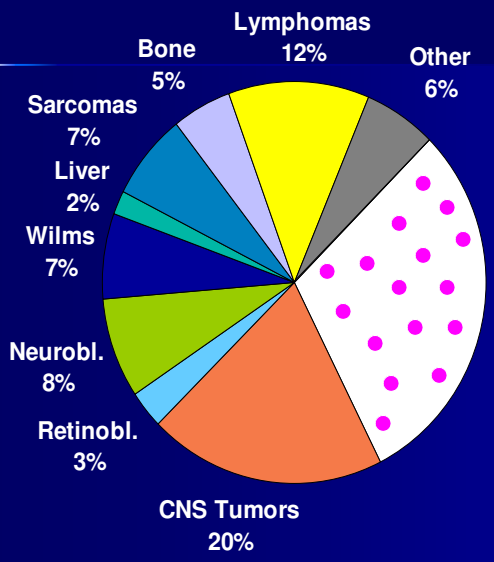
Pediatric ALL

Update on Treatment and Follow-Up Care

someday is today | LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers

Welcome & Introductions

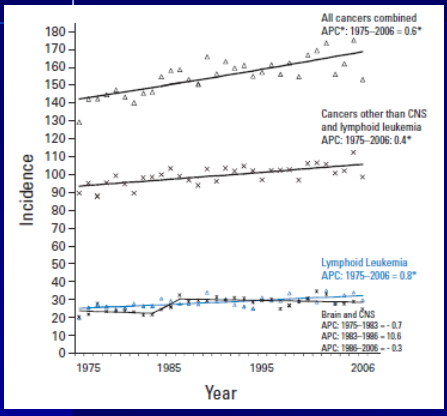
Types of Childhood Cancer

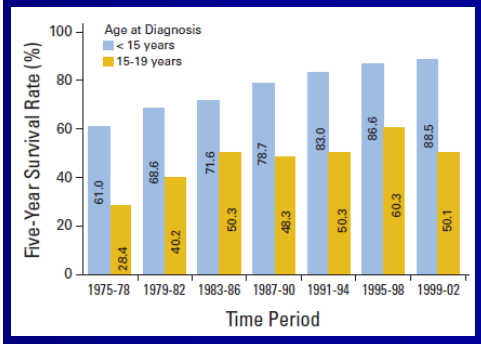


LEUKEMIA 30%
(25% ALL)

~2,500 children/yr diagnosed with ALL and rising

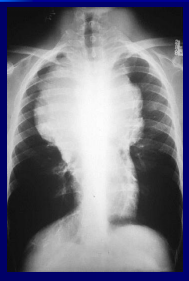
ALL Incidence and EFS

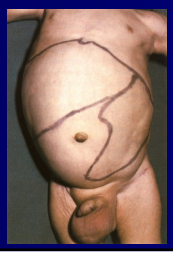


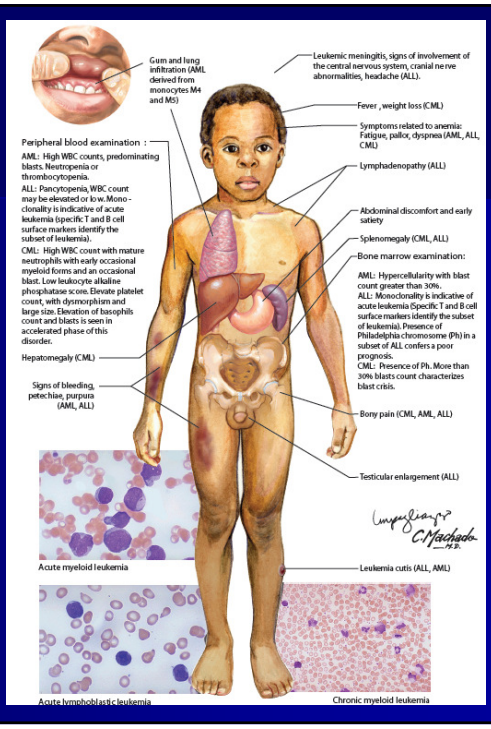


Smith MA et al. JCO May 2010

Clinical Presentation of ALL



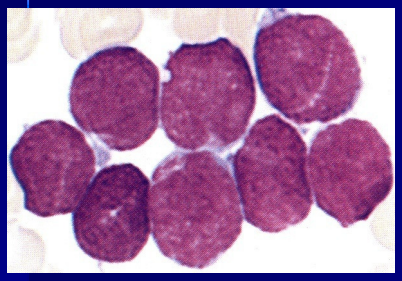


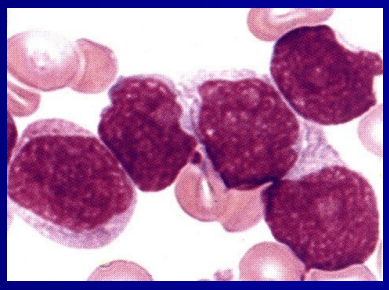


Diagnostic Procedures

- BM Aspirate & Biopsy
  - Morphology
  - Immunohistochemistry / Flow Cytometry
  - Cytogenetics
  - Microarray (SNP)
  - Biology studies
- Spinal Tap – CNS 1 (no leukemia)
  - CNS 2 (minimal leukemia)
  - CNS 3 (lots of leukemia)

