The Leukemia & Lymphoma Society®

Fighting Blood Cancers

LEUKEMIA | LYMPHOMA | MYELOMA

THE PEDIATRIC TREATMENT APPROACH TO ADULT ACUTE LYMPHOCYTIC LEUKEMIA:

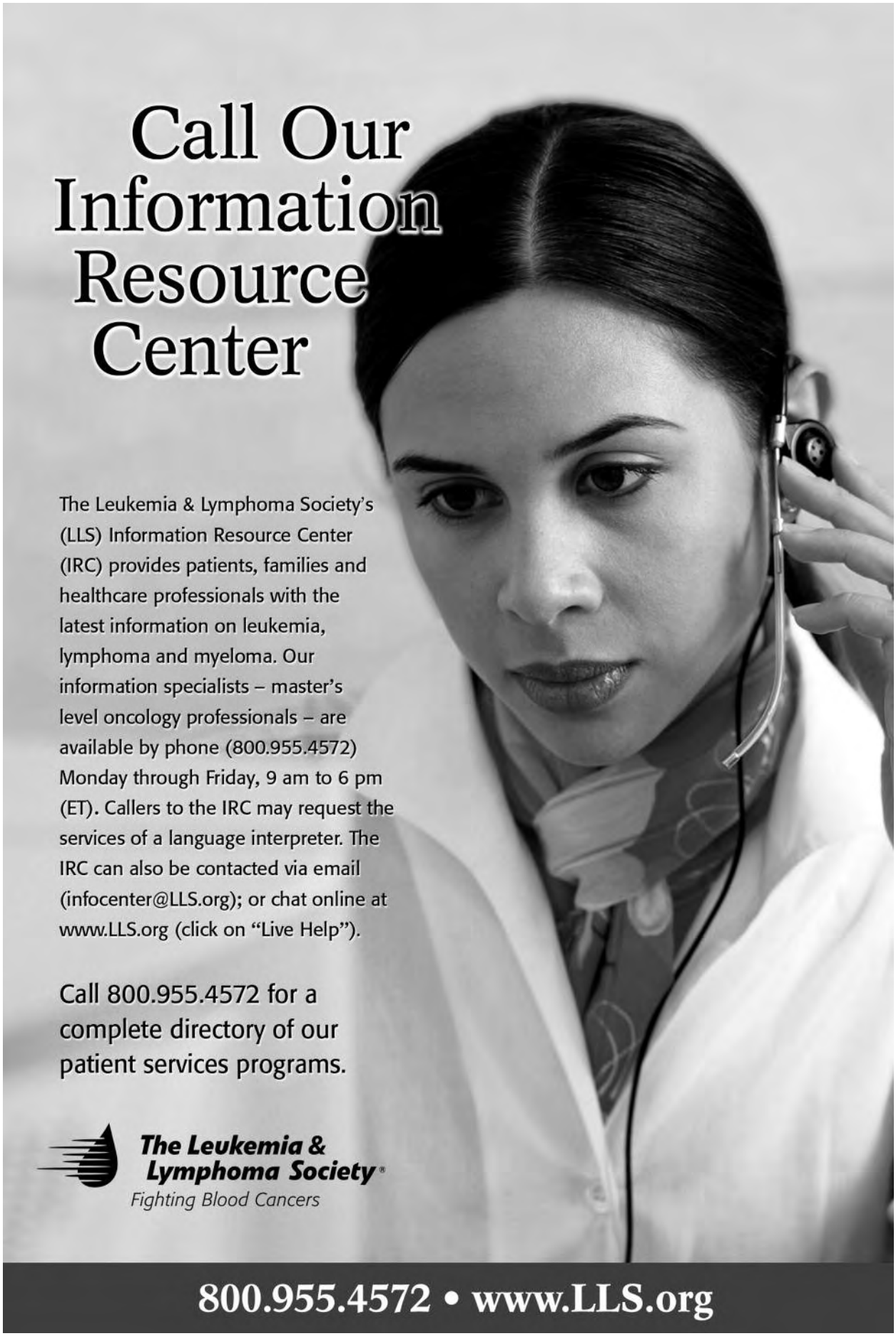
A complimentary ONLINE continuing education activity for registered nurses

PERSPECTIVES FOR ONCOLOGY NURSES

ACTIVITY WORKBOOK

Supported by a grant from Enzon Pharmaceuticals, Inc.

ENZON PHARMACEUTICALS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Agenda

Welcome

Carson Jacobi, MPH
Vice President, National Education Programs
The Leukemia & Lymphoma Society
White Plains, NY

Treating Young Adults and Adults With Acute Lymphocytic Leukemia: Why and How

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

Acute Lymphocytic Leukemia in the Adolescent and Young Adult

Katherine A. Breitenbach, BA, RN
Clinical Research Nurse
Section of Hematology/Oncology
University of Chicago Medical Center
Chicago, IL

Question-and-Answer

Overview

TARGET AUDIENCE

Oncology nurses and other healthcare professionals involved in the care of patients with adult acute lymphocytic leukemia (ALL).

ACTIVITY PURPOSE

This activity is designed to educate oncology nurses about the pediatric treatment approach to adult acute lymphocytic leukemia (ALL).

STATEMENT OF NEED

Acute lymphocytic leukemia (ALL) is a disease that affects both children and adults.[1] Although it is more prevalent in children, approximately 1,000 new cases of adult ALL are diagnosed annually in the United States. Treatment of adult ALL typically consists of combination therapy given in induction, consolidation and occasionally maintenance phases.[1] Most adult regimens are adopted from pediatric protocols and modified to utilize lower doses and shorter duration of asparaginase therapy. However, several recent studies suggest that pediatric regimens, including larger amounts of steroid, chemotherapy and asparaginase therapy, may result in improved outcomes.[2,3] Moreover, recent reports from overseas suggest superior outcomes in adult ALL patients when oncologists adhere to and successfully deliver pediatric therapy regimens.[2,3] As nurses play a major role in the treatment of adult ALL patients,[4] it is imperative that these individuals be aware of the challenges and benefits associated with administration of pediatric ALL treatment protocols in the setting of adult ALL.

