ALL
Understanding Diagnosis and Treatment for Adults

someday is today | LEUKEMIA & LYMPHOMA SOCIETY fighting blood cancers

Welcome and Introductions

ALL
Understanding Diagnosis and Treatment for Adults

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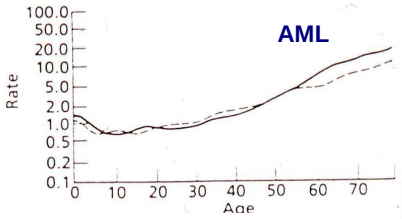
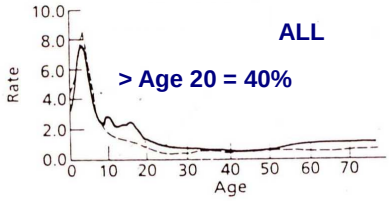
ALL Topics

- How ALL is diagnosed and how risk assessment is determined?
- Risk assessment and treatment plan development
- Treatment options
- The role of clinical trials in the advancement of ALL treatment for patients
- Communication touch points among patients and healthcare providers

Epidemiology
Age Specific Incidence Per 100,000 Population

- In 2013: 6,300 new cases in US
- In the United States: more in Hispanics[1]
- Most common cancer in children (30% of all pediatric cancers)
- Pediatric ALL, the most curable cancer

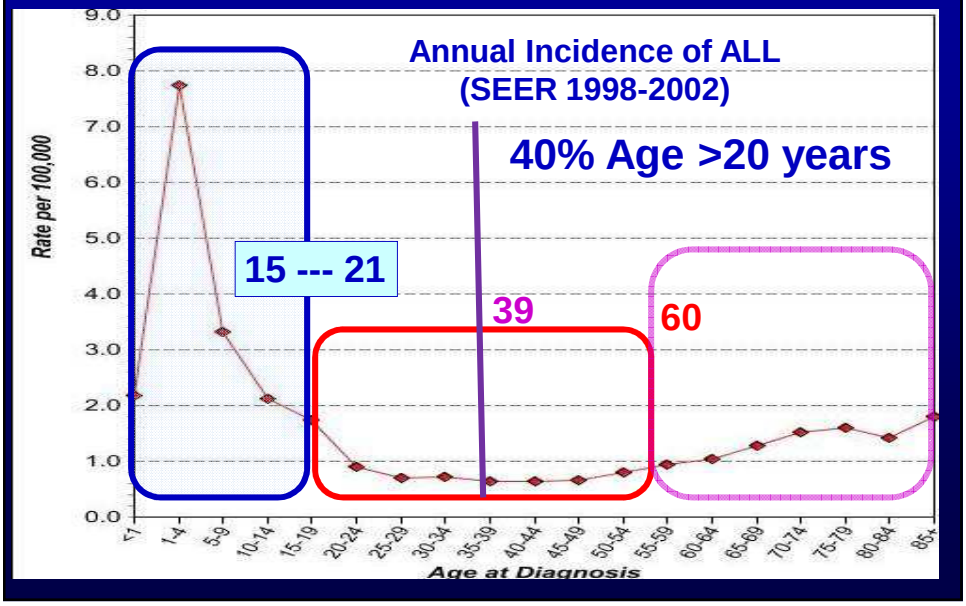




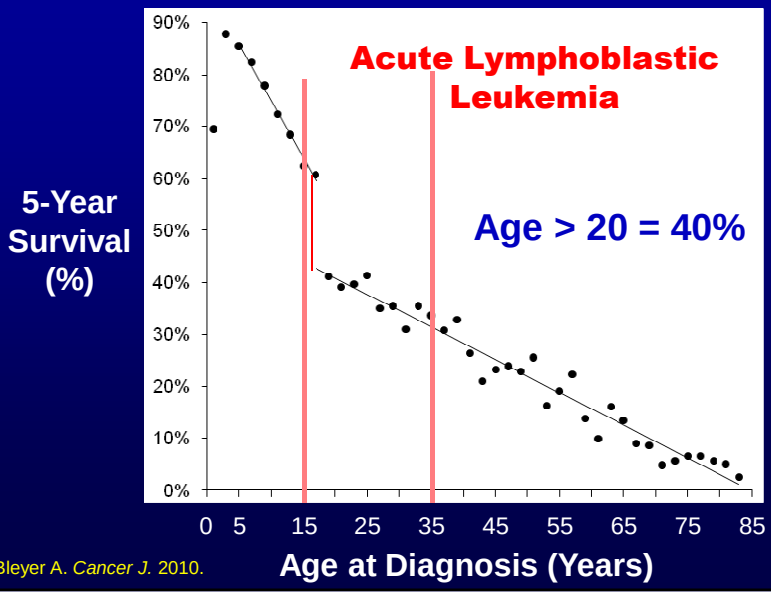
Leukaemias: age-specific incidence rates per 100 000 population. Female, – – –; male, —— [5].