Under the microscope





NCI/Rome Risk Classification for ALL

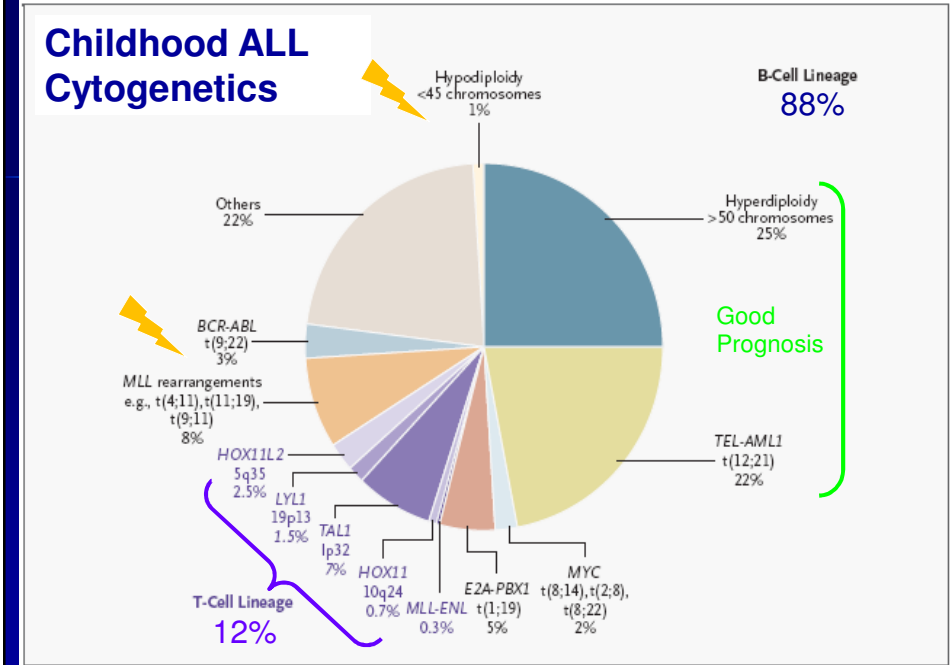
Age	WBC < 50,000/µl	WBC ≥ 50,000/µl
< 1 year	Infants (3%)	
1-10 years	Standard risk (58%)	
≥ 10 years		High risk (39%)

Immunophenotyping / Flow

Table 2. Common Markers Used in Flow Cytometric Immunophenotyping[a]

Antigen	Myelo-blasts	Promyelo-cytes	Maturing Grans	Mono-cytes	Erythroids	Megakar-yocytes	B Lym-phoid	T Lym-phoid	Comments
CD2	–	–	–	–	–	–	–	+	LFA-2; pan T-cell marker
CD3	–	–	–	–	–	–	–	+	OKT3; pan T-cell marker
CD4	–	–	–	–	–	–	–	Sub[b]	MHC-II associated; helper T cells
CD5	–	–	–	–	–	–	–	+	Leu-1; pan T-cell marker
CD7	–	–	–	–	–	–	–	+	Leu-9; pan T-cell marker
CD8	–	–	–	–	–	–	–	Sub	MHC-I associated; cytotoxic T cells
CD19	–	–	–	–	–	–	+	–	Leu-12; pan B-cell marker
CD20	–	–	–	–	–	–	+		L26; B-cell marker
CD22	–	–	–	–	–	–	+	–	BL-CAM; pan B-cell marker
CD79a	–	–	–	–	–	–	+	–	MB-1; pan B-cell marker
CD13	+	+	+	+	–	–	–	–	Aminopeptidase N; pan myeloid marker
CD14	–	–	+	++	–	–	–	–	LPS receptor; bright on monocytes
CD15	–	+	+	–	–	–	–	–	LeuM1; maturing granulocytes
CD33	+	+	+	++	+	–	–	–	Sialic acid adhesion molecule; pan myeloid marker
CD36	–	–	–	+	+	+	–	–	GP IIb/IV
CD117	+	+	–	–	+	–	–	–	c-kit; bright on mast cells
CD64	–	–	+	+	–	–	–	–	FC-γ receptor
MPO	Sub	+	+	–/+	–	–	–	–	Myeloperoxidase; definitive myeloid marker
CD71	–	–	–	–	++	–	–	–	Transferrin receptor; dim expression on activated cells
GlyA	–	–	–	–	++	–	–	–	CD235a; carries MN antigens on red cells
CD41	–	–	–	–	–	+	–	–	GP IIb; megakaryocytic
CD61	–	–	–	–	–	+	–	–	GP IIIa; megakaryocytic
CD10	–	–	+	–	–	–	Sub	–	CALLA, also expressed by hematogones
CD38	+	Var[c]	Var	+	–	–	Var	Var	Broadly expressed
CD45	+	+	+	+	–	+	+	+	Leukocyte common antigen
HLA-DR	+	–	–	+	–	–	+	–	Class II MHC component
CD34	+	–	–	–	–	–	Sub	–	Adhesion molecule; marker of immature cells
TdT	–	–	–	–	–	–	Sub	–	Nucleotide transferase; marker of immature cells