1. Seiter K. Available at http://emedicine.medscape.com/article/207631-overview. Accessed July 13, 2009.
2. Wetzler M, et al. *Blood*. 2007;109:4164-4167.
3. Huget F, et al. 2008 ASCO Annual Meeting. Abstract 7005.
4. Viele CS. *Semin Oncol Nurse*. 2003;19(Suppl):98-108.

EDUCATIONAL OBJECTIVES

At the conclusion of the activity, the participant should be better able to:

- Examine data from clinical trials using pediatric acute lymphocytic leukemia (ALL) treatment protocols in adult ALL patients
- Describe therapeutic options for ALL
- Apply knowledge of administration and drug interactions to ALL treatments
- Develop a plan for side effect management that maximizes patient safety, treatment adherence and quality of life

STATEMENT OF SUPPORT

This continuing education program is supported by a grant from Enzon Pharmaceuticals, Inc.

Faculty Biographies

Barton A. Kamen, MD, PhD
Chief Medical Officer
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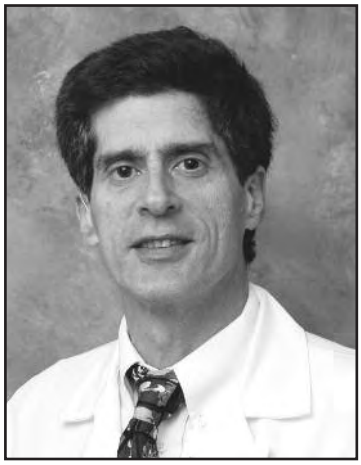
New Brunswick, NJ



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*.

Faculty Biographies

Katherine A. Breitenbach, BA, RN
Clinical Research Nurse
Section of Hematology/Oncology
University of Chicago Medical Center
Chicago, Illinois

Katherine A. Breitenbach is a clinical research nurse in the section of Hematology/Oncology at the University of Chicago Medical Center. In her current position, she coordinates the care of patients with acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML) and acute promyelocytic leukemia (APL), maintains protocol adherence for patients on clinical trials and works closely with the bone marrow transplant program to ensure continuity of care for patients. Ms. Breitenbach graduated magna cum laude from Luther College in Decorah, Iowa, with a Bachelor of Arts in Nursing, and is currently enrolled in a dual Master of Science program in Adult and Geriatric Advanced Practice Nursing at the University of Illinois in Chicago, Illinois.

Ms. Breitenbach is an Oncology Nursing Society Chemotherapy and Biotherapy Provider and a member of the Honor Society of Nursing, Sigma Theta Tau International.

Faculty Disclosures

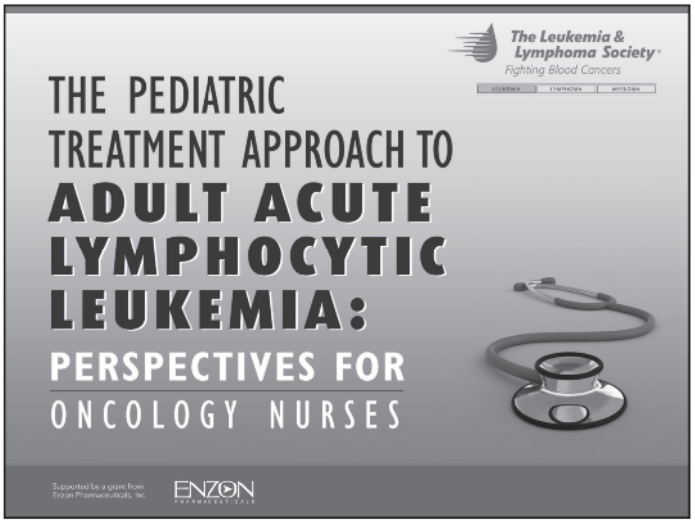
DISCLOSURE OF CONFLICTS OF INTEREST

All faculty participating in continuing education (CE) activities by The Leukemia & Lymphoma Society are expected to disclose to the activity participants any significant financial interest or other relationships with the manufacturer(s) of any commercial product(s) discussed in their presentations. Faculty also are expected to disclose any unlabeled or investigational uses of products discussed in their presentations.

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 CE activity:

- **Barton A. Kamen, MD, PhD,** has no affiliations with commercial interests to disclose.
- **Katherine A. Breitenbach, BA, RN,** has no affiliations with commercial interests to disclose.

Presentations



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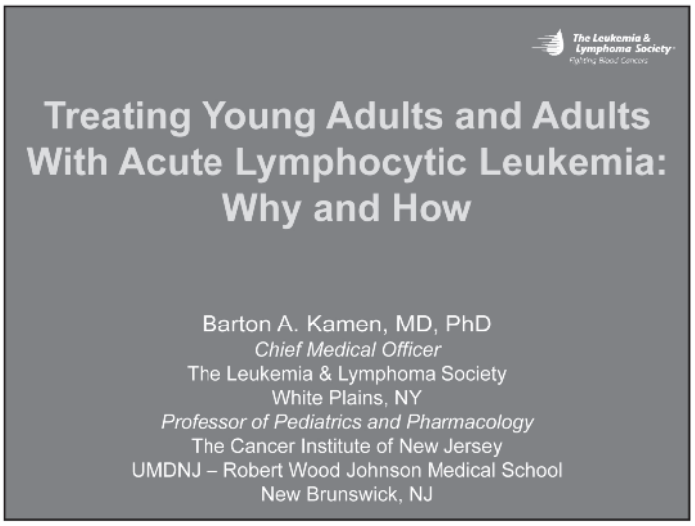

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Presentations

Disclosure of Conflicts of Interest

Barton A. Kamen, MD, PhD

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

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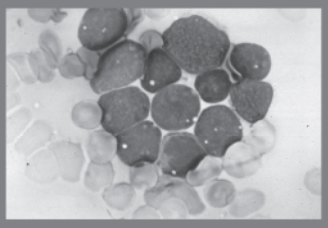
What Is Acute Lymphocytic Leukemia (ALL)?

