Blood Cancer: Early Diagnosis, Treatment & Survivorship

Cancer Case Studies for the Primary Care Physician

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Program Overview
Hildy J. Dillon, MPH
Senior Vice President, Patient Services
The Leukemia & Lymphoma Society
White Plains, NY

Early Diagnosis of Blood Cancers:
Symptoms Seen in the Frontline of Care
Barton A. Kamen, MD, PhD

Risk-Based Healthcare for Adult Survivors
of Pediatric Cancer
Kevin C. Oeffinger, MD

Question-and-Answer Session
TARGET AUDIENCE  
This activity has been designed to meet the educational needs of physicians, nurses and social workers involved in the care of patients with blood cancers.

ACTIVITY PURPOSE  
This activity is intended to assist healthcare professionals in recognizing the signs, symptoms, treatments and survivorship issues associated with blood cancers using representative case studies.

STATEMENT OF NEED  
Blood cancers are projected to be responsible for more than 53,000 deaths in 2009.\(^1\) Diagnosis of these conditions can be difficult, particularly in the early stages, because patients may be asymptomatic, and the signs and symptoms are nonspecific and generally related to common blood cytopenias. Treatment of these conditions is equally challenging, as malignancies and therapies alike are associated with significant short- and long-term side effects. Thus, healthcare professionals who treat patients with blood cancers must be mindful of traditional therapy targeted at achieving remission as well as supportive and follow-up care. This educational activity is designed to improve care and overall quality of life in patients with blood cancers.


EDUCATIONAL OBJECTIVES  
After completing this activity, the participant should be better able to:

- Recognize the distinct signs and symptoms associated with hematologic malignancies to improve patient outcomes through early diagnosis
- Select appropriate methods for diagnosis in patients with signs and symptoms of hematologic malignancies
- Identify the late effects associated with treatments for hematologic malignancies
- Describe follow-up tests used to screen for malignancy recurrence to improve long-term survival

STATEMENT OF SUPPORT  
This activity is supported in part by educational grants from Cephalon Oncology and Celgene Corporation.
Barton A. Kamen, MD, PhD
Chief Medical Officer
The Leukemia & Lymphoma Society
White Plains, NY
Professor of Pediatrics and Pharmacology
The Cancer Institute of New Jersey
UMDNJ – Robert Wood Johnson Medical School
New Brunswick, NJ

Barton A. Kamen, MD, PhD, is the executive vice president and chief medical officer of The Leukemia & Lymphoma Society (LLS), as well as professor of pediatrics and pharmacology at the Cancer Institute of New Jersey at Robert Wood Johnson Medical School. Dr. Kamen has been a recipient of a scholar award from LLS, a Damon Runyon Walter Winchell Fellowship, a Burroughs Wellcome Clinical Pharmacology Award, and an American Cancer Society Clinical Research Professorship. He has authored approximately 300 peer-reviewed articles and book chapters and is the current editor-in-chief of the Journal of Pediatric Hematology/Oncology.
Kevin C. Oeffinger, MD  
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Director, Living Beyond Cancer  
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New York, NY

Kevin C. Oeffinger, MD, is an attending physician and director of Living Beyond Cancer, a program for adult survivors of pediatric cancer at Memorial Sloan-Kettering Cancer Center in New York City. After receiving his medical degree from the University of Texas Medical School at San Antonio (Texas), he completed residency training at Baylor College of Medicine in Houston, Texas, and went on to pursue advanced research training in the National Cancer Institute's Division of Cancer Epidemiology and Genetics. Dr. Oeffinger's research interests focus on better understanding the long-term health problems related to cancer and cancer therapy, particularly cardiovascular health and follow-up care optimization. His findings have been reported in over 50 peer-reviewed publications, including *Journal of Clinical Oncology*, *Journal of Pediatric Hematology/Oncology*, *Cancer*, and *Journal of the American Medical Association*. 
PHYSICIAN CONTINUING MEDICAL EDUCATION CREDIT

Accreditation Statement
This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Postgraduate Institute for Medicine (PIM) and Robert Michael Educational Institute LLC (RMEI). PIM is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation
PIM designates this educational activity for a maximum of 1.5 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

AAFP Credit
This activity has been reviewed and is acceptable for up to 1.5 prescribed credits by the American Academy of Family Physicians (AAFP).