Childhood ALL Cytogenetics



Pui, NEJM 2004

Microarray/SNP

RESULTS

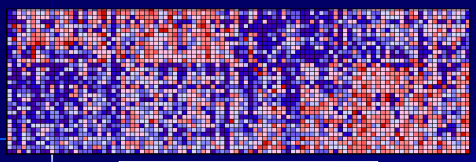
46,XX,t(1;15)(p2?2;q1?5),del(20)(q11.22q13.33),der(21)t(21;22)(q22;q11.2),
der(22)?t(9;22;21)(q34;q11.2;q22)[16].ish der(21)(RUNX1+,BCR+),der(22)
(RUNX1-,BCR+,ABL1+)/46,XX[1]

nuc ish 9q34(ABL1x3),22q11.2(BCRx3)(ABL1 con BCRx1)[160/200]
nuc ish 12p13(ETV6x2),21q22(RUNX1x2)[200/200]
nuc ish 20ptel(ptelx2),20q12(D20S108x1)[164/200]

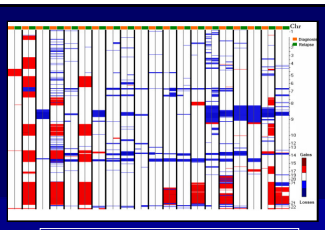
The probes used in this study have been developed and/or validated for FISH analysis by the laboratory. The probes have not yet been approved by the FDA for clinical diagnostic testing.

Whole genome SNP array results:

Chromosome/Arm	Start	End	Abnormality/ Notes
2p16.1	57,404,022	57,445,471	Gain/(no genes)
6q21	106,898,421	106,959,155	Htz del
6q23.3	135,366,309	135,437,585	Htz del
7p14.1	38,298,285	38,385,938	Hmz del/ TCRG
7p12.2	50,418,242	50,462,935	Htz del/IKAROS
7q11.21	61,970,117	62,458,262	Htz del/(no genes)
7q34	142,340,496	142,474,939	Htz del/ TCRB
8p21.3	22,213,283	22,366,642	Gain
11p11.12	50,477,559	51,372,036	Htz del
12p12.2	21,010,048	21,025,445	Htz del
14q11.2	22,895,875	22,921,280	Htz del/ TCRA
14q32.33	107,032,603	107,160,654	Htz del/ IGVH
16p13.11	16,001,084	21,561,382	CNLOH/ABCC1
16q13	57,221,865	57,336,624	Htz del
17q21.31	44,161,441	44,791,322	Gain
20q11.21q13.33	31,965,966	60,593,396	Htz del
22q11.22	22,504,946	22,521,158	Htz del/ IGLV

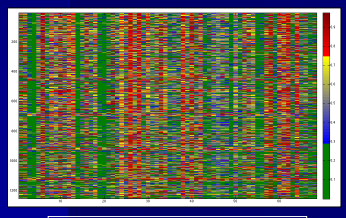


Gene Expression

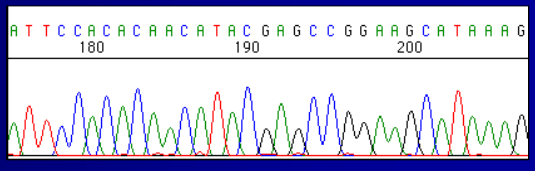


Copy Number

Why mapping the human genome was worth every penny: Genome-Wide Analyses to Discover Cancer Pathways



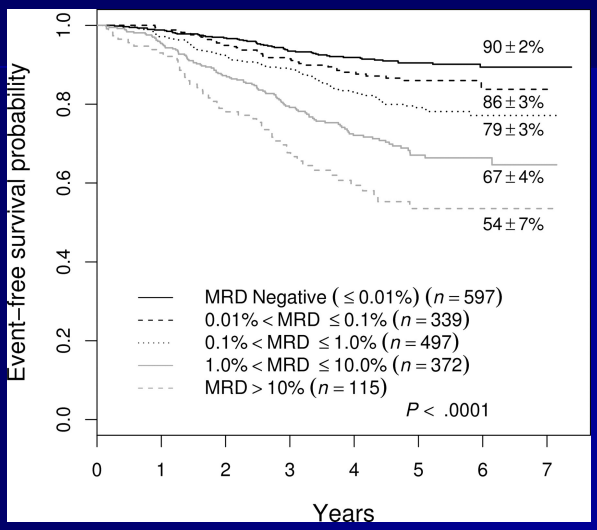
Methylation



Sequencing

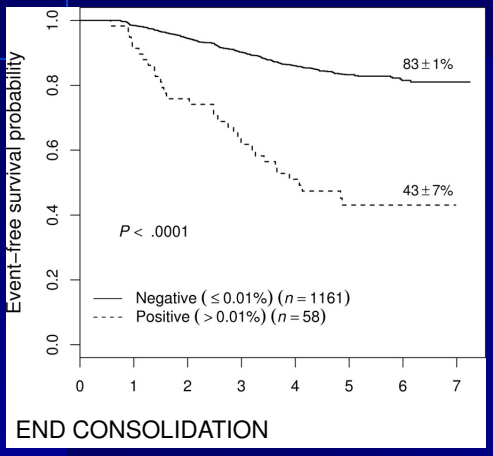
MRD: A stronger predictor of outcome in ALL

Day 29
MRD



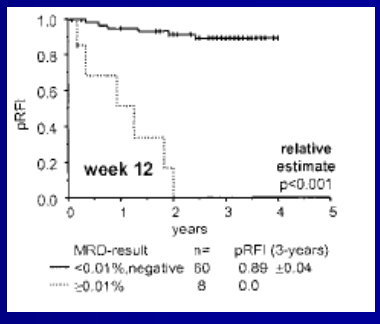
Borowitz, M. J. et al. Blood 2008;111:5477-5485