[1]Pullarkat. *Cancer Epidem Biomark.* 2009;18:611.

ALL - Not Just a Pediatric Disease
Treatment Age Groups



Survival by Age at Diagnosis
2 Year Age Intervals, 2000-2007, SEER17



Bleyer A. *Cancer J.* 2010.

Acute Leukemia
Clinical Features (I)

- Acute presentation
- Blood
  - Anemia → weakness, tiredness
  - Low platelets → bleeding
  - Low neutrophils → infections
  - Blast cells appear with time
- Bone marrow
  - Blast cells ≥ 20%
  - Normal hematopoiesis suppressed or not detectable

Acute Leukemia
Clinical Features (II)

- Extramedullary infiltrations
  - Spleen, liver
  - Lymph nodes (ALL)
  - Non-hematological tissues
    - Skin
    - Gums
    - CNS (ALL)
    - Other organs

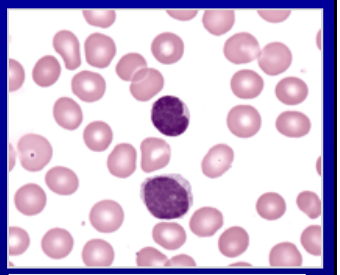
Diagnostic Evaluation for Acute Leukemia

- CBC with differential
- Examination of peripheral blood smear
- Coagulation studies
- Blood chemistries
- Bone marrow aspiration and biopsy
  - Leukemia blast:
    - Immunophenotype
    - Cytogenetics
    - Molecular genetics

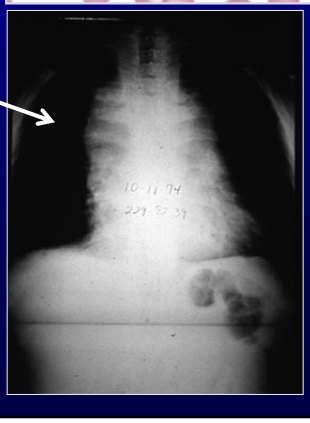
Diagnostic Tests

- Immature cells: CD34
- Myeloid/monoctyic: MPO,CD13, CD33, CD15, CD14
- Immature lymphoid markers: TdT
- Pre B-cells - TdT, CD10, CD19, CD22, CD20
- T-cells - CD3, CD5, CD7, CD8, CD4, CD1a
- True biphenotypic acute leukemia (very rare)

T-cell ALL
25% of Adult ALL



- Young adults
- Without marrow involvement - T-cell lymphoblastic lymphoma (mediastinal mass)
- High WBC
- Better prognosis
- Higher rate of CNS relapse



ALL: Karyotype and Outcome

Decreased event-free or overall survival
t(9;22) (Ph+)
t(4;11)
Complex karyotype (≥ 5 abnormalities)
Low hyperdiploidy / near triploidy (Ho-Tr)
Improved event-free or overall survival
Hyperdiploidy
Del (9p)

Ph = Philadelphia chromosome

Moorman AV, et al. *Blood*. 2007;109:3189-3197.

Other Poor Prognostic Indicators

- Increasing age
- Increasing WBC count
  - 30,000 for B-cell lineage
  - 100,000 for T-cell lineage
- Immune phenotype
  - Non T-cell lineage
  - Pro B ALL - CD10 negative
- Slow response to therapy
  - Adults, CR 4 weeks
  - Minimal residual disease (MRD)

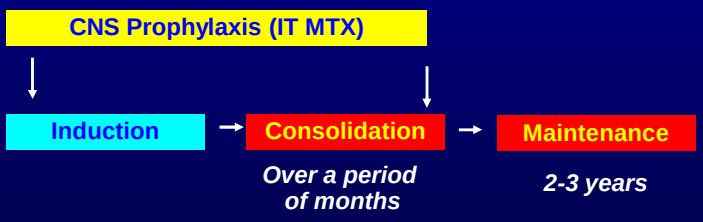
Bassan R, et al. *Crit Rev Oncol Hematol.* 2004;50:223-261.