NURSES AND SOCIAL WORKERS CONTINUING EDUCATION CREDIT

Nursing Professionals
Approval for nurses has been obtained by the National Office of The Leukemia & Lymphoma Society under provider number CEP 5832 to award 1.5 continuing education contact hours through the California Board of Registered Nursing.

Social Workers
The Leukemia & Lymphoma Society (LLS), provider number 1105, is approved as a provider for social work continuing education by the Association of Social Work Boards (ASWB) www.aswb.org Approved Continuing Education Program (ACE). Approval Period: 12/2008–12/2011. LLS maintains responsibility for the program. Social workers should contact their regulatory board to determine course approval. Social workers will receive 1.5 CE clinical clock hours.

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The faculty reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:
• Dr. Barton A. Kamen has no affiliations with commercial interests to disclose.
• Dr. Kevin Oeffinger has no affiliations with commercial interests to disclose.

The following planners and managers reported the following financial relationships:

The Leukemia & Lymphoma Society
• Hildy J. Dillon, MPH, has no affiliations with commercial interests to disclose.

Robert Michael Educational Institute LLC
• Sherri Kramer, MD, has no affiliations with commercial interests to disclose.
• Laura Altobelli, MS, has no affiliations with commercial interests to disclose.

Postgraduate Institute for Medicine
• Jan Hixon, RN, BSN, MA, has no affiliations with commercial interests to disclose.
• Linda Graham, RN, BSN, has no affiliations with commercial interests to disclose.
• Trace Hutchison, PharmD, has no affiliations with commercial interests to disclose.
• Julia Kirkwood, RN, BSN, has no affiliations with commercial interests to disclose.
• Jan Schultz, RN, MSN, CCMEP, has no affiliations with commercial interests to disclose.

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DISCLAIMER
Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient’s conditions and possible contraindications on dangers in use, review of any applicable manufacturer’s product information, and comparison with recommendations of other authorities.
Blood Cancer: Early Diagnosis, Treatment & Survivorship

Cancer Case Studies for the Primary Care Physician

Presentations

1

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Early Diagnosis of Blood Cancers: Symptoms Seen in the Frontline of Care

Barton A. Kamen, MD, PhD
Chief Medical Officer
The Leukemia & Lymphoma Society
White Plains, NY
Disclosure of Conflicts of Interest

Barton A. Kamen, MD, PhD

Dr. Barton A. Kamen has no affiliations with commercial interests to disclose.

I thank you, and I salute you for being on the front line of patient care.

Goal for This Session:

- Review the scope of the problem of blood cancers
- Discuss symptoms, signs, laboratory and radiological findings as you might see them at initial presentation

Format will include some actual (or representative) cases I have seen in the ER or clinic over 30 years and will emphasize the young adult population.
Scope of the Problem

Approximately 135,000 new cases of blood and related cancers in the US in 2007

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphomas</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin</td>
<td>63,000</td>
</tr>
<tr>
<td>Hodgkin</td>
<td>8,000</td>
</tr>
<tr>
<td>Leukemias</td>
<td></td>
</tr>
<tr>
<td>CLL</td>
<td>15,000</td>
</tr>
<tr>
<td>CML</td>
<td>5,000</td>
</tr>
<tr>
<td>AML</td>
<td>13,000</td>
</tr>
<tr>
<td>ALL</td>
<td>5,000</td>
</tr>
<tr>
<td>Myeloma</td>
<td>10,000</td>
</tr>
</tbody>
</table>

ALL = acute lymphoblastic leukemia; AML = acute myelogenous leukemia; CLL = chronic lymphocytic leukemia; CML = chronic myelogenous leukemia.


---

Scope of Problem in Young Adults

Cancer in 15- to 29-Year-Olds by Primary Site
(SEER Site Recode) U.S., SEER 1975-2000

[Diagram showing cancer distribution by primary site]

### Leukemias & Lymphoreticular Malignancies in Pediatrics and Young Adults

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>% of all cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–15</td>
<td>40–45</td>
</tr>
<tr>
<td>15–19</td>
<td>35–40</td>
</tr>
<tr>
<td>20–25</td>
<td>35–40</td>
</tr>
<tr>
<td>25–29</td>
<td>15–20</td>
</tr>
<tr>
<td>30–34</td>
<td>12–15</td>
</tr>
<tr>
<td>35–39</td>
<td>10–12</td>
</tr>
</tbody>
</table>

### WHY Is Early Detection Important?

*Intuitively:*

Earlier detection = lower stage = better outcome?