- Most common pediatric malignancy (25%–30%)
- Virtually the only common cancer in which more kids are affected than adults



Reality is that like other cancers, ALL is a really heterogenous disease

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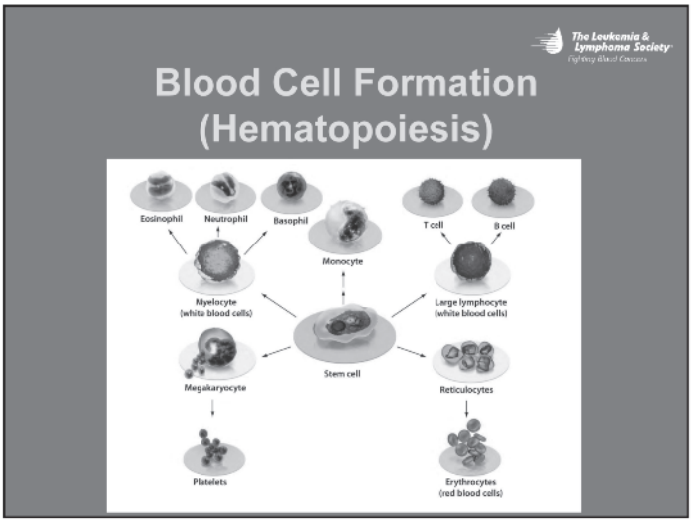

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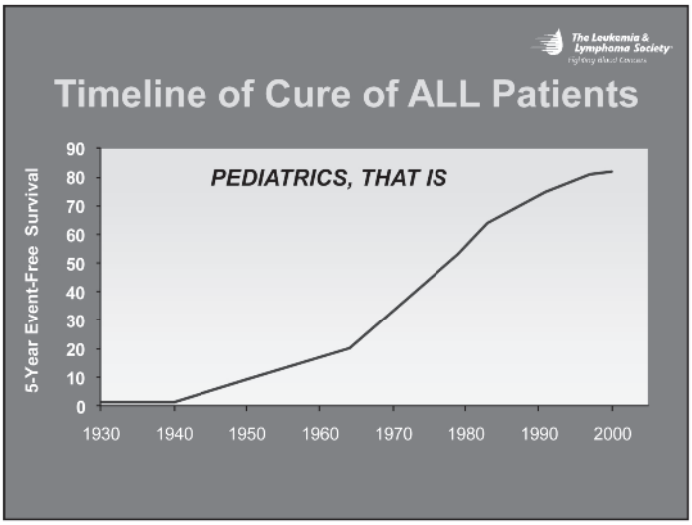

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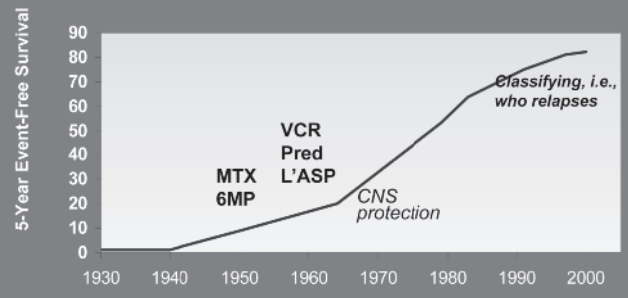
Outcomes of Patients Treated on Either Pediatric or Adult ALL Clinical Trials

Study Group	Years	Age (years)	Event-Free Survival by Regimen Type	
			Pediatric	Adult
USA	1988–2001	16–20	63	34
Dutch	1985–1999	15–18	69	34
Sweden	1992–2000	15–20	74	39
UK	1997–2002	15–17	65	49

Barry EV, Silverman LB. *Curr Hematol Malig Rep.* 2008;3:161-166.

7

Timeline of Cure and Introduction of New Drugs in Treatment of ALL Patients



L'ASP=L=asparaginase; 6MP=6-mercaptopurine; MTX=methotrexate; Pred=prednisone; VCR=vincinstine.

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Basically, the drugs for ALL are

40+ years old…

Knowing how to use them wisely is how we cure patients

Personalizing/tailoring

Independent variable for success is:
DID THE MEDICINE GET IN?!!

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Induction Therapy

- Vincristine
- L-Asparaginase
- Steroid (prednisone or dexamethasone)

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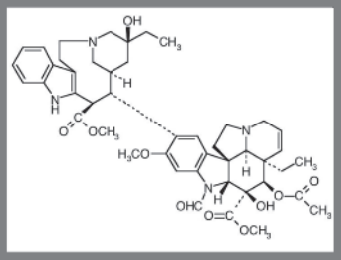
Vincristine



The rosy periwinkle (*Catharanthus roseus*)

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Vincristine Side Effects

Common	Less Common	Rare?
• Constipation • Hair loss • Feeling tired	• Pain or redness at the infusion site • Nausea/vomiting* • Loss of appetite • Diarrhea • Changes in how things taste • Lowered white blood cell count with increased risk of infection* • Lowered blood platelet count with increased risk of bleeding* • Lowered red blood cell count (anemia)	• Numbness, tingling, or pain in the hands, feet • Trouble urinating • Jaw pain • Deep tendon reflex decrease, foot drop, weakness

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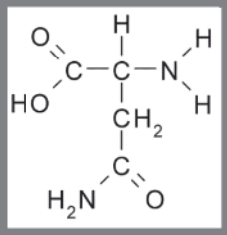
L-Asparaginase



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L-Asparaginase Side Effects

- Allergic reactions: important to separate local from systemic
- Hyperglycemia
- Pancreatitis
- Clotting
- Bleeding
- Azotemia

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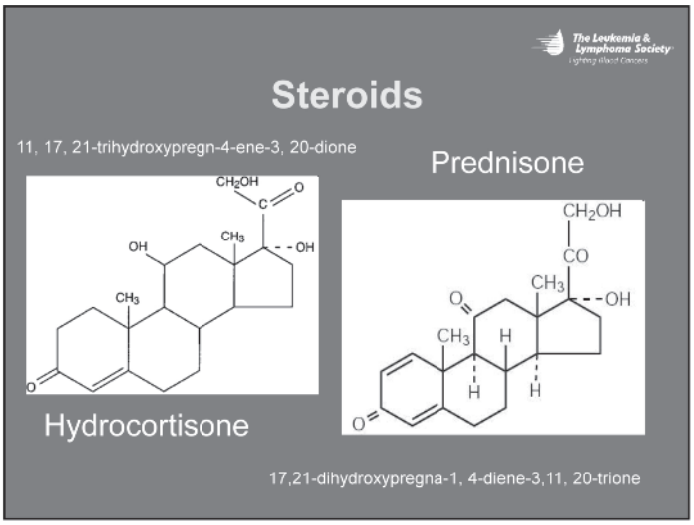