Specific Recurrent Genetic Abnormalities

Gene	Outcome
Pre-B	
IKZF 1 (IKAROS)	Poor
RCLF2	Poor
MLL-v t(v;1)	Poor
T-cell	
FBXW7	Good
NOTCH 1 (70%)	Good
NUP-ABL1 (6%)	Response to TKI

ALL: Treatment Elements

Induction, consolidation, maintenance phases and CNS prophylaxis



Challenges in Establishing "State-of-the-Art" Treatment

- Very wide age range
  - AYA — 15 to 39 yrs
  - Adults ("younger") — 40 to 60/65 yrs
  - Older adults — 60/65+
- Multiple chemotherapy regimens with few comparable trials
- Uncertainty about the role of allo BMT
- Pediatric or "Pediatric-inspired" regimens

NCCN guidelines – clinical trial or pick your favorite

Principals of Adult ALL Protocols
(All include maintenance and CNS prophylaxis)

- **"BFM model" variants (CALGB, GMALL, ECOG)**
  - Induction: 2 phases, 8 drugs w/asparaginase
  - Consolidation
    - Complex multi-agent cycles
    - Asparaginase
    - Delayed re-induction

- **Hyper-CVAD (alternate Parts A and B x 4)**
  - More myelosuppressive drugs (inpatient)
  - No asparaginase
  - 6-MP only in maintenance

Adult ALL - Recent Large Front-line Clinical Trials

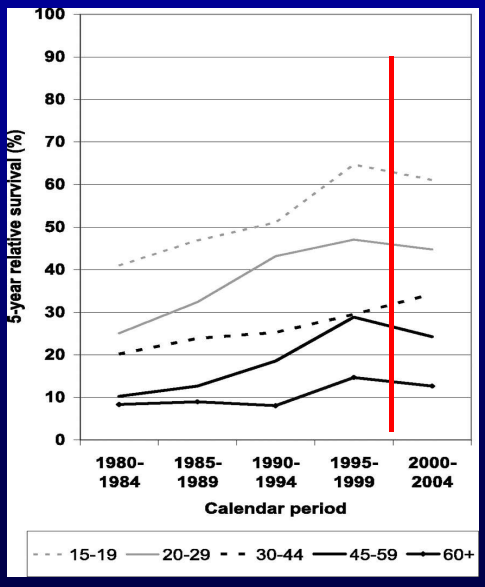
	Years of study	N	Age	Treatment	CR (%)	DFS (%)
GMALL 05/93[1]	'93-'99	1163	35	BFM, HD-Ara-C, HD- MTX	87	35
CALGB 8811[2]	'88-'91	198	35	BFM, ↑Cy, ↑ASP	85	36
CALGB 19802[3]	'99-'01	163	41	BFM, ↑Cy, ↑DNR	78	35
MRC/ECOG-UKALLXII/E2993[4]	'93-'06	1913	15-64	BFM + HD-MTX ± SCT	90	OS 39
Hyper CVAD[7]	'92-'00	288	40	A) Cy, DEX, ADR, VCR B) HD-MTX+HD-Ara-C	92	38
UCSF 8707[5]	'87-'98	84	27	VPDA + Intensified	93	52
LALA 94[6]	94-02	922	33	VPD + Cy, HD-Ara-C	84	37
L-2	00-06	78	33	HD-MITO+ HD-Ara-C	85	34

[1]Gökbuget. *Blood*. 2001;98:802a; [2]Larson. *Blood*.1995;85:2025-2037; [3]Larson. *Ann Hematol*. 2004;83:Suppl 1:S127-S128; [4]Goldstone. *Blood*. 2008;111:1827-1833; [5]Linker. *J Clin Oncol*. 2002;20:2464-2471; [6]Thomas. *J Clin Oncol*. 2004;22:4075-4086; [7]Kantarjian. *Cancer*. 2004;101:2788.