More Predictive With Time



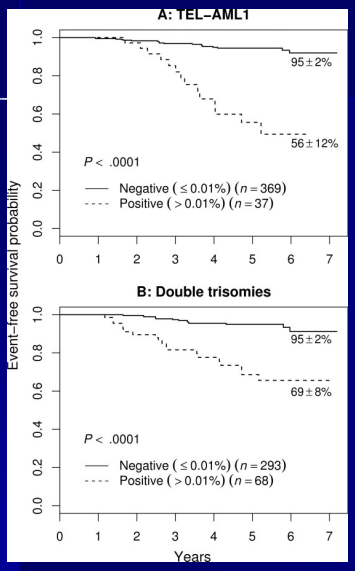
END CONSOLIDATION

POG 9900 series
Borowitz, M. J. et al.
Blood 2008;111:5477-5485



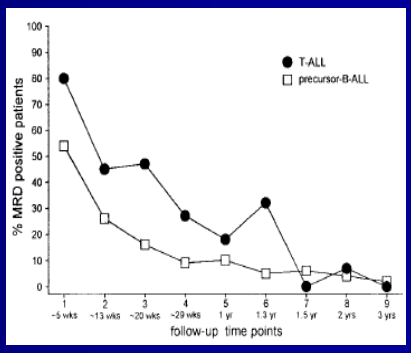
St. Judes
Coustan-Smith, et. al.
Blood 2000

MRD Trumps Cytogenetics



Borowitz, M. J. et al. Blood 2008;111:5477-5485

MRD in B vs T-ALL



Willemse. et al. Blood 2008 (BFM)

COG ALL treatment allocation -2013

B-cell

T-cell	Age	WBC < 50,000/µl	WBC ≥ 50,000/µl
	< 1 year	Infants (3%)	
LOW	1-9.99 yrs	Standard Risk (52%)	
INTER	10-13 years	High Risk (25%)	
HIGH	>13 years	Very High Risk (20%)	
			Ph+ chemo/TKI

B-ALL Post-Induction Risk Groups

Risk Group	Low	Average		High			Very High	
5-yr EFS	>95%	90-95%		88-90%			<80%	
NCI Risk Group	SR	SR	SR	SR	SR	HR <13yo	SR	HR
Favorable genetics	Yes	Yes	No	Yes	No	-	No	-
MRD d8 (PB)	<0.01	≥0.01	<1	-	≥1	-	-	-
MRD d29 (BM)	<0.01	<0.01	<0.01	≥0.01	<0.01	<0.01	≥0.01	≥0.01

Therapy and Biology

CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

DANA-FARBER Boston Children's

CANCER AND BLOOD DISORDERS CENTER

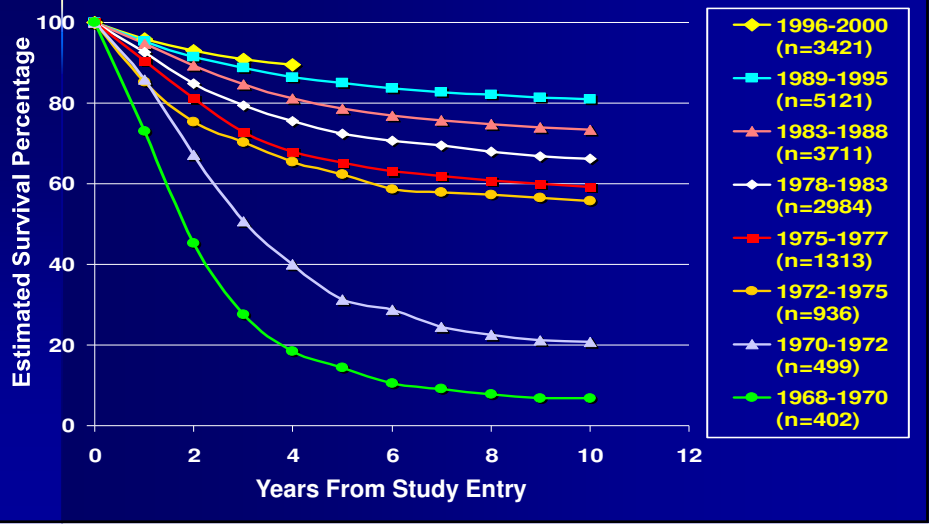
St. Jude Children's Research Hospital

ALSAC • Danny Thomas, Founder

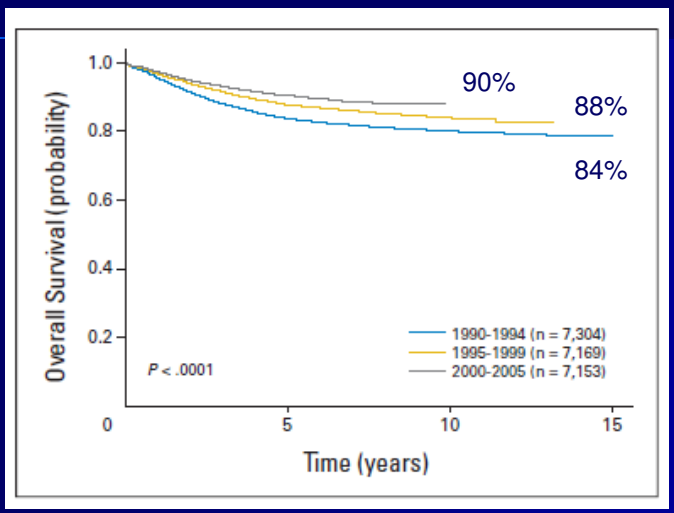
TACL

Therapeutic Advances in Childhood Leukemia & Lymphoma

Why do Clinical Trials? (COG ALL trial outcome)