Not necessarily always true, but patient may be healthier and Rx morbidity less

Improvements in Cancer Survival

Outcomes of Patients Treated on Either Pediatric or Adult ALL Clinical Trials

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Years</th>
<th>Age (years)</th>
<th>EFS by Regimen Type (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>1991–2001</td>
<td>16–20</td>
<td>63</td>
</tr>
<tr>
<td>Dutch</td>
<td>1990–1999</td>
<td>15–18</td>
<td>69</td>
</tr>
<tr>
<td>Sweden</td>
<td>1990–2000</td>
<td>15–20</td>
<td>74</td>
</tr>
<tr>
<td>UK</td>
<td>1997–2002</td>
<td>15–17</td>
<td>65</td>
</tr>
</tbody>
</table>

EFS = event-free survival.
### Diagnostic Strategies

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Sign</th>
<th>Lab/Radiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>Pain</td>
<td>Anemia</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>Wheezing</td>
<td>Chest x-ray</td>
</tr>
<tr>
<td>Pain (arthralgia, bone)</td>
<td>Swelling</td>
<td>Pan cytopenia</td>
</tr>
<tr>
<td></td>
<td>Telangiectasia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>&quot;WNL&quot;</td>
</tr>
<tr>
<td>Headache</td>
<td>Bruising</td>
<td>Pan cytopenia</td>
</tr>
<tr>
<td></td>
<td>Petechiae</td>
<td>Leukocytosis</td>
</tr>
<tr>
<td></td>
<td>CNS findings</td>
<td>&quot;WNL&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT scans</td>
</tr>
<tr>
<td>Sweating; fever</td>
<td>Lymphadenopathy</td>
<td>CBC, CT chest</td>
</tr>
</tbody>
</table>

CBC = complete blood count; CNS = central nervous system; CT = computed tomography; WNL = within normal limits.

### Diagnostic Strategies (Cont’d)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Sign</th>
<th>Lab/Radiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of appetite</td>
<td>Lymphadenopathy</td>
<td>CBC, CT scans</td>
</tr>
<tr>
<td></td>
<td>Jeundice</td>
<td>Metabolic panel</td>
</tr>
<tr>
<td></td>
<td>Splenomegaly</td>
<td></td>
</tr>
<tr>
<td>Pruritis</td>
<td>Rash(es)</td>
<td>CBC, eosinophilia</td>
</tr>
<tr>
<td>Bloating, swelling</td>
<td>Pitting edema</td>
<td>CBC</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>Organomegaly</td>
<td>Metabolic panel</td>
</tr>
<tr>
<td>NONE</td>
<td>NONE</td>
<td>CBC, chest x-ray, UA</td>
</tr>
</tbody>
</table>

UA = urinalysis
Presentations

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Sign</th>
<th>Lab/Radiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>Pale</td>
<td>Anemia</td>
</tr>
</tbody>
</table>

Anemias: Normocytic
- Microcytic
- Macrocytic

Marrow failure syndromes:
- Premalignant conditions, such as myelodysplasia

Teenage boy with 6-week history of increasing pallor
- Hemoglobin: 3 g/dL
- Mean corpuscular volume: 98 fl
- Platelets: 30,000/mm³

Treated with weekly IM vitamin B12

Hyperleukocytosis: 900,000/mm³
Hyperleukocytosis Signs and Symptoms

- Cerebral and pulmonary circulation most commonly affected
  - CNS
    - Change in mental state
    - Seizures
    - Headache
    - Papilledema
  - Respiratory
    - Dyspnea
    - Hypoxemia
    - Right ventricular failure
    - Bilateral "hairy infiltrates" on chest x-ray
  - Other
    - Rales/tampons
    - Fractures
    - Dulciatis

All That Wheezes Is Not Asthma!