Central Nervous System Prophylaxis

- Intrathecal methotrexate
- Systemic high-dose methotrexate
- Cranial irradiation
  - Probably not necessary with systemic high-dose treatment (methotrexate, Ara-C) and extended intrathecal methotrexate

5-year Survival of ALL by Major Age Groups 1980-1984 to 2000-2004



Age

15-19

20-29

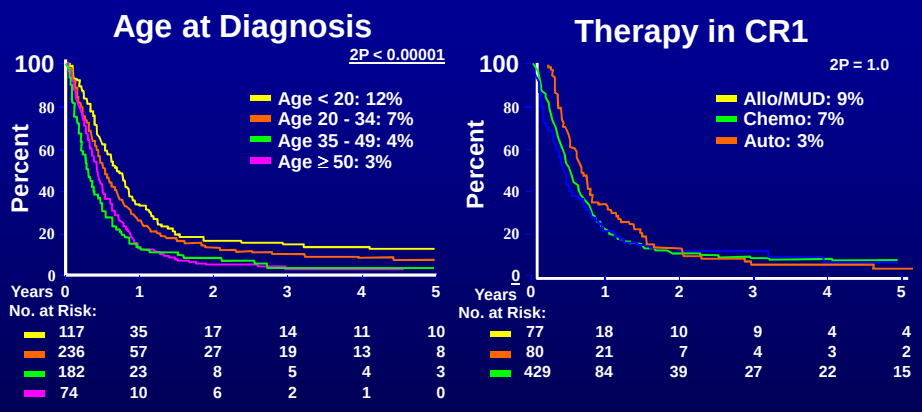
30-44

45-59

60+

Pulte. *Blood.* 2009.

Adult ALL – First Relapse Survival



Fielding, et al. *Blood.* 2007.

Strategies to Improve Outcome of Adult ALL

- Transplantation
- Pediatric-inspired regimens
- Identify special subtypes for different treatment
  - Mature B cell (Burkitt's) ALL
  - Ph+ ALL
- New drugs

Bone Marrow Transplantation
CIBMTR Recommendations

- **CR 1**
  - **Allogeneic transplant in high-risk patients**
  - **Role in standard-risk patients unclear but not recommended**
  - **Autologous SCT: no benefit over chemotherapy**
- **CR 2**
  - **Allogeneic SCT**

Hahn T, et al. *Biol Blood Marrow Transplant*. 2006;12:1-30.

Allogeneic Stem Cell Transplantation
MRC/ECOG UKALLXII/E2993 Trial
Ph Negative ALL

	Overall survival		Relapse		Non-relapse death	
	Donor	No donor	Donor	No donor	Donor	No donor
High risk	41%	35%	37%	63%	36%	14%
	NS		*P*<0.0005		*P*<0.05	
Standard risk	62%	52%	24%	49%	20%	7%
	P<0.02		*P*<0.05		*P*<0.05	

High risk any of: Age ≥ 35 years

WBC > 30,000/μL (*B Lineage*)

> 100,000/μL (*T Lineage*)

Time to CR > 4 weeks

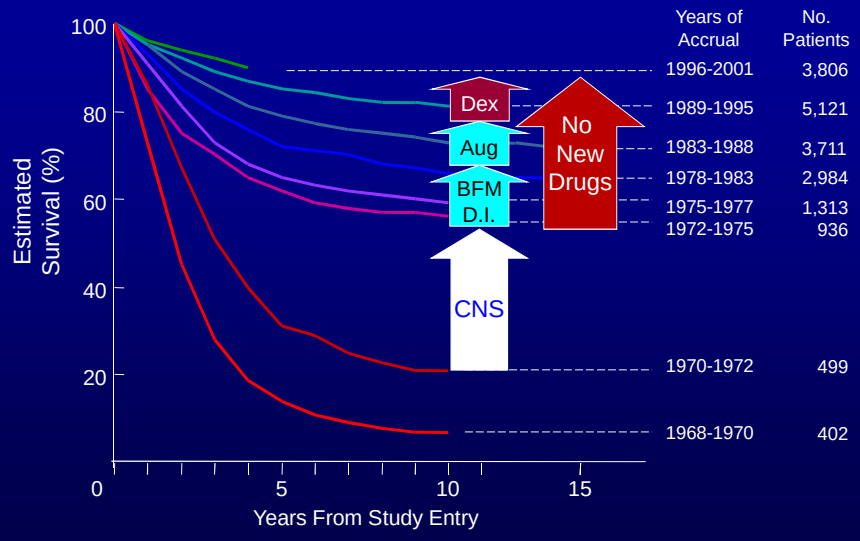
Goldstone. *Blood*. 2008;11:1827.