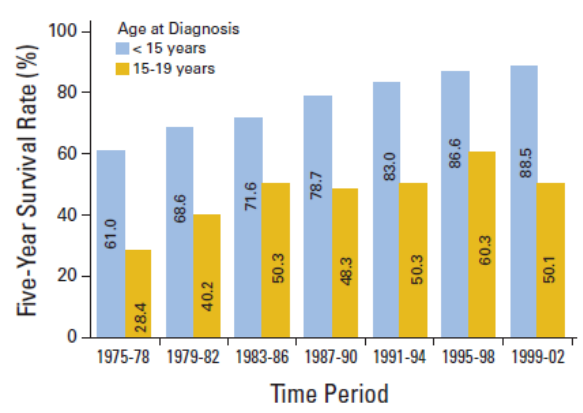


How far have we come? COG 5yr EFS



Hunger SP et al. JCO May 2012

Why aren't the 15-21 year olds doing better?



Best Therapy for Adolescents (15-21 years)

Table 1. Retrospective data for AYAs treated on representative pediatric or adult ALL protocols

Trial	Pediatric	Adult
FRALLE-93/LALA-94[28]	5-y EFS: 67%	5-y EFS: 41%
CALGB/CCG[34]	7-y EFS: 63%	7-y EFS: 34%
MRC ALL 97-99/UKALLXII-E2993[29]	5-y EFS: 65%	5-y EFS: 49%
GIMEMA/AIEOP[30]	2-y OS: 80%	2-y OS: 71%
HOVON/DCOG[31]	5-y EFS: 71%	5-y EFS: 38%
Adult ALL Grp/NOPHO-92[32]	5-y OS: 74%	5-y OS: 39%
Finnish Leukemia/NOPHO[33]	5-y OS: 67%	5-y OS: 60%

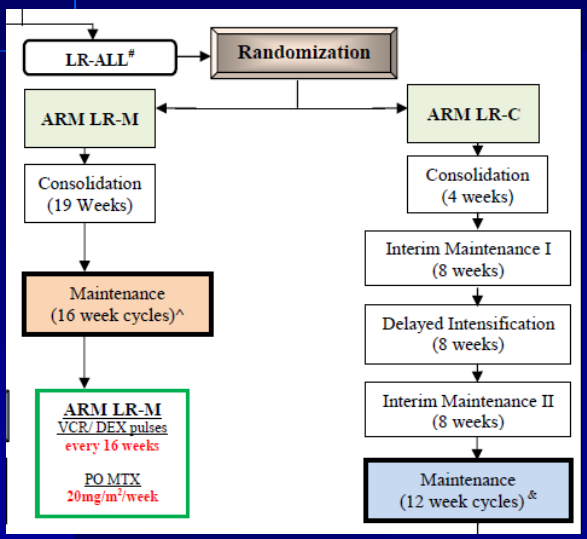
Last COG Trial
> 16 years – 79% 5yr EFS

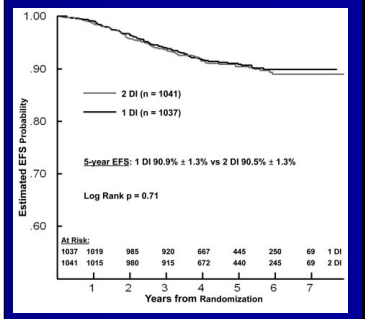
Wood, W. Blood 2011

What do Clinical Trials for ALL Ask?

1) Reduction in Therapy Questions:
   Decrease toxicity and late effects
2) "Re-arranging the Deck Chairs":
   Varying the drug, dose, order
3) Introducing New Agents:
   Higher cure rates?
   Toxicity / Tolerability