Young boy treated for protracted respiratory airway disease
Tracheal Compression From Anterior Mediastinal Mass


<table>
<thead>
<tr>
<th>Symptom</th>
<th>Sign</th>
<th>Lab/Radiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain (arthritis, bone)</td>
<td>Swelling</td>
<td>Pancytopenia</td>
</tr>
<tr>
<td></td>
<td>Petechiae</td>
<td>Leukocytosis</td>
</tr>
<tr>
<td></td>
<td>Adenopathy</td>
<td>&quot;WNL&quot;</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>X-rays</td>
</tr>
</tbody>
</table>

- Bone pain is an early presentation of leukemia, especially in children
- Often normal or borderline abnormalities in CBC initially
- Fractures
- Differential diagnosis:
  - Often appears to be acute infectious or autoimmune disease
  - Labs, such as CBC, sedimentation rate, lactate dehydrogenase, alkaline phosphatase, may be helpful


Presentations
## Infectious Mononucleosis

- First described by Emil Pfeiffer as “glandular fever”
- Referred current name in 1920 by T.P. Sprunt and F.A. Evans, who associated the disease with blood cellular morphology
- Relationship to Epstein-Barr virus was discovered in 1968
- Affects primarily young adults (14–20 years of age)
- Clinical symptoms & laboratory findings may include:

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrexia</td>
<td></td>
</tr>
<tr>
<td>Enlarged cervical lymph node</td>
<td></td>
</tr>
<tr>
<td>Splenomegaly (25% of patients)</td>
<td></td>
</tr>
<tr>
<td>Headaches (in 20% of patients)</td>
<td></td>
</tr>
<tr>
<td>WBC count = 12,000 to 26,000/uL</td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td></td>
</tr>
<tr>
<td>Lethargy</td>
<td></td>
</tr>
<tr>
<td>Splenomegaly (25% of patients)</td>
<td></td>
</tr>
<tr>
<td>Vomiting (in 20% of patients)</td>
<td></td>
</tr>
<tr>
<td>Jaundice (in 5% of patients)</td>
<td></td>
</tr>
<tr>
<td>Abnormal liver function tests</td>
<td></td>
</tr>
</tbody>
</table>
A Wright-stained bone marrow aspirate smear of patient with precursor B-cell ALL

Acute Lymphocytic Leukemia (ALL)

Most common Pediatric Malignancy (25-30%)

Presentation usually with signs or symptoms of bone marrow failure

However can present with arthralgias and mimic Lupus or other autoimmune disease

Other presentations......
Presentations

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Sign</th>
<th>Lab/Radiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>Bruising</td>
<td>Panocytopenia</td>
</tr>
<tr>
<td></td>
<td>Petechiae</td>
<td>Leukocytosis</td>
</tr>
<tr>
<td>CNS findings</td>
<td>CT scans</td>
<td></td>
</tr>
</tbody>
</table>

- Leukemia and lymphoma, some types more than others, have a predilection for the CNS spread or even primary presentation (CNS lymphoma).
- Findings may be typical of any mass effect seen with a hemorrhage or tumor.
- Invasion of specific cranial nerves can present with focal deficits.

Primary CNS Lymphoma in Immunocompromised Patients

- Usually no systemic disease at diagnosis
- Typically (95%) a B-cell non-Hodgkin lymphoma (NHL)
- Almost always supratentorial

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Sign</th>
<th>Lab/Radiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweating</td>
<td>Lymphadenopathy</td>
<td>CBC, CT chest</td>
</tr>
<tr>
<td>Fever</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Unexplained fever, especially night sweats, are often seen part of the initial presentation of lymphomas; pathophysiological basis is likely cytokine release
- CBC may be normal or show anemia of chronic disease (microcytic) if the presentation is indolent (or if the patient is too tolerant of the presenting symptoms)
<table>
<thead>
<tr>
<th>Symptom</th>
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<th>Lab/Radiology</th>
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</thead>
<tbody>
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<td>CBC, CT scans</td>
</tr>
<tr>
<td></td>
<td>Jaundice</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spleenomegaly</td>
<td></td>
</tr>
</tbody>
</table>

One of the initial descriptions of a young man with what was probably CML: massive abdominal organomegaly, jaundice.