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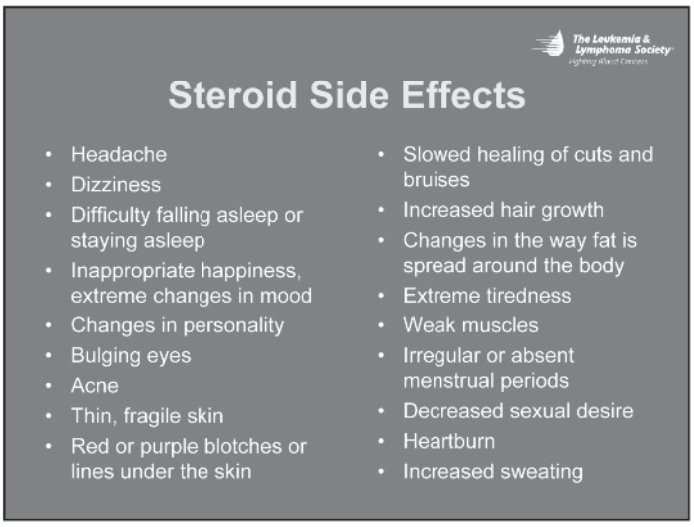

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Continuation Therapy

(Also known as maintenance therapy)

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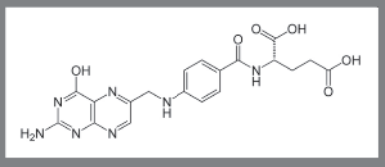
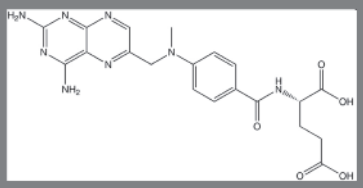


Folic acid



Methotrexate

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Presentations

Methotrexate Side Effects

- "Blahs," malaise, zoned out
- Impotent
- Skin rash
- Decreased blood counts
- Stomatitis
- Encephalopathy
- Acute stroke-like event
- Photosensitivity
- Transaminitis
- Renal failure

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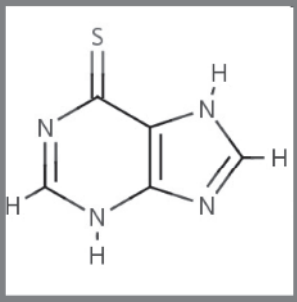
6-Mercaptopurine (Purinethol)



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6-Mercaptopurine Side Effects

- Hepatic dysfunction
- Pancytopenia
- Ulcers

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FUTURE??

(while awaiting the magic bullet)

There are pharmacogenetic/pharmacodynamic parameters for most of the drugs that we just discussed

How to use them correctly should increase the cure and decrease the toxicity

And the Future is NOW

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Presentations

1

Acute Lymphocytic Leukemia in the Adolescent and Young Adult

Katherine Breitenbach, BA, RN
Clinical Research Nurse
Section of Hematology/Oncology
University of Chicago Medical Center
Chicago, IL

2

Disclosure of Conflicts of Interest

Katherine Breitenbach, BA, RN

Ms. Katherine Breitenbach has no affiliations with commercial interests to disclose.

Presentations

The Leukemia & Lymphoma Society
Fighting Blood Cancers

Objectives

- Examine data from clinical trials using pediatric acute lymphocytic leukemia (ALL) treatment protocols in adult ALL patients
- Review therapeutic options for ALL
- Apply knowledge of administration and drug interactions to ALL treatments
- Develop a plan for side effect management that maximizes patient safety, treatment adherence and quality of life

3

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Estimated New Leukemia Cases & Deaths
US, 2008

	New Cases	Deaths
Leukemia	44,270	21,710
AML	13,290	8,820
ALL	5,430	1,460
CML	4,830	450
CLL	15,110	4,390
Other	5,610	6,590

American Cancer Society. *Cancer Facts & Figures 2008*. Atlanta: American Cancer Society; 2008.

4

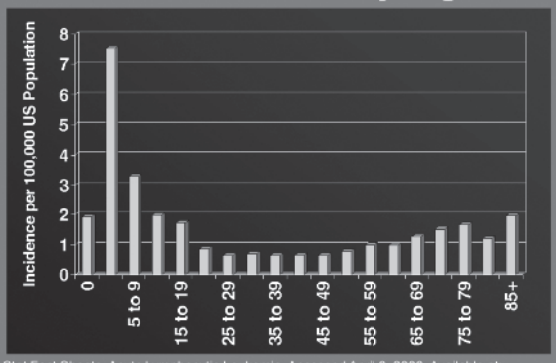
Presentations

ALL: Prognostic Factors

- Age
  - May be the most significant prognostic factor
- Cytogenetics
- Leukocyte count at presentation
- Immunophenotype
- Time to achieve complete remission (CR)

5

ALL: Incidence by Age



Cancer Stat Fact Sheets. Acute Lymphocytic Leukemia. Accessed April 8, 2008. Available at: www.seer.cancer.gov/statfacts/html/alyl.html.

6

ALL: Childhood vs Adult Disease Outcomes

- Both adults and children achieve high initial remission rates
- However, most children are cured whereas most adults relapse

	Complete Remission	Leukemia-Free Survival
Adults	80%–90%	35%–40%
Children (2–10 years of age)	>95%	80%–90%

Pui CH, Evans WE. *N Engl J Med.* 2006;354:166-178.