Outcome
Adults vs. Childhood ALL

	CR	LFS
Adults	80%-90%	35-40%
Children (2-10 years)	>95%	80%

Pui. *N Engl J Med.* 2006;354:166-178.

Survival of 18,772 Pediatric Patients With ALL Treated on Sequential CCG Clinical Trials Over Three Decades



Tubergen DG, Bleyer A. The Leukemias. *Nelson's Textbook of Pediatrics.* 17th Ed. Philadelphia, Pa: Saunders; 2003:1694-1698.

Adolescents and Young Adults Retrospective Comparison Pediatric vs. Adult Protocols

Study	N	Age	EFS @ 5 years	
			Pediatric protocol	Adult protocol
US[1]	321	16-20	63%	34%
France[2]	177	15-20	67%	41%
Netherlands[3]	120	15-20	69%	34%
Sweden[4]	59	15-20	75%	39%
UK[5]	128	15-17	65%	49%
Italy[6]	248	14-18	83%	55%

1.Stock. *Blood.* 2008;112:646; 2.Boissel. *J Clin Oncol.* 2003;21:774; 3.de Bont. *Leukemia.* 2004;18:2032; 4.Hallböök. *Cancer.* 2006;107:1551; 5.Ramanujachar. *Pediatr Blood Cancer*. 2006;47:748; 6.Testi. *Blood. 2005;*104:1954a.

Age - A Complex Prognostic Factor

- Age "per se" - children
  - Favorable cytogenetic
  - Better chemotherapy tolerance….. but….also in young adults
- Treatment - adults
  - Less intense
  - Very few randomized trials
  - Lower compliance: physician and patient

Pediatric Treatment Approaches Principals

- More intense non-myelosuppressive agents
- Prolonged asparaginase (asparagine depletion)
- Delayed re-induction
- Early CNS prophylaxis (induction)
- Allo BMT only for very high-risk e.g., t(4:11), Ph+

Asparaginase Activity in ALL Summary

- Active as a single agent (35%-60% in relapsed children)
- In children several randomized trials showed that asparaginase alone, (with multiple agents) improved overall outcome
- Duration of post-remission asparaginase
  - Children - long (5-6 cycles)
  - Adults - short (0-2 cycles)

Unique Toxicities of Asparaginase

- **Hypersensitivity:** allergic reactions
  - Neutralizing antibodies
  - "Silent hypersensitivity"
- **Pancreatitis**
- Hemostasis
  - **Clotting:** low antithrombin III, protein S
  - Bleeding: low clotting factors
- Liver dysfunction
  - Liver enzymes, hyperbilirubinemia
  - Low albumin
- Diabetes mellitus
- Neurological (lethargy, somnolence)

Stock and Douer, *Leukemia & Lymphoma.* 2011.

Asparaginase Intensification Pediatric and Pediatric - "Inspired" Regimens

	Asparaginase	Upper age	OS @ 3-7 yrs
True Pediatric			
DFCI[1]	E. coli	50	74%
CALGB 10403	Pegaspargase 2,500	39	Pending
Pediatric "Inspired"			
PETHEMA[2]	E. coli	30	69%
GRAALL-2003[3]	E. coli	45/60	64%/47%
USC[4]	Pegaspargase 2,000	57	58%
Princess Margaret[5]	E. coli (retrospective)	60	65%
Asparaginase Intensification			
GMALL 7/03[6]	PEG 500/1000 → 2,000	55	67%

[1]DeAngelo. ASH. 2007; [2]Ribera. *JCO.* 2008;Abst #587; [3]Huguet. *JCO.* 2009; [4]Douer. ASH. 2012;Abst #1495; [5]Storring J. *Br J Haematol.* 2009; [6]Goekbuget. ASH. 2010;Abst #404.