Wood GB. A Treatise on the Practice of Medicine. 1848.
Burkitt’s Lymphoma

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Sign</th>
<th>Lab/Radiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea, vomiting</td>
<td>Organomegaly</td>
<td>Metabolic panel</td>
</tr>
</tbody>
</table>

Organ failure: metabolic (tumor lysis syndrome) and anatomic compromise

- Acute onset of edema, clinical symptoms may be related to uremia, acute renal failure associated with aggressive B-cell lymphoma or leukemia (Burkitt’s)
- May be both anatomic and metabolic causes for organ failure
- Rapid appreciation and treatment is critical
- Often dialysis is initiated before chemotherapy


L3 (aka Burkitt’s Leukemia)

Presentation: abdominal pain

Serum Chemistries
- BUN: 50 mg/dL
- Creatinine: 1.6 mg/dL
- Uric acid: 15 mg/dL
- Phosphorus: 8 mg/dL
- Calcium: 4 mg/dL
Promyelocytic Leukemia (AML-M3)
A proclivity to present with DIC

Leukemia Cutis Resembling a Flare-Up of Psoriasis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Sign</th>
<th>Lab/Radiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpura</td>
<td>Rash(es)</td>
<td>CBC, eosinophilia</td>
</tr>
<tr>
<td>Purpura</td>
<td>No rash</td>
<td></td>
</tr>
</tbody>
</table>

Gingival hyperplasia
?
Acute myelogenous leukemia

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Sign</th>
<th>Lab/Radiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>None</td>
<td>CBC, chest x-ray, ultrasound</td>
</tr>
</tbody>
</table>

- Some indolent lymphomas, especially Hodgkin disease in young adults and some of the chronic leukemias, may be found by accident
- The lymphoma is found on a school or military physical and routine chest x-ray, and the CML is found on a scheduled CBC
- Routine CBC shows signs of marrow failure: myelodysplasia, aplastic anemia
- Urinalysis showing proteinuria could be sign of myeloma
Presentations

What we know is infinitely less than all that remains unknown.

– William Harvey (1578–1657)

Why are we doing what we are doing?
Risk-Based Healthcare of Adult Survivors of Pediatric Cancer

Kevin C. Oeffinger, MD
Director, Adult Survivor Program
Departments of Pediatrics and Medicine
Memorial Sloan-Kettering Cancer Center
New York, NY

Disclosure of Conflicts of Interest

Kevin C. Oeffinger, MD

Dr. Kevin C. Oeffinger has no affiliations with commercial interests to disclose.
Presentations

Outline

- Background
- Mortality and morbidity
- Three illustrative cancers
- Risk-based healthcare of survivors
  - Emphasize the potential to modify outcomes through risk-based care

5-Year Survival Rates, Ages 0–19 Years

**Pediatric Cancer Survivors**

- Over 80% 5-year survival
- 329,000 childhood cancer survivors in the United States
- About 1:570 young adults in the United States is a pediatric cancer survivor

**Mortality Rates of >5-Year Childhood Cancer Survivors vs US Population**

- Late causes of mortality:
  - Second cancers
  - Cardiac disease
  - Pulmonary disease
- Standard mortality ratio is higher for women than men

Cumulative Cause-Specific Mortality


5-Year Survival Rates, Hodgkin Lymphoma


Years From Diagnosis

Percent

0 10 20 30 40 50 60 70 80 90 100

0 5 10 15 20 25 30 35

13% 36%

- Hodgkin lymphoma at age 13 (1979)
  - Stage IA
  - Martie radiation therapy (RT)
- October 2005
  - Esophageal strictures
  - Moderately severe aortic insufficiency
  - Severe restrictive disease
  - Severe 3-vessel coronary artery disease (CAD)
  - Asplenic
  - Kyphosis
- Died, August 22, 2006

Cumulative Incidence of Chronic Physical Health Conditions Among 10,397 Young Adult Survivors of Childhood Cancer