7

ALL and Cytogenetics: Predictors of Outcome

Cytogenetic Characteristic	*Incidence in Children*	*Incidence in Adults*
Hyperdiploidy >51 chromosomes	25%	5%
*TEL-AML t(12,21) *Trisomies 4,10, 17	20%–25%	1%–3%
Philadelphia/BCR-ABL+ t(9,22) q(34,11)	5%	25%–30%
MLL-AF4 t(4,11) q23 Other 11q23 MLL rearrangements	4%–7%	2%–3%
Hypoploidy <45	5%	5%

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Presentations

ALL: Leukocyte Count at Presentation and Outcome

- Elevated WBC count at diagnosis may indicate:
  - Decreased CR rate
  - Decreased remission duration
  - Decreased overall survival
  - Increased risk of central nervous system (CNS) relapse
- Definition varies between clinical trials
  - > 30 × $10^3/mm^3$ – 100,000 × $10^3/mm^3$
- May play a more significant role in B-cell ALL vs T-cell ALL

Gökbuget N, et al. *Hematology*. 2006;133-141.
Rowe JM, et al. *Blood*. 2005;106:3760-3767.

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ALL: Childhood vs Adult Disease Biology

	Children	Adults
Peak incidence	5 years old	50 years old
% of all	80%–85%	5%
T-cell	10%–15%	20%–25%
Mature B-cell	1%–2%	3%–5%
Ph+ ALL	3%	20%–30%

Ph=Philadelphia chromosome.

Sallan SE, et al. *Hematology*. 2006;128-132.

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ALL: Immunophenotyping

B-cell Lineage Immunophenotype		T-cell Lineage Immunophenotype	
Early pre-B-cell ALL	CD 19, CD 79a, CD 22	Pre-T-cell ALL	CD 1a, CD 2, CD 5, CD 7, CD 8, CD 3
Common ALL	CD 10 (CALLA)	Mature T-cell ALL	Surface CD 3 with any other T-cell marker
Pre-B-cell ALL	Cytoplasmic IgM		
Mature B-cell AL	Cytoplasmic or surface Igκ, Igλ		

CALLA = common ALL antigen

Bene MC. *Leukemia*. 1995;9:1783-1786.

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Minimal Residual Disease (MRD) Is a Strong Prognostic Variable

Validation of end of induction (day 29) as a strong prognostic factor*

Variable	Hazard Ratio	*P* value
Day 29 MRD >0.01%	4.3	<0.001
NCI risk group	2.3	<0.001
Day 8 PB MRD >0.01%	1.5	0.018
Trisomies 4 and 10	0.57	<0.001
TEL/AML1	0.78	0.151

PB=peripheral blood.
*Cox multivariate analysis included 1971 patients from COG studies P9904, P9905, and P9906.

"End-induction MRD appeared to predict both early (within 3 years) and late relapse" – Borowitz et al, 2008

Borowitz MJ, et al. *Blood*. 2008;111:5477-5485.

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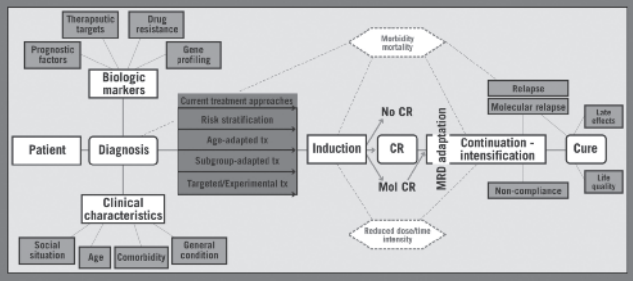
Presentations

ALL: Factors Influencing Treatment



Gökbuget N, Hoelzer D. *Hematology Am Soc Hematol Educ Program*. 2006;1:133-141; with permission.

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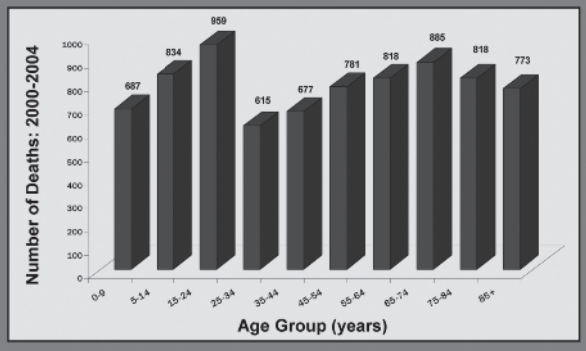
ALL Mortality: 2000–2004

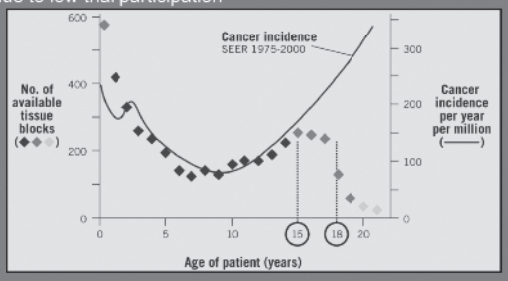


Bleyer A. 2008 ASCO Annual Meeting [Abstract 18034].

14

Adolescents and Young Adults (AYAs): Low Trial Participation

- Fewer tumor specimens were available from AYAs during 2003–2004 due to low trial participation



Bleyer A. *Pediatr Hematol Oncol.* 2007;24:325-336. with permission.

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Impact of Children's Cancer Group (CCG) vs Cancer and Leukemia Group B (CALGB) Analysis on the Design of Ongoing and Future Prospective Trials

- Stock et al. *Blood* 2008
- Retrospective comparison
  - Presenting clinical and molecular cytogenic features
  - Type and dosage of planned treatment
  - CR rate
  - Clinical outcome of AYAs treated on CCG or CALBG protocols during 1988–2001

Stock W, et al. *Blood.* 2008;112:1646-1654.

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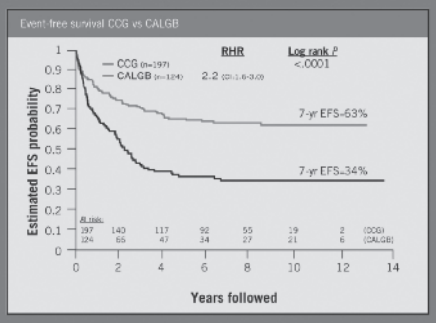
Significant Survival Differences: CCG vs CALGB



Stock W, et al. *Blood*. 2008;112:1646-1654; with permission.