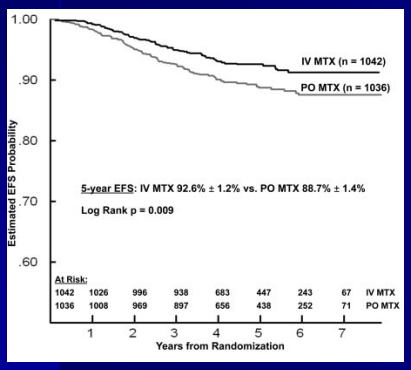
Reduction in Therapy

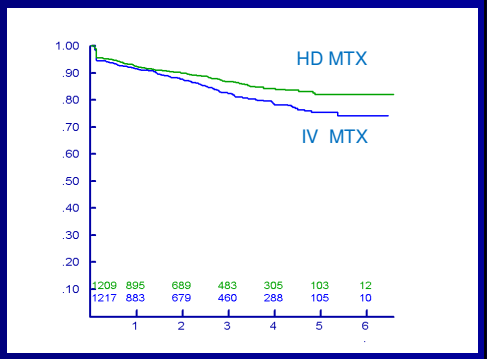




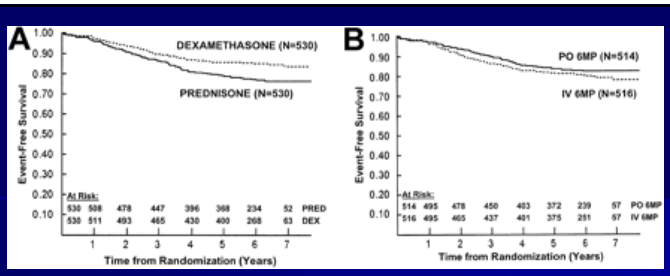
Changing Drug or Dose

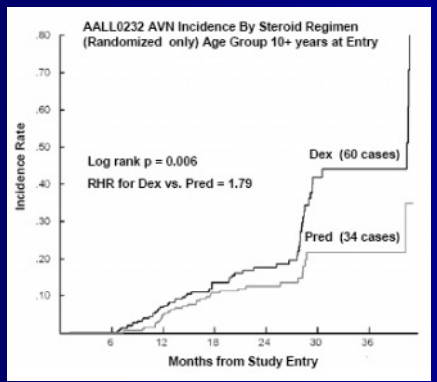
What is the best way to give Methotrexate?