Presentations

<table>
<thead>
<tr>
<th>System</th>
<th>Exposure</th>
<th>Potential Late Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>RT, Anthracyclines</td>
<td>Vascular disease, Pericarditis, Myocardial infarction, Congestive heart failure, Restrictive lung disease</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>RT, Camptothecines (CPT-11)</td>
<td>Exercise intolerance</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>RT, Pegylated liposomal paclitaxel, Topoisomerase inhibitors</td>
<td>Alcoholic liver toxicity, Nodal insufficiency or failure</td>
</tr>
<tr>
<td>Endocrine</td>
<td>RT, Alkylation agents</td>
<td>Growth failure, Thyroid, adrenal disease, Ovarian or testicular failure, Delayed 2nd sex characteristics, Infertility</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>RT, Intrathecal chemotherapy</td>
<td>Learning disabilities, Cognition dysfunction</td>
</tr>
<tr>
<td>Psychologic</td>
<td>Cancer</td>
<td>Fatigue, insomnia, Sleep disturbance, Emotional and mental health, Employment and educational problems, Insurance discontinuation, Adaptation/problem solving</td>
</tr>
<tr>
<td>Leukemia/lymphoma</td>
<td>RT, Alkylation agents, Etoposide, Lykomel (lymphoma)</td>
<td>Bone tumors, Leukemia, Lymphoma</td>
</tr>
</tbody>
</table>
Illustrative Examples

- Breast cancer following chest RT
- Coronary artery disease post chest RT
- Cardiovascular disease post–acute lymphoblastic leukemia (ALL)
- Key points:
  - Common rather than rare
  - Window of time – clinically silent
  - Role of prevention and early intervention

• 1-year-old girl
  - Cervical adenopathy
  - Mediastinal mass
- Hodgkin lymphoma at age 17 (1982)
  - MOPP
  - Mantle 3630 cGy/36 1630 cGy
  - MACOP-B – doxorubicin 200 mg/m²
- Breast cancer – age 33 years
  - Infiltrating ductal CA – 4.5 mm
  - T₂N₁M₀
  - Modified radical mastectomy
  - Doxorubicin 221 mg/m²
- Congestive heart failure – age 34
  - Ejection fraction = 20%–25%
  - Ejection fraction increased to 40% on 3 drugs

Cumulative Incidence of Breast Cancer in Hodgkin Lymphoma Survivors

20% at 45 years of age

Breast Cancer Post-RT

- Onset – 8 years post-RT
- Median interval – 16 years post-RT
- Median age at diagnosis – early 30s
- 5-year prognosis strongly associated with stage of disease at diagnosis
- Limitations in treatment options
  - RT
  - Anthracyclines

Cumulative Incidence of Breast Cancer in Hodgkin Lymphoma Survivors

Early Detection of Breast Cancer

- Starting at the age of 25 or 8 years after RT:
  - Breast self-examination every month
  - Examination by a clinician every 6 months
  - Mammogram annually with breast MRI as an adjunct where available

Breast Cancer Surveillance Practices Among Women Treated With Chest RT for a Childhood Cancer

- Breast cancer screening post–chest RT recommended, starting at age 25
- Of 551 survivors treated with chest RT:
  - 47% of women ages 25–39 had never had a mammogram
  - 53% of women ages 40–50 were being regularly screened
Mantle/Mediastinal RT

- Average of 11.2 years follow-up – standardized mortality ratio of myocardial infarction (MI) = 3.2
- By 30 years, cumulative incidence of MI = 12.9%
- By 20 years post–moderate dose RT (37.2 Gy), actuarial risk of symptomatic CAD = 21.2%
  - 294 asymptomatic Hodgkin lymphoma survivors
  - Stress echo and radionuclide perfusion scan
  - 21% with abnormal testing
  - 11% with CAD proven by cardiac catheterization
  - Functional (not anatomic) method of detection

CT Coronary Angiography

Figure 1.
CT showing a normal left anterior descending artery with curved reconstruction.

Figure 2.
CT showing a curved reconstruction of left main and proximal left anterior descending arteries with numerous calcified plaques.

- ALL at age 3.5 years
  - Chem including prednisone
  - 24 Gy cranial RT
- Age 23 years
  - BMI = 40.2 kg/m²
  - Waistcirc = 138.5 cm
  - High-density lipoprotein = 38 mg/dL
  - Triglycerides = 223 mg/dL
  - Low-density lipoprotein = B pattern
  - Glucose = 92 mg/dL
  - Insulin = 53 IU/mL
  - Insulin resistance index (HOMA) = 12.0
  - High-sensitivity C-reactive protein = 12.1 mg/dL