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Treatment Outcome by Phenotype and Genotype

Patient Characteristics	CCG 16 to 20 years (n=197)	CALGB 16 to 20 years (n=124)	*P* Value
Median age, y	16	19	<0.001
Sex, no. (%) male	129 (65)	87 (70)	0.45
Ethnic distribution, no. (%)			0.89
White	141 (72)	90 (73)	
Hispanic	32 (16)	19 (15)	
African American	13 (7)	10 (8)	
Other	11 (5)	5 (4)	
Immunophenotype, no. (%), evaluable	143	92	
Precursor-T	23 (16)	23 (25)	0.56
Precursor-B	93 (65)	64 (70)	0.13
Other	27 (19)	5 (5)	0.006
Cytogenetics, no. (%), evaluable	67	81	
t(9;22)	2 (3)	5 (6)	0.60
t(4;11)	2 (3)	2 (2)	0.75
Initial WBCs more than 50 x 10^9 L, no. (%)	47 (24)	26 (21)	0.64

Stock W, et al. *Blood*. 2008;112:1646-1654.

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ALL: Age-Adapted Therapy

Adolescents/Young Adult ALL Outcomes

Country	National Trial	Age (Years)	Pts.	5-Yr EFS (%)
US	CCG (P)	16 - 21	196	64[a]
	CALGB (A)		103	38[a]
France	FRALLE 93 (P)	15 - 20	77	67
	LALA94 (A)		100	41
Holland	DCOG (P)	15 - 18	47	69
	HVON (A)		44	34
UK	ALL97 (P)	15 - 17	61	65
	AKALLXII (A)		67	49
Italy	AIEOP (P)	14 - 18	150	80[b]
	Ginema (A)		95	71[b]

[a]6-yr EFS; [b]2-yr OS.

P=pediatric; A=adult; EFS=event-free survival.
Sallan SE. *Hematology*. 2006;128-132.

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Why Do AYAs Do Better With a Pediatric Approach?

- Protocol design
- Dose intensity
- Degree of adherence
  - "Emancipated adolescents"
  - Adult physicians
- More frequent dosing of non-myelosuppressive drugs
- Earlier and more frequent CNS prophylaxis/treatment

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Presentations

What Has Been Learned From Past Pediatric Studies?

- Intensified post-induction therapy improves event-free survival
- Response tailored therapy
- Pattern of disease recurrence shifting to CNS relapse
- Less radiation, more upfront CNS prophylaxis
- Dexamethasone may be more efficacious than prednisone, but may increase osteonecrosis
- Discontinuous dexamethasone lessens osteonecrosis
- Methotrexate essential component of therapy
- Prolonged maintenance phase is necessary

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AYAs Are a Unique Population

- Cancer biology not as well understood
- Physiologic and psychological differences
- Differences may be due to varying factors
  - Environment
  - Health services
  - Compliance
  - Pharmacokinetics

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Presentations

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ALL: Treatment Therapy Children vs Adults

Pediatric Protocols <21 years of Age	Adult Protocols >16 years of Age
• More doses of non-myelosuppressive therapy (vincristine, peg-asparaginase, glucocorticoids) • Earlier and more frequent CNS treatment • Continuous maintenance therapy for 2–3 years	• More myelosuppresive therapy • Shorter therapy duration

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CALGB 10403

Induction

Vincristine
Daunorubicin
Peg-Asparaginase
IT Cytarabine
IT Methotrexate

Consolidation

Cyclophosphamide
Cytarabine IV or SQ
IT Methotrexate
Mercaptopurine
Peg-Asparaginase
Vincristine

Interim Maintenance

Escalating IV methotrexate
Vincristine
Peg-Asparaginase
IT Methotrexate

Delayed Intensification

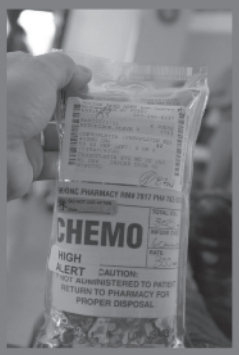
Vincristine
Doxorubicin
Dexamethasone
Peg-Asparaginase
IT Methotrexate
Cyclophosphamide
Cytarabine IV or SQ
Thioguinine

Maintenance

Vincristine
Mercaptopurine
Dexamethasone
IT Methotrexate
(testicular/cranial irradiation)

Cytarabine (ARA-C)

- Administer IV or SQ
- Myelosuppression
- ARA-C syndrome
  - Fever
  - Rash
  - Conjunctival irritation



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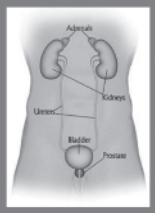
Cyclophosphamide

- IV
- Myelosuppression: leukopenia/thrombocytopenia
  - Delayed effect (nadir, 8–14 days)
- Hemorrhagic cystitis
  - Urinate frequently
  - Increase fluids
  - Check urine if genitourinary symptoms present
  - Mesna? 200 mg/m^2 15 min before, 3, 6, and 9 hours post-infusion
- Gastrointestinal toxicities: anorexia/nausea/vomiting



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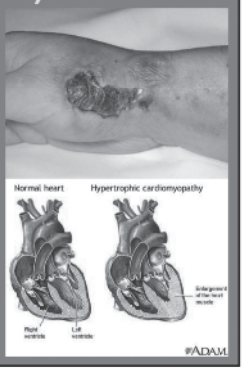
Daunorubicin/Doxorubicin (Anthracyclines)

- **IV: potent vesicant**
- Myelosuppression
- Alopecia: usually complete and reversible
- Nausea/vomiting
  - Doxorubicin is highly emetogenic
- **Cardiotoxicity**: based on cumulative lifetime dose
  - Congestive heart failure
  - Decreased ejection fraction
  - Cardiomegaly @ dose >550 mg/m^2 (daunorubicin)
  - Cardiomyopathy @ dose >450 mg/m^2 (doxorubicin)



