Cancer Survivorship Care: Meeting the needs of our heros

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Disclosures

- There are no disclosures
Outline

- Epidemiology of childhood cancer
- Survivors have unique health needs
- Strategies for intervention
- Long-term follow up care
Currently, ~80% of children with cancer will be long term survivors
Five-Year Survival in Childhood Leukemia and Lymphoma

Percent Survival


Hodgkin’s
Acute lymphoblastic leukemia
Other Lymphoma
Acute Myelogenous Leukemia

AML
NHL
ALL
HD
Five-Year Survival in Childhood Solid Tumors

- Wilms Tumor
- Brain Tumors
- Neuroblastoma
- Bone Tumors

Percent Survival

- 1960-63
- 1974-76
- 1983-85
- 1989-94
- 1995-00

Survival Rates:
- 0%
- 25%
- 50%
- 75%
- 100%
How many childhood cancer survivors are there?

- In 1997, there were 270,000 survivors of childhood cancer in the U.S.
- 1 in 1000 of the total U.S. population
- 1 in 460 adults in the U.S. between the ages of 20 and 39 years currently
- Estimated to increase to 1 in 250 young adults by the year 2010

Institute of Medicine 2003
Why the impressive gains in survival?

- High rates of participation on clinical trials (60%-80%)
- More intensive therapy
- Combination therapy: chemotherapy and/or radiation and/or surgery
  (44% receive all 3 types of therapy)
Cure comes at a cost: survivors are at increased risk of late complications

**Early mortality**
- Subsequent neoplasms
  - Cardiomyopathy
  - Early myocardial infarction
  - Pulmonary fibrosis
  - Renal insufficiency
  - Hearing loss
  - Cataracts and glaucoma
  - Osteoporosis
  - Osteonecrosis
  - Bladder dysfunction

**And more…**
- Peripheral neuropathy
- Stroke
- Hepatitis
- Growth problems
- Delayed puberty
- Precocious puberty
- Infertility
- Immunodeficiency
- Hormone deficiencies
- Neurocognitive impairment
- Psychosocial maladjustment
Chronic health conditions in adult survivors of childhood cancer.

- Childhood Cancer Survivor Study, a multi-site retrospective cohort of 14,000 cases diagnosed with cancer at age <18 years and surviving >5 years
- 10,397 survivors >18 years at evaluation
- Determine frequency, cumulative incidence, and relative risk of serious health conditions
- Compare to normative group of 3034 siblings of cases
- Mean ~18 years since diagnosis
Grading Disease Severity

Scoring schema based on:

Common Terminology Criteria for Adverse Events, CTCAEv3.0

Grade 1    Mild
Grade 2    Moderate
Grade 3    Severe
Grade 4    Life-threatening or disabling
Grade 5    Death
Examples of Grade 3 Conditions

- Pulmonary fibrosis on O-2
- Deaf or blind
- Congestive heart failure
- Cirrhosis
- Joint replacement or limb amputation
- Gonadal failure, on replacement therapy
Grade 4 Conditions

- Second cancer (except basal cell carcinoma)
- Myocardial infarction
- Stroke
- Organ transplant: heart, lungs, kidney
- Paralysis with major daily limitations
- Cognitive dysfunction with major limitations
Frequency of Conditions in Survivors (N=10,397)

- Any condition: 77%
- Grade 1 or 2: 66%
- Grade 3-5: 38%
- Multiple conditions: 44%
Relative risk with 95% CI of physical health conditions in survivors compared with siblings
Adjusted for age, sex, and race

Survivors  N=10,397
Siblings    N= 3,034

Relative risk:
- Any Grade: 1.9
- Grade 3 or 4: 4.2
- ≥ 2 Conditions: 2.4
Relative risk of physical health conditions in survivors compared with siblings
Adjusted for age, sex, and race

<table>
<thead>
<tr>
<th>Primary Cancer</th>
<th>Any Grade</th>
<th>Grade 3 or 4</th>
<th>&gt; 2 Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin</td>
<td>2.6</td>
<td>5.8</td>
<td>4.4</td>
</tr>
<tr>
<td>CNS tumor</td>
<td>2.1</td>
<td>5.3</td>
<td>2.7</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>2.1</td>
<td>3.9</td>
<td>1.8</td>
</tr>
<tr>
<td>Wilms tumor</td>
<td>1.9</td>
<td>4.6</td>
<td>2.2</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>1.8</td>
<td>4.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Leukemia</td>
<td>1.7</td>
<td>3.2</td>
<td>1.9</td>
</tr>
<tr>
<td>NHL</td>
<td>1.7</td>
<td>2.7</td>
<td>2.1</td>
</tr>
<tr>
<td>Bone tumor</td>
<td>1.6</td>
<td>4.1</td>
<td>2.2</td>
</tr>
</tbody>
</table>