AALL0232





Dex x 14 days for ≤ 10 years

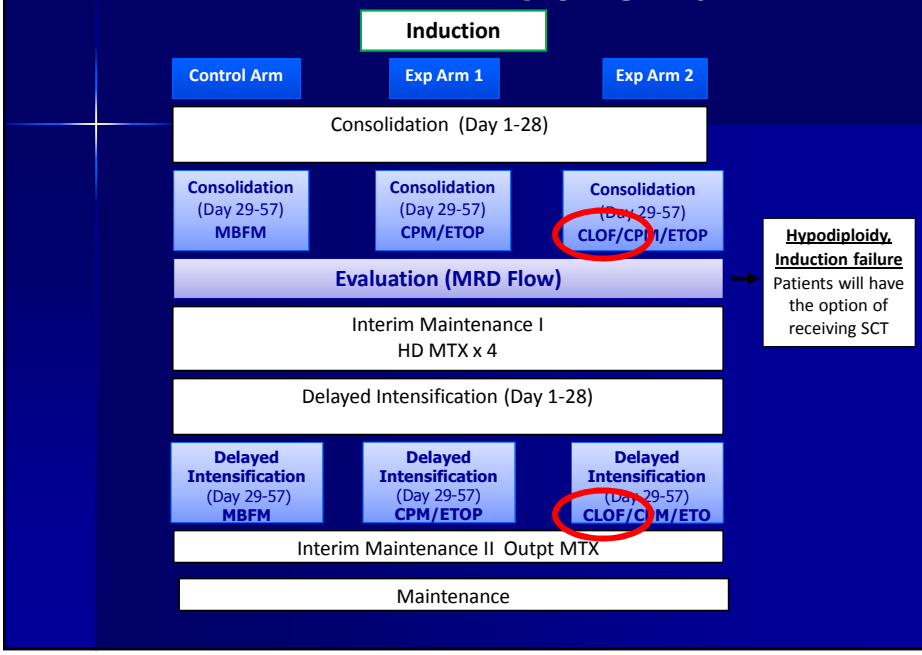
Pred x 28 days for > 10 years

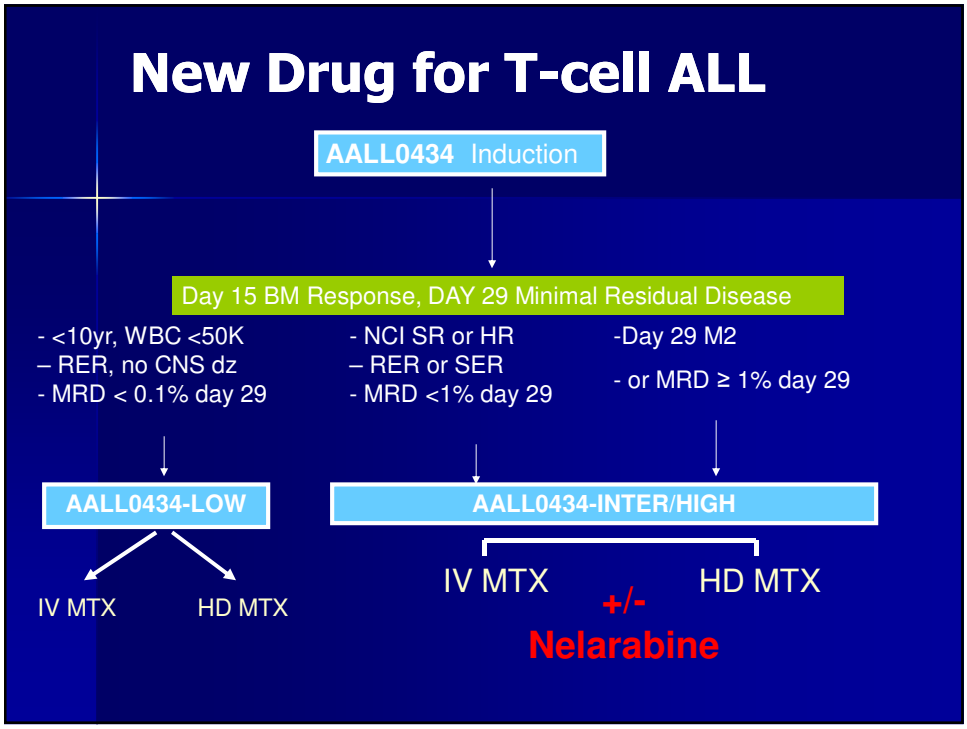
AALL0232

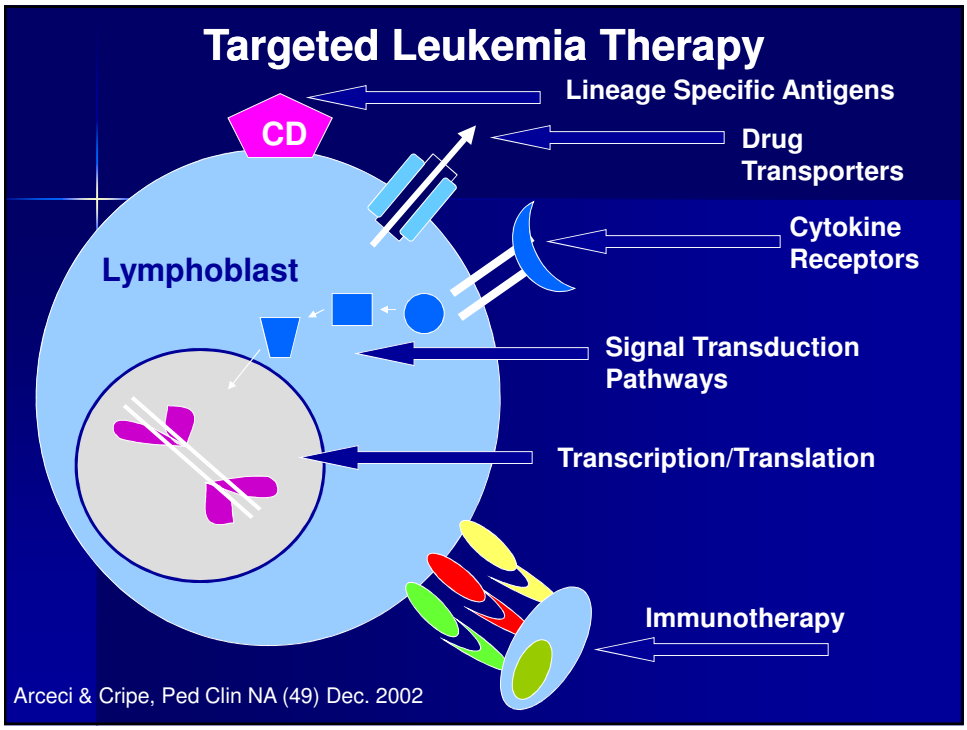
Adding New Agents

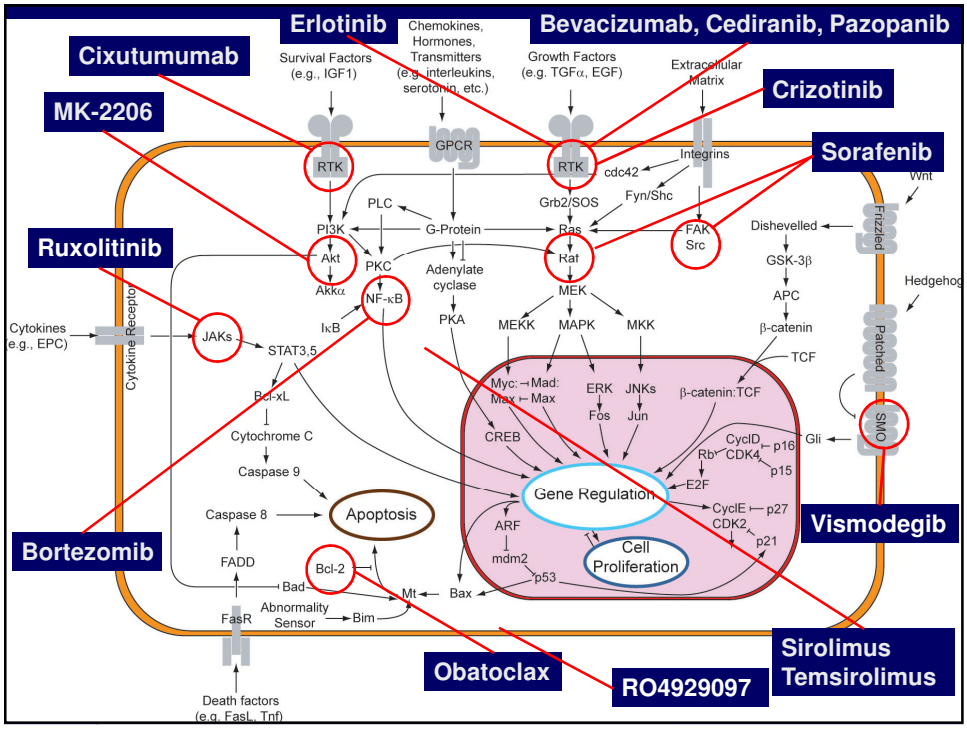
- Newer chemotherapy agents
  - Clofarabine
  - Nelarabine - T cell targeted drug
- Targeted agents
  - Imatinib/Dasatinib
  - Lestaurtinib for MLL
- Immunotherapy
  - Monoclonal Antibodies
  - Engineered T-cells