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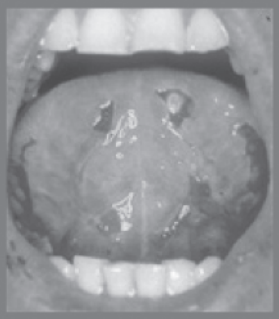
Methotrexate



- IV and PO
- Myelosuppression (pancytopenia)
- Gastrointestinal toxicities
  - Diarrhea
  - Nausea/vomiting
  - GI bleeding
  - The "itis": gingivitis/glossitis/mucositis/stomatitis
  - Hepatic toxicity
- Renal toxicities
  - Increased creatinine
  - Crystalluira mainly at doses >1 g

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Presentations

ALL: Lumbar Puncture/CNS Treatment

Classification of CNS Status

- **CNS1**: No blasts (regardless of WBC in cerebrospinal fluid [CSF])
- **CNS2**: Blasts present, CSF WBC <5/µL
- **CNS3**: Blasts present, CSF WBC >5/µL
  - Clinical symptoms evident (facial nerve palsy, brain/eye symptoms, hypothalamic syndrome
  - Administration should be done intraventricularly (i.e., via Ommaya port)

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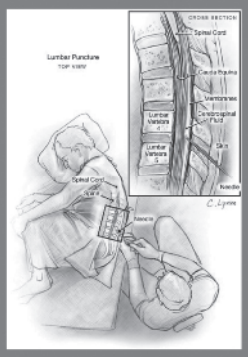
Lumbar Punctures: Side Effects



- **Headache**
  - Blood Patch for CSF leak
  - Caffeine
  - Laying flat for appropriate amount of time
- Arachnoiditis
- Nausea/vomiting
- Other CNS effects not as commonly seen: ataxia, coma, confusion, dementia, seizures, **paresis**
- **Involved process
- **Potential late effects
  - Neurologic deficits
  - Leukoencephalopathy
  - Seizures

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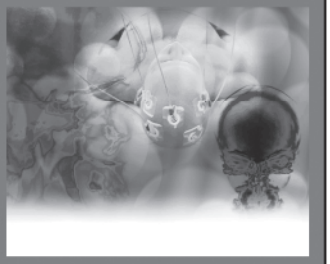
ALL (T Cell): Cranial Irradiation

- Side effects: fatigue, headache, nausea/vomiting and scalp irritation
- Potential late effects:
  - Endocrine issues
  - Neurocognitive defecits
  - Leukoencephalopathy
  - Seizures
  - Cerebrovascular complications
  - Cataracts
  - Second malignancies

**Testicular irradiation is indicated for males who present with ALL and testicular involvement



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Mercaptopurine/Thioguinine (6MP/6TG)

- Myelosuppression
- GI toxicity
  - Nausea/vomiting
  - Stomatitis
  - Hyperbilirubinemia
  - Serum aspartate aminotransferase and alanine aminotransferase (AST/ALT) elevation
- Drug interactions
  - Do NOT give concurrently with allopurinol
  - Do not administer with milk products
  - Enhanced effect if taken at bedtime with empty stomach

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Vincristine (VCR)

- Vesicant
- Non-myelosuppressive
- Main side effect: neurotoxicities
  - Numbness of extremities
  - Paresthesias
  - Loss of deep tendon reflex
  - Neuropathic pain/muscle weakness
  - Cranial nerve manifestations: diplopia, hoarsness, tinnitus, jaw pain…seen with first dose
- GI toxicity
  - Ileus/constipation
  - Hyperbilirubinemia
  - Increased AST/ALT

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Glucocorticoids

- PO/IV prednisone and dexamethasone
- Dexamethasone: may be more efficacious than prednisone
  - Longer half-life
  - Increased affinity for steroid receptors
  - Better CNS penetration
  - Greater risk for chronic toxicities
- Some research suggests that 14-day course of steroid may provide the same cytoreduction as 28 days[1]

1. Brisco MJ, et al. *Cancer Res*. 2000;60:5092-5096.

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Glucocorticoids: Side Effects

Abdominal pain, acne vulgaris, adrenocortical insufficiency, amenorrhea, angioedema, anorexia, anxiety, ***appetite stimulation***, arthralgia, ***avascular necrosis***, bone fractures, cataracts, constipation, Cushing's syndrome, depression, ***diabetes mellitus***, diaphoresis, diarrhea, dysmenorrhea, ecchymosis, ***edema***, EEG changes, emotional lability, erythema, esophageal ulceration, euphoria, exfoliative dermatitis, exopthalmus, fever, ***fluid retention***, gastritis, ***headache***, heart failure, hirsutism, hypercholesterolemia, ***hyperglycemia***, hypernatremia, hypertension, hypocalcemia, hypokalemia, hypotension, immunosuppression, infection, ***insomnia***, lethargy, menstrual irregularity, mood lability, myalgia, myopathy, nausea/vomiting, ocular hypertension, optic neuritis, ***osteoporosis***, palpitations, pancreatitis, papilledema, peptic ulcer, peripheral neuropathy, petechiae, phlebitis, pseudotumor cerebri, **psychosis**, ***restlessness***, retinopathy, seizures, sinus tachycardia, skin atrophy, thrombocytopenia, thrombosis, urinary incontinence, urinary urgency, urticaria, vertigo, visual impairment, weakness, ***weight gain or loss***.

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Asparaginase: Mechanism of Action Review

- Asparaginase hydrolyzes asparagine to its main components, aspartic acid and ammonia[1,2]
- Hydrolysis of asparagine results in the depletion of circulating serum asparagine, starving leukemic cells, and inducing apoptosis[1,2]
- Asparaginase allows for selective treatment options in ALL given its lack of effect on normal cells[1]
- Glutamine depletion by asparaginase may also contribute to its antileukemic effect[3,4]

1. Asselin BL. *Drug Resistance in Leukemia and Lymphoma III.*
2. Graham ML. *Adv Drug Deliv Rev.* 2003;55:1293-1302.
3. Kafkewitz D et al. *Am J Clin Nutr.* 1983;37:1025-1030.
4. Reinert RB et al. *J Biol Chem.* 2006;281:31222-31233.