All estimates are significant at p < 0.001
Cumulative Incidence of Physical Health Conditions

- Grades 1-5
- Grades 3-5

Years Since Diagnosis

Cumulative Incidence
Late mortality among 5-year survivors of childhood cancer

- Childhood Cancer Survivor Study Cohort
- National Death Index and review of death certificates
- Describe mortality risk by demographic and clinical characteristics
- Compare cause-specific mortality rates with U.S. population
- Assess treatment factors associated with excess cause-specific mortality
Deaths

Total deaths 2823

- Death certificate received 2435 (84%)
- Death cause, other sources 121 (4%)
- Unable to determine cause 267 (12%)
All cause mortality- sex specific survival
## Overall mortality

<table>
<thead>
<tr>
<th></th>
<th># deaths</th>
<th>SMR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>2823</td>
<td>8.23</td>
<td>(7.9-8.5)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1687</td>
<td>6.6</td>
<td>(6.3-6.9)</td>
</tr>
<tr>
<td>Female</td>
<td>1136</td>
<td>13.1</td>
<td>(12.3-13.9)</td>
</tr>
<tr>
<td><strong>Years survived after diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-9</td>
<td>1336</td>
<td>21.4</td>
<td>(19.3-22.6)</td>
</tr>
<tr>
<td>10-14</td>
<td>611</td>
<td>7.1</td>
<td>(6.5-7.7)</td>
</tr>
<tr>
<td>15-19</td>
<td>431</td>
<td>4.6</td>
<td>(4.2-5.0)</td>
</tr>
<tr>
<td>20-24</td>
<td>269</td>
<td>4.3</td>
<td>(3.8-4.8)</td>
</tr>
<tr>
<td>25-29</td>
<td>145</td>
<td>4.9</td>
<td>(4.1-9.6)</td>
</tr>
</tbody>
</table>
Causes of death

<table>
<thead>
<tr>
<th>Causes of death</th>
<th>Count</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>1469</td>
<td>57%</td>
</tr>
<tr>
<td>Treatment-related</td>
<td>703</td>
<td>28%</td>
</tr>
<tr>
<td>Other causes</td>
<td>384</td>
<td>15%</td>
</tr>
</tbody>
</table>
Cumulative cause specific mortality
# Treatment-related mortality

<table>
<thead>
<tr>
<th></th>
<th># deaths</th>
<th>SMR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New cancer</td>
<td>380</td>
<td>15.0</td>
<td>(13.7-16.4)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>179</td>
<td>6.9</td>
<td>(5.8-8.1)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>45</td>
<td>8.7</td>
<td>(6.7-11.0)</td>
</tr>
</tbody>
</table>
## Non-treatment related mortality

<table>
<thead>
<tr>
<th></th>
<th># deaths</th>
<th>SMR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>External causes</td>
<td>182</td>
<td>0.9 (0.8 - 1.0)</td>
</tr>
<tr>
<td>auto accident</td>
<td>80</td>
<td>1.0 (0.8 - 1.3)</td>
</tr>
<tr>
<td>other accidents</td>
<td>49</td>
<td>1.3 (1.0 - 1.7)</td>
</tr>
<tr>
<td>suicide</td>
<td>39</td>
<td>1.0 (0.7 - 1.4)</td>
</tr>
<tr>
<td>homicide</td>
<td>23</td>
<td>0.5 (0.3 - 0.7)</td>
</tr>
</tbody>
</table>
Strategies to limit late effects
Sperm banking for post-pubertal boys
Give less toxic therapy *without* compromising cure
Hodgkin Therapy: Then and Now

**Circa 1980**
- 3500-4400 centigray
- Extended field radiation
- High doses of alkylator chemotherapy (e.g. MOPP)
- 8-12 months of chemotherapy

**Circa 2008**
- 0 to 2100 centigray
- Involved-field radiation
- Less alkylator chemotherapy
- 3-6 months of chemotherapy
Neurobehavioral outcomes in acute lymphoblastic leukemia patients according to previous treatment randomization

- Cross-sectional study
- Previously randomized on 2 large clinical trials

1st Randomization
- Prednisone
- Dexamethasone

2nd Randomization
- IT Methotrexate
- IT Methotrexate and Cytarabine/Hydrocortisone
• Amifostine to reduce cisplatinum-associated ototoxicity

• Psychosocial intervention to child or parents to reduce later distress
Health-Related Quality of Life in children undergoing leukemia therapy

- Identify predictors of quality of life outcomes that will be used in future intervention studies, and the critical time points when such interventions should occur.

- Prospective, longitudinal study

- Child and parent-completed surveys during and in the year after therapy at 5 time points
Health-Related Quality of Life study

- Surveys of:
  - Child quality of life
  - Child behavior and symptoms of anxiety/depression
  - Family coping

- Imbedded into a national therapeutic study as required measurements

- Funded by NCI Division of Cancer Prevention

- Study ongoing
• Early breast mammogram/MRI for females treated with $\geq 2000$ centigray radiation (start at 25 years)

• Cognitive remediation program to improve attention and academic achievement in survivors

• Long-term survivorship care
Health

Education

Research

Outcomes

for

Survivors of Childhood Cancer
HEROS Clinic Experience

Patients Make Appointment

Abstract Medical History

Pre-Clinic Conference

Clinic Visit

Report sent to Patient

3-6 Months before visit

2 Weeks before visit

1 Week before visit

Patient seen by:
  Nurse
  Physician
  Neuropsychologist
  Research Coordinator

2-3 Weeks after Visit
Patient Referral

- **Who?**
  - History of cancer diagnosed at younger than 21 years and any age now

- **How?**
  - oncologists
  - primary care physicians
  - patients (self-referral from Web, Newspaper, or word of mouth)

- **When?**
  - As early as 3 years after diagnosis
HEROS Clinic Experience

- **Patients Make Appointment**: 3-6 Months before visit
- **Abstract Medical History**: 2 Weeks before visit
- **Pre-Clinic Conference**: 1 Week before visit
- **Clinic Visit**: Patient seen by: Nurse, Physician, Neuropsychologist, Research Coordinator
- **Report sent to Patient**: 2-3 Weeks after Visit
Medical Record Abstraction

- Detailed review of treatment history performed before clinic visit

### Patient Information
- **Name:** Doe, John
- **Current Age (yrs):** 12.8
- **Gender:** Male
- **YMM: 11111111

### Age at dx (yrs): 1.9
- **Years since therapy completion:** 8.9

### FMH and Diagnosis Hx

### Treatment Hx

### Complications During and After therapy

### Family Med Hx

### Outcomes

### Visits

### Study

### Note on Treatment Hx:
The patient's medical history is detailed as follows:

### Protocol(s):
- 1.
- 2.
- 3.
- 4.
- 5.

### CHEMOTHERAPY

- **Drug:**
  - Cytarabine (50, IT, IV, low dose IV)
  - Methotrexate (PO, IV, low dose IV)
  - Methotrexate (IT, IV)

- **Total Cumulative Dose:**
  - Cytarabine: 1000 mg/m^2
  - Methotrexate: 0.7 mg/m^2

- **Date Start:** 12/1/2005
- **Date Stop:** 12/31/2005
- **Field:**
  - Cerebral radiation
  - Spinal radiation

### RADIATION

- **Date Start:** 12/1/2005
- **Date Stop:** 12/31/2005
- **Field:**
  - Spinal radiation

### SURGERY

- **Type of Surgery:**
  - Craniotomy
  - Neurosurgery [brain]

### STEM CELL TRANSPLANT

- **Transplant Date:** 1/1/2006
- **Source:** Peripheral stem cells
- **Chemo:** Hematopoietic cell transplantaion
HEROS Clinic Experience

Patients Make Appointment
3-6 Months before visit

Abstract Medical History
2 Weeks before visit

Pre-Clinic Conference
1 Week before visit

Clinic Visit
Patient seen by:
Nurse
Physician
Neuropsychologist
Research Coordinator

Report sent to Patient
2-3 Weeks after Visit
Pre-Clinic Conference

- Each case is discussed in a multidisciplinary conference which includes oncologist, psychologist, internist and endocrinologist.
- Individualized plan of care according to long-term follow-up guidelines from Children's Oncology Group (www.survivorshipguidelines.org).

<table>
<thead>
<tr>
<th>CHEMOTHERAPY</th>
<th>ALKYLATING AGENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sec #</strong></td>
<td><strong>Therapeutic Agent(s)</strong></td>
</tr>
<tr>
<td>7</td>
<td><strong>ALKYLATING AGENTS</strong></td>
</tr>
<tr>
<td></td>
<td>Busulfan</td>
</tr>
<tr>
<td></td>
<td>Chlorambucil</td>
</tr>
<tr>
<td></td>
<td>Melphalan</td>
</tr>
<tr>
<td></td>
<td>Lomustine (CCNU)</td>
</tr>
<tr>
<td></td>
<td>Melphalan</td>
</tr>
<tr>
<td></td>
<td>Procarbazine</td>
</tr>
<tr>
<td></td>
<td>Thiotepa</td>
</tr>
<tr>
<td></td>
<td><strong>HEAVY METALS</strong></td>
</tr>
</tbody>
</table>
HEROS Clinic Experience