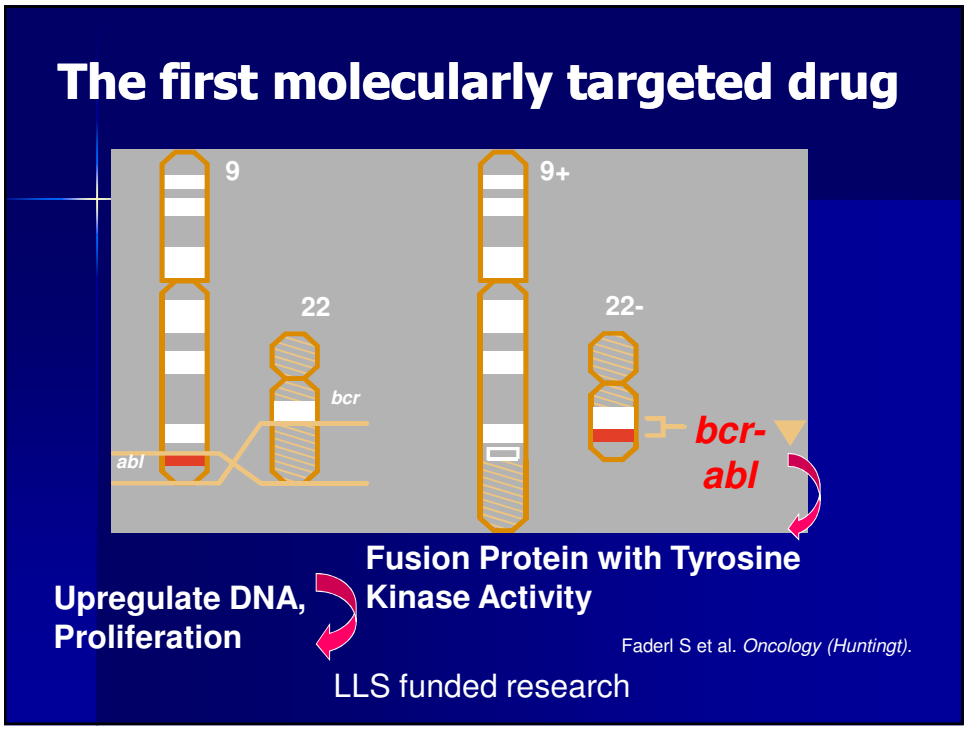
VHR ALL - Schema




New Drug for T-cell ALL
AALL0434 Induction
Day 15 BM Response, DAY 29 Minimal Residual Disease
- <10yr, WBC <50K
– RER, no CNS dz
- MRD < 0.1% day 29
- NCI SR or HR
– RER or SER
- MRD <1% day 29
-Day 29 M2
- or MRD ≥ 1% day 29
AALL0434-LOW
AALL0434-INTER/HIGH
IV MTX
HD MTX
IV MTX
HD MTX
+/-
Nelarabine

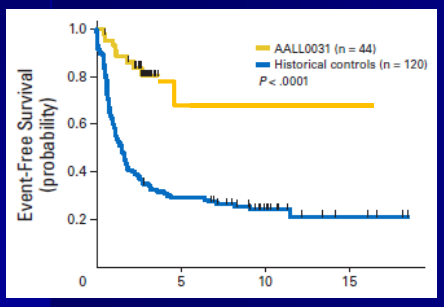

Targeted Leukemia Therapy
Lineage Specific Antigens
CD
Drug Transporters
Cytokine Receptors
Lymphoblast
Signal Transduction Pathways
Transcription/Translation
Immunotherapy
Arceci & Cripe, Ped Clin NA (49) Dec. 2002

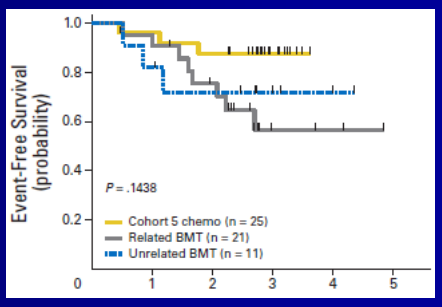

Erlotinib
Bevacizumab, Cediranib, Pazopanib
Cixutumumab
MK-2206
Crizotinib
Sorafenib
Ruxolitinib
Bortezomib
Vismodegib
Sirolimus
Temsirolimus
Obatoclax
RO4929097
Survival Factors (e.g., IGF1)
Chemokines, Hormones, Transmitters (e.g. interleukins, serotonin, etc.)
Growth Factors (e.g. TGFα, EGF)
Extracellular Matrix
RTK
GPCR
Integrins
cdc42
Fyn/Shc
Grb2/SOS
Ras
PLC
PI3K
G-Protein
FAK
Src
Akt
PKC
Raf
Adenylate cyclase
Akkα
NF-κB
MEK
PKA
MEKK
MAPK
MKK
IκB
JAKs
STAT3,5
Cytokines (e.g., EPC)
Cytokine Receptor
Bcl-xL
Cytochrome C
Caspase 9
Caspase 8
Apoptosis
FADD
Bcl-2
Bad
Mt
Bax
FasR
Abnormality Sensor
Bim
Death factors (e.g. FasL, Tnf)
Myc: Mad: Max Max
ERK
JNKs
Fos
Jun
β-catenin:TCF
CREB
Gene Regulation
CyclD
p16
CDK4
p15
Rb
E2F
CyclE
p27
CDK2
p21
ARF
mdm2
p53
Cell Proliferation
Dishevelled
GSK-3β
APC
β-catenin
TCF
Wnt
Frizