MD Anderson.
- The blast phase, also referred to as blast crisis, is most often defined as >20% blasts WBC of peripheral blood

Source: [Pediatric Myeloid Neoplasm NCI PDQ for Health Professionals](http://cancer.gov)

Treatment Options – CML/AML

- Ph+ chronic phase CML is typically treated with a tyrosine kinase inhibitor (TKI).
- TKIs include imatinib, nilotinib or dasatinib.
- All TKIs are given orally so there will be no “administration” documentation rather the patient will be given prescriptions
- Other treatment options include clinical trial or Hematopoietic Stem Cell Transplant (HSCT).

Source: [Pediatric Myeloid Neoplasm NCI PDQ for Health Professionals](http://cancer.gov)
Treatment Options – CML/AML

- Patients are evaluated for a cytogenetic response
- Treatment is based on response
  - Complete Response – no Ph+ positive metaphases
  - Partial Response – 1%-35% Ph+ positive metaphases
  - Major Response – 0%-35% Ph+ positive metaphases
    - Complete + Partial
  - Minor - > 35% Ph+ positive metaphases

Source: [Pediatric Myeloid Neoplasm NCI PDQ for Health Professionals](http://cancer.gov)

Treatment Options – CML/AML

- Patients achieving a complete hematologic response are continued on their current medication at the same dose.
- Patients who fail to achieve a complete hematologic response are evaluated for compliance, drug-drug interaction and possibly mutational status but generally are switched to an alternate TKI as second line treatment.
- Other treatment options include evaluation and discussion of HSCT and clinical trial.

Source: [Pediatric Myeloid Neoplasm NCI PDQ for Health Professionals](http://cancer.gov)

Treatment Options – CML/AML

- Growth Factors
  - filgrastim (Neupogen®)
  - pegfilgrastim (Neulasta®)
- Diuretics (aldactone, hydrochlorothiazide [HCTZ]), steroids (prednisone 20mg/day x 3 for effusions)
- Topical steroids (hydrocortisone cream)
- Antidiarrheal agents (loperamide [Imodium®])
- Analgesics (acetaminophen, ibuprofen)

Source: [Pediatric Myeloid Neoplasm NCI PDQ for Health Professionals](http://cancer.gov)

Treatment Options – Brain and CNS

Treated Based on Histology and Location

Source: [Pediatric Brain Tumors NCI PDQ for Health Professionals](http://cancer.gov)
Treatment Options – Brain and CNS

Treated Based on Histology and Location

- CNS
- Non-CNS
- Both CNS and Non-CNS Involvement
- Rhabdomyosarcoma (see Sarcoma)
- Rhabdoid Tumor of Kidney

Source: [http://cancer.gov](http://cancer.gov)

Treatment Options - Teratoid/Rhabdoid Tumor

- CNS
- Non-CNS
- Both CNS and Non-CNS Involvement
- Rhabdomyosarcoma (see Sarcoma)
- Rhabdoid Tumor of Kidney

Source: [http://cancer.gov](http://cancer.gov)

Treatment Options – Soft Tissue Sarcoma

- Primary Tumor Resection with Negative Margins
- Regional Lymph Node Involvement is Rare
- Radiation Therapy depends upon potential for surgery plus or minus chemotherapy to obtain local control
  - Age
  - Gender
  - Tumor size
  - Tumor grade
- Role for Adjuvant Chemotherapy Controversial
  - Vincristine, dactinomycin, cyclophosphamide, doxorubicin

Source: [http://cancer.gov](http://cancer.gov)

Treatment Options – Ewing Sarcoma

- Pre-Treatment Factors
  - Site of Tumor
  - Tumor Size or Volume
  - Age of Patient
  - Gender (favorable girls)
  - Metastases
  - Standard Cytogenetics
  - Detectable Fusion Transcripts
- Surgery
- Chemo – vincristine, doxorubicin, cyclophosphamide
- Radiation Therapy

Treatment Options – Wilms Tumor

- Preoperative chemotherapy prior to nephrectomy is indicated in the following situations:[10,17,20-23]
  - Metachronous bilateral Wilms tumor.
  - Wilms tumor in a solitary kidney.
  - Extension of tumor thrombus above the level of the hepatic veins.
  - Tumor involves contiguous structures whereby the only means of removing the kidney tumor requires removal of the other structures (e.g., spleen, pancreas, colon but excluding the adrenal gland).
  - Pulmonary compromise due to extensive pulmonary metastases.
- Patients with massive, nonresectable unilateral tumors, bilateral tumors, or venacaval tumor thrombus are candidates for preoperative chemotherapy

Source: [http://cancer.gov](http://cancer.gov)

Treatment Options – Wilms Tumor

- Pre-Surgical Chemotherapy for High Risk Group
- Nephrectomy
- Chemotherapy
- Radiation Therapy

Source: [http://cancer.gov](http://cancer.gov)
Treatment Options – Neuroblastoma

- Low-Risk Neuroblastoma
  - Surgery
  - Chemo: carboplatin, cyclophosphamide, doxorubicin, etoposide
- Intermediate-Risk Neuroblastoma
  - Surgery
  - Chemo as above x 2 cycles
  - Dose Intensive Multi-Agent Chemo
- High-Risk Neuroblastoma
  - Dose Intensive Multi-Agent Chemo as above plus ifosfamide, cisplatin
  - Surgery
  - Response Assessment – then next steps

Late Effects of Treatment

- Childhood Cancer Survivors Study
  - Chance for long-term effects increase over time
  - > 70% at least 1 chronic illness related to treatment
  - > 25% have 3 or more chronic illnesses related to tx
  - Kidney Disease
  - Second Cancers
  - Cognitive Dysfunction
  - Cardiovascular Disease
  - Endocrine Abnormalities
  - Musculoskeletal Conditions

References and Resources

- NCI Cancer Bulletin, Pediatric Oncology Partnerships are Models for Success, Volume 5/Number 6, March 18, 2008
- Advances in Neuroblastoma Risk Assessment and Treatment, Susan L Cohn, MD, University of Chicago Department of Pediatrics
- Florida Association of Pediatric Tumor Programs (FAPTP)
- Children’s Oncology Group (COG)

Future Pediatric Oncology Webcasts

- Coming Soon!
Questions