USC II Modified CCG Augmented Pediatric Arm (BFM)

Nachman N Engl J Med 1998;338:1663

PEG Asparaginase 2,000 u/m² IV per dose X 2

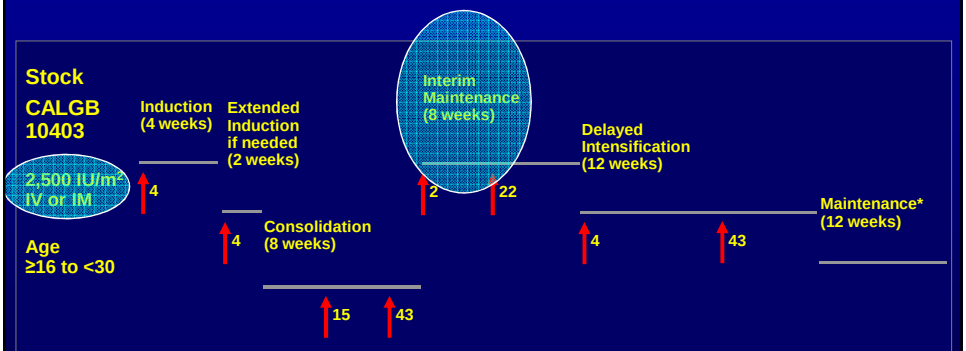
Induction1	Induction2	Consolidation1	Consolidation2	Delayed Re-induction1
DNR VCR PRED Peg-ASP IT-MTX	Cyclo VCR PRED Peg-ASP Ara-C 6MP IT-MTX	HD-MTX x2 Peg-ASP PRED	Days 1-5 Ara-C VM 26	DNR VCR Peg-ASP Cyclo DEX Ara-C 6-TG IT-MTX

Total Peg-ASP Doses = 6

Maintenance: 6 MP/ MTX/vincristine/prednisone therapy continues for 2 years

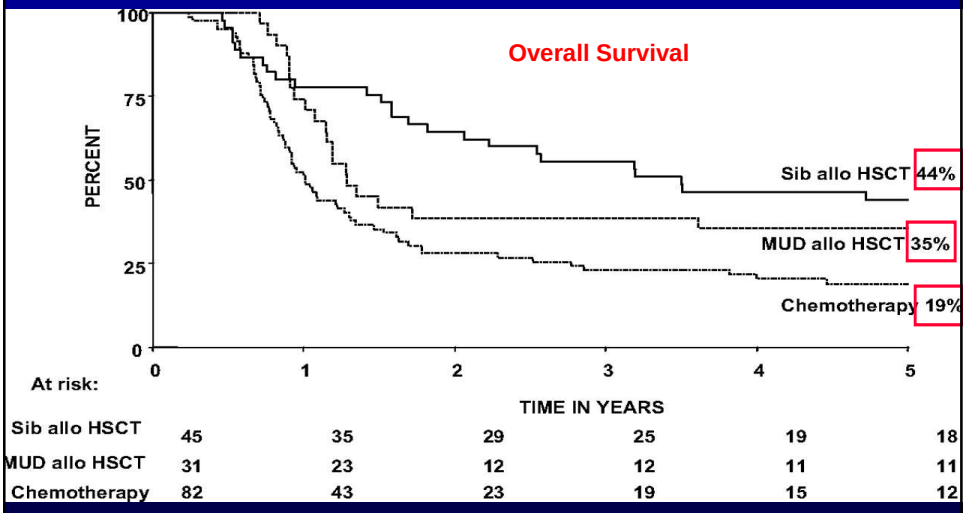
Douer, et al. ASH. 2012.

Current CALGB C10403 Trial Adolescents and Young Adults Age 15 – 39 years



*Repeat Maintenance Therapy courses (12 week courses; 84-day cycles) until total duration of therapy is 2 years from start of Interim Maintenance Therapy for female patients, or for male patients 3 years from the start of Interim Maintenance Therapy.