---

Cardiovascular Disease: Potential Mechanisms

- Methotrexate
  - HoY spikes ≥ 30 mos
  - Endothelial Damage
- CRT
  - Steroids
  - Body fat redistribution
  - Oxidative stress
  - Physical Inactivity
  - LV dysfunction
- Vincristine
  - Gait or balance abnormalities
  - Cardiac function
- Anthracyclines
  - LV dysfunction
- CVD
BMI Among Adult Survivors of Childhood ALL Following Cranial RT: Childhood Cancer Survivor Study

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Baseline</th>
<th>Follow-up</th>
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</thead>
<tbody>
<tr>
<td>Male</td>
<td>24.9 yrs</td>
<td>21.0 yrs</td>
<td>24.9 yrs</td>
<td>21.0 yrs</td>
</tr>
<tr>
<td>Female</td>
<td>24.9 yrs</td>
<td>21.0 yrs</td>
<td>24.9 yrs</td>
<td>21.0 yrs</td>
</tr>
</tbody>
</table>


Insulin Resistance Comparisons Between ALLIFE and DHS

<table>
<thead>
<tr>
<th>DHS versus</th>
<th>ALLIFE vs DHS P value* adjusted for Race only</th>
<th>Race and BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLIFE: all</td>
<td>&lt;.000</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ALLIFE: CRT</td>
<td>&lt;.000</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ALLIFE: no CRT</td>
<td>&lt;.000</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ALLIFE: all</td>
<td>&lt;.000</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ALLIFE: CRT</td>
<td>&lt;.000</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ALLIFE: no CRT</td>
<td>&lt;.000</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Log transformed analysis

**Presentations**

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**Percentage With a CVD Risk Factor**

- **Women**
  - (HOMA, TG, HDL, BP, Waist, CRP)

<table>
<thead>
<tr>
<th>CVD Risk Factors</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>40</td>
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<td>60</td>
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<tr>
<td></td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>100</td>
</tr>
</tbody>
</table>

*HOMA, insulin resistance, triglycerides, high-density lipoproteins, blood pressure, waist circumference, C-reactive protein*


---

**VO₂ Maximum Testing**

**NHANES Fitness Classification**

- (mL/kg per minute)
- **Women**
- **Men**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Women (%)</th>
<th>Men (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>78.5</td>
<td>64.0</td>
</tr>
<tr>
<td>Moderate</td>
<td>16.9</td>
<td>32.0</td>
</tr>
<tr>
<td>High</td>
<td>4.6</td>
<td>4.0</td>
</tr>
</tbody>
</table>

*Age and sex-specific norms for VO₂ max values.*

NHANES = National Health and Nutrition Examination Survey.
Model for Risk-Based Care

- High-risk population
- Wide array of potential late effects
- Risk often does not plateau with aging
- Clinically silent period for many late effects – 20–30 years
- Potentially modifiable by secondary or tertiary prevention and early diagnosis and intervention
### Presentations

#### Plan for Risk-Based Care

- Monitor for recurrence of cancer
- Surveillance for second cancers and late effects
  - Early diagnosis and intervention
- Prevention
  - Tobacco use, physical activity, calcium intake
- Counseling and education

---

#### Standardized Screening

- Late Effects Screening Guidelines from the Children's Oncology Group
- [www.survivorshipguidelines.org](http://www.survivorshipguidelines.org)
- Melissa Hudson/Wendy Landier
- Multidisciplinary
- Strength of the association of treatment exposure to late effects
- Principles of screening/surveillance in a high-risk population
Most Childhood Cancer Survivors Are Not Followed at a Cancer Center

Future Directions of Care

- There is not adequate capacity to care for pediatric cancer survivors in the United States
- Increasing numbers and capacity of long-term follow-up programs
- Partnerships with the community
- Hybrid programs
  - Stratified by risk of survivor – low, medium, high
  - Frequency and location based on risk
Summary

- Cancer survivors face long-term risks
- Many late effects are modifiable
- Goal of risk-based survivor care
  - Reduce morbidity and mortality rates
  - Enhance quality of life

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- ALLIFE Co-Investigators
- Our survivors and their families
Presentations

Question-and-Answer Session

Thank You
References

Barton A. Kamen, MD, PhD


References

Kevin C. Oeffinger, MD


Mission Statement

For information on leukemia, lymphoma and myeloma, call The Leukemia & Lymphoma Society’s Information Resource Center at (800) 955-4572 or visit www.LLS.org.

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