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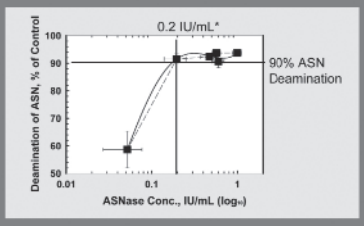
Presentations

Correlation of Asparaginase Activity and Asparagine Depletion

- Asparaginase levels are highly correlated with extent of asparagine and glutamine deamination



*This study evaluated the pharmacokinetics and pharmacodynamics of pegylated L-asparaginase administered intravenously in newly diagnosed patients with ALL ≤55 years of age (during remission induction).
Douer D et al. *Blood.* 2007;109:2744-2750; with permission.

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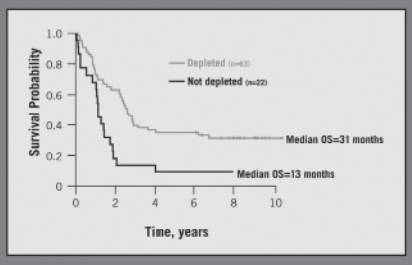
Improved Survival in Young and Mature Adults Who Achieved Asparagine Depletion

Survival Comparison Based on Achievement of Asparagine Depletion



Pegylated L-asparaginase dosing[1]:
- Induction:
  First 21 patients received 2000 IU/m² SC (capped at 3750 IU) on day 5. Additional patients enrolled received pegylated L-asparaginase on day 22 also
- Early intensification:
  Days 15 and 43 (not all patients)

Adapted from Wetzler M, et al. *Blood.* 2007;109:4164-4167; with permission.

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Peg L-asparaginase (PEG)

- IM or IV…IV preferred
- IM injections 2 mL max volume per site
- Monitor blood sugar
  - Hyperglycemia may start after PEG, and last days to weeks
  - If high, give PEG and treat hyperglycemia
- Observe 30 min to 4 hours post-administration for signs of allergic reaction
  - Administer epinephrine, diphenhydramine, methlprednisone
  - Educate patient regarding delayed hypersensitivity reactions
  - Reactions can last for days
  - If hypersensitivity reaction occurs, switch to erwinia asparaginase if available
    - Do not retest reaction!
- Monitor patient for coagulopathies, deep venous thrombosis, cerebrovascular episodes, and pancreatitis

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Additional Issues in Treating the AYA With ALL

- Optimizing chemotherapy, dosing, & schedule
  - **ALL** treatment should be given **ON SCHEDULE**
  - *"There should be no delay in administering the prescribed treatment on the required schedule for non-medical reasons such as vacations."*
  - Are adult physicians/nurses part of this problem?
- Adherence to treatment regimen
  - Is non-compliance a side effect of ALL
    - Missed visits
    - Refused treatment
    - Taking medications incorrectly
  - "Emancipated adults"
- Maximizing supportive care options
  - Reduce side effects of treatment to increase adherence
  - Caveat of adding more medications to an already complicated treatment regimen

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Presentations

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Teach, teach, teach…and if that doesn't work, nag and then educate some more!

- Visual aids: calendars/medication lists/treatment plan
  - Medication cards
  - Technology era: handheld devices/cell phones
  - Keep on hand in clinic setting
    - Update/change: give patient a copy
- Continue to review treatment plan
- Educate about adherence

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Teach, Teach, Teach…

- At EACH clinic visit:
  - Review all medications
  - Assess for toxicities/side effects
  - Assess for adherence
  - Give end-of-visit summary: JCAHO requirement
- Important for the oncologist and oncology nurse to realize that AYA population does not seek regular medical care
  - Likely only physician AYA is seeing
  - Must understand need to address primary care issues
    - Maintenance of healthy lifestyle
    - Alcohol/drugs

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Assessing Quality of Life

"Cancer is in the car with me but it's not driving"

- Numerous psychosocial issues with AYAs
  - Identify their social network: who supports them?
  - Transportation
  - Finances
- Sense of normalization is imperative
  - Length of treatment
  - Loss of lifestyle
  - Body image changes
- Identify resources
  - Support groups
  - The Leukemia & Lymphoma Society
  - Social workers
  - Psycho-oncologists

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Survivorship: Potential Late Effects

- Anthracyclines, total 175 mg/m^2
  - Cardiomyopathy, low risk
  - Echocardiogram every 5 years
  - Counsel regarding healthy lifestyle
- Intrathecal methotrexate
  - Neurocognitive deficits
  - Leukoencephalopathy, seizures
- Cranial radiation
  - Endocrine issues
  - Neurocognitive defecits
  - Leukoencephalopathy, seizures
  - Cerebrovascular complications
  - Cataracts
  - 2nd malignancies

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Presentations

Survivorship: Potential Late Effects (*Cont'd*)

- Testicular radiation
  - Infertility
  - Hypogonadism
- Cyclophosphamide, low total dose
  - Infertility
  - Premature menopause
  - Secondary acute myeloid leukemia, low risk
- Steroids
  - Cataracts
  - Osteopenia/osteoporosis
  - Osteonecrosis/avascular necrosis

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Future Directions in Research to Improve Outcomes in ALL

- Development of novel therapies to treat ALL
  - Enhancing our understanding of the genetics and epigenetics of ALL
  - New generations of testing and genetic sequencing technologies
- Applying the model of treatment for young adults and adolescents to an older population
  - Where is the age cut-off for adult treatment on a pediatric regimen?
- Quality of life: factors affecting adherence to treatment regimen and changing patient behaviors
- Longitudinal research into long-term complications and survivorship

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Question-and-Answer Session

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Fighting Blood Cancers

For more information about
Adult Acute Lymphocytic Leukemia
and other LLS programs, contact:

Information Resource Center (IRC)
Toll-free Phone: 1-800-955-4572
E-mail: infocenter@lls.org

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The Leukemia & Lymphoma Society®

Fighting Blood Cancers

Mission Statement

The Leukemia & Lymphoma Society's mission: Cure leukemia, lymphoma, Hodgkin's disease and myeloma, and improve the quality of life of patients and their families

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.

The Leukemia & Lymphoma Society
1311 Mamaroneck Avenue
White Plains, NY 10605

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