- **Patients Make Appointment**: 3-6 Months before visit
- **Abstract Medical History**: 2 Weeks before visit
- **Pre-Clinic Conference**: 1 Week before visit
- **Clinic Visit**: Patient seen by: Nurse, Physician, Neuropsychologist, Research Coordinator
- **Report sent to Patient**: 2-3 Weeks after Visit
Clinic Visit

- Comprehensive history and physical to screen for potential late effects
- Education on disease prevention and screening
- Screening for psychological and neurocognitive problems and referral if necessary
- Introduction of open cancer survivorship research studies at Yale and around the country
HEROS Clinic Experience

**Patients Make Appointment**
3-6 Months before visit

**Abstract Medical History**
2 Weeks before visit

**Pre-Clinic Conference**
1 Week before visit

**Clinic Visit**
Patient seen by:
- Nurse
- Physician
- Neuropsychologist
- Research Coordinator

2-3 Weeks after Visit

**Report sent to Patient**
After the Clinic Visit

- Follow-up on findings from physical exam and studies (by phone if abnormalities)
- Detailed summary letter sent to the survivor, oncologist, and primary care doctor
  - Summary letter includes concise treatment history, clinical findings and recommended wellness care
HEROS CLINIC
Clinic Visit Summary

Patient: Doe, John  DOB: 2/1/1985  MRN: 111111
Current Age: 23.8 yrs  Gender: Male  Referred by: patient's parent
Primary Oncologist: Jack van Hoff, MD  PCP: John Smith, MD
Date of HEROS Visit: 4/1/2006  Date of Multidisciplinary Pre-Clinic Conference: 3/21/2006

I. REASON FOR REFERRAL
Consult on cancer survivorship care

II. CANCER HISTORY
1. Sarcoma, Ewing's sarcoma
   Site: Femur  Side: Left  Stage: III
   Date of Dx: 1/1/1998  Age at Dx: 12.9  Date of Therapy Completion: 12/31/2006  Yrs since Therapy Completion: 7.9

III. TREATMENT HISTORY
***This treatment summary was abstracted to the best of our ability with the medical records available at the time of our review.
Please bring any discrepancies to our attention***

Note on Treatment History: The patient

Chemotherapy: Yes
- Cyclophosphamide (Cytoxan) IV, 10000 mg/m²
- Etoposide (VP-16) IV, 600 mg/m², BMT Prep
- Vincristine IV, 20 mg/m²
- Daunorubicin (Adriamycin) IV, 400 mg/m²
- Bleomycin IV, 300 mg/m²

Radiation Therapy: Yes
- Femur, 3100 cGy, 5 Fractions, Start Date: 12/31/2005, Stop Date: 12/31/2005
- Chest, 2500 cGy, Start Date: 12/31/2005, Stop Date: 12/31/2005

Surgery: Yes
- Resection of Ewing's sarcoma, Date: 1/23/2001

Stem Cell Transplant: Yes
- 1/2006, Stem Cell Source: peripheral stem cells, Donor: self

IV. ISSUES IDENTIFIED
1. Peripheral neuropathy
2. Hypogonadism
3. Basal cell carcinoma in previous radiation field
4. Cardiomyopathy
5. Anxiety

V. ASSESSMENT AND PLAN
John is a 23 yo young man who is almost 8 years after successful therapy for Ewing's that included intensive chemotherapy, radiation therapy, and surgery. He has several late complications related to his previous therapy. For the peripheral neuropathy, John is taking low dose nortriptyline with good relief. John is aware that he has a low sperm count and that there is only a small chance that it will recover. Fortunately, he stored sperm prior to beginning therapy. John has already had one second skin cancer in

Yale School of Medicine  Department of Pediatrics  P.O. Box 208064  New Haven, CT 06520-8064
Phone: 203-737-5460  Fax: 203-737-2229
Date: John  Page 1 of 2
Challenges with Current Model

- Reaches only a small proportion of cancer survivors
- Survivors do not realize that they have special health needs ("silent condition")
- Returning to cancer treatment center raises anxiety
Conclusions

- Cure is the rule, not the exception, for children with cancer
- Childhood cancer survivors are at increased risk for medical, neurocognitive, and psychosocial outcomes that impact their quality of life
- Clinical and research efforts are needed to prevent and mitigate late treatment effects while preserving cure
“Cure is not enough”
----Dr. Giulio D’Angio
Acknowledgements

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The Connecticut Challenge

American Cancer Society

St. Baldrick’s Foundation

The Tommy Fund

The HEROS Team