Ph+ ALL in CR1 – Pre-imatinib Era
MRC UKALLXII/ECOG 2993

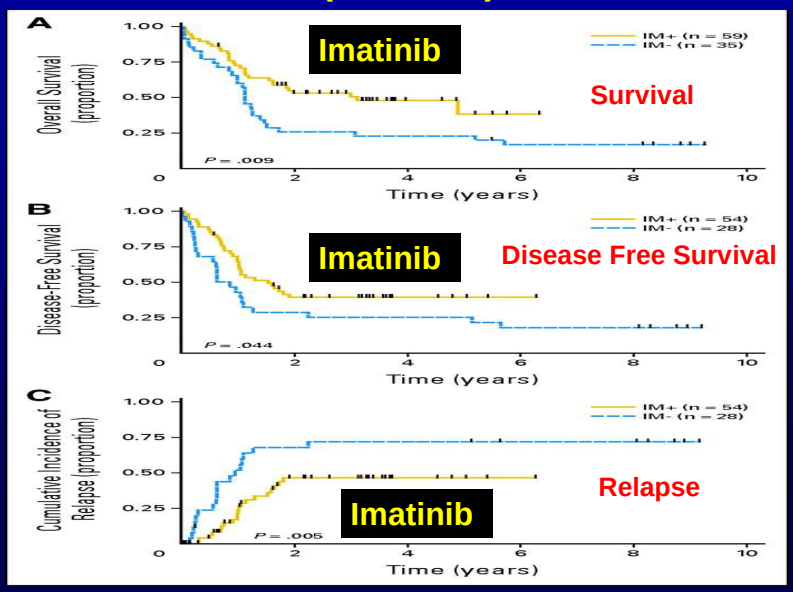


Fielding. *Blood.* 2009;113:4489-4496.

Philadelphia Chromosome (Ph$^+$) ALL

- t(9;22) bcr/abl translocation
- Precursor B-cell
- Incidence continuously increases with age (rare in children; ~50% in ages >55)
- Tyrosine kinase inhibitor activity
  - First generation – imatinib (Gleevec®)
  - Second generations – dasatinib (Sprycel®); nilotinib (Tasigna®)
  - Third generation ponatinib (Iclusig™)

Northern Italy Leukemia Group Protocol (Ph+ ALL)



Bassan R, et al. *JCO.* 2010;28:3644-3652.

Treatment of Ph+ ALL Summary

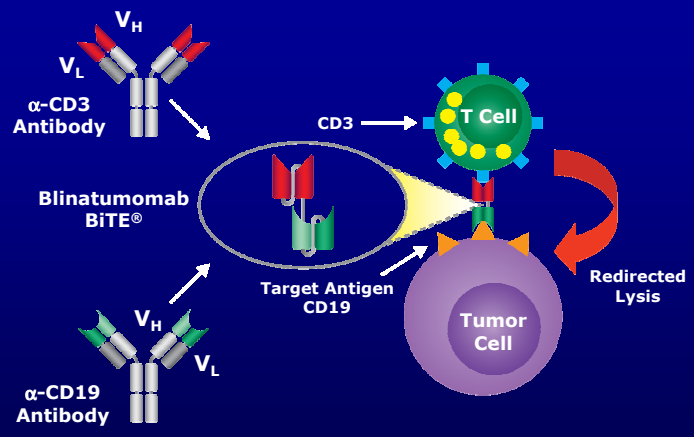
- TKI + concomitant multi-agent chemotherapy
  - Improved overall survival to 35-50%
  - Ideal chemotherapy?
- Allo HSCT
  - May improve outcome but not clear to what extent
  - In children no additional benefit after TKI + chemotherapy
- Second and third generation TKIs effective in imatinib-resistant or intolerant patient
- Changed outcome of Ph+ ALL [t(4;11) is now the worst ALL]

New Agents Targeting (Immunotherapy) B-cell ALL

Target	Agent	Single agent activity
CD 20	Rituximab[1,2]	Minimal (w/chemo may improve outcome in young CD20+)
CD 19	Blinatumomab[3,4]	CR 70% in molecular or overt relapsed/refractory
	19-28z CAR-targeted autologous T-cells[5]	Yes
CD22	Epratuzumab[6]	Minimal
	Inotuzumab ozogamycin[7]	CR + CRp = ~50%
	Moxetumomab pasudotox (HA22)[8]	CR 24%

[1]Hoelzer. ASH. 2010;Abst #170; [2]Thomas. *JCO.* 2010; [3]Topp. *JCO.* 2011; [4]Topp. ASH. 2011;Abst #252; [5]Davila. ASH. 2012;Abst #3566; [6]Raetz. *JCO.* 2008; [7]Wayne. ASH. 2011; Abst #248; [8]O'Brien. ASH. 2011;Abst #857.

Mode of Action of BiTE® Antibody Blinatumomab



- Blinatumomab (MT103) is a Bispecific T-cell Engager (BiTE®) antibody designed to direct cytotoxic T-cells to CD19 expressing cancer cells

Bargou R, et al. *Science.* 2008;321(5891):974-977.

Blinatumomab – Single Agent Refractory/Relapsed Pre-B ALL

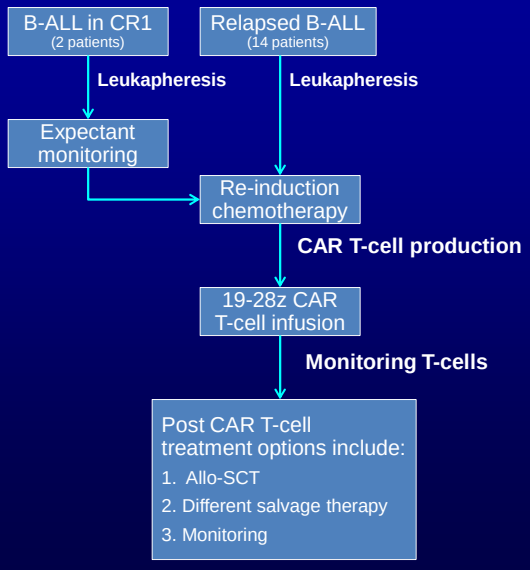
Disease Status	Pts. #	Response	Outcome
Molecular (MRD+)[1]	21 (5 Ph+)	MRD neg: 80%	RFS 78%
Clinical[2]	18	*CR 12 (67%) (all MRD neg)	Remission duration 7.8 Mo

*MRD negative after two cycles

[1]Topp, et al. *J Clin Oncol.* 2011;29;2433.
[2]Topp. ASH. 2011;Abst #252.

MSKCC CAR T-cell Protocol Eligibility and Treatment Schema

- Adult patients (>18 years old)
- Patients B-ALL refractory, relapsed, MRD+, or in CR1
- Ph+, extramedullary disease, CNS leukemia, and/or relapsed after prior allo-stem cell transplant are all eligible



Davila, et al. ASH. 2013;Abst #69.

Adverse Events

- Fevers
- Hypotension
- Hypoxia
- Neurologic changes
  - Mental status change, obtundation, seizures
- Malaise
- ICU care

CAR T-cells Summary
N=16 (overt ALL =8)

- CR=88%, CRm=76
- Median to CR =24 days
- 44% → allo-SCT (70% of eligible patients)
- Steroids
  - Effective at ameliorating the CRS
  - Cost of lymphotoxicity, resulting in eventual relapses
- Tocilizumab effective for CRS without lymphotoxicity
- Similar anti-leukemia efficacy in patients with only MRD as patients with morphologic residual leukemia
- To date, there have been no relapses post allo-SCT

Novel Targeted Agents

Target	Drug
Notch1 (T-ALL)	γ secretase inhibitors (GSI)
MLL (q11.34)	DOT1L inhibitor, FLT3 inhibitors
PP2A (Ph+ ALL)	FTY720 Fingolimod (MS)
PNP (T-ALL)	Forodesine (Bcx-1777)
NUP214-ABL1 T	Thyrosine kinase inhibitors
mTOR	Everolimus, temsirolimus
JAK	JAK inhibitors

State-of-the-Art Therapy for Adult ALL A Changing Landscape

- Pediatric or "pediatric inspired" regimens
  - Young adult: upper age limit is unclear
- Treatment changes based on new stratification models
  - Philadelphia positive
  - Early MRD status
  - "BCR-ABL1 – like" ALL (frequency in adults?)
  - Other mutations (RCLF2, IKZF……)
- No !!! State-of-the art therapy – relapse, older adults

State-of-the-Art Therapy for Adult ALL A Changing Landscape

Novel Agents

- Immunotherapy
  - Monoclonal antibodies (CD19, 22, 20)
  - Cell therapy – Chimeric antigen receptor (CAR)
- Small molecule targeting driver mutations (e.g., Notch1, Dotil, JAK2)

Allogeneic Hematopoietic Stem Cell Transplantation in CR1

- Only very high risk ALL?

Communication Touch Points Among Patients And Healthcare Providers

- Complex regimens – optimal adherence
  - Patient compliance
  - Physician compliance
  - Time and effort commitment: travel, parking, work, life events, etc.
- Reduce toxicities
  - Teaching of side effects (e.g. asparaginase)
  - Anticipating side effects
  - Monitoring for early detection of side effects
- Communication with healthcare provider
  - Major cancer center
  - Local community oncologists

THANK YOU

Dan Douer, MD
Memorial Sloan Kettering Cancer Center

Question & Answer Session

The speaker's slides are available for download at www.LLS.org/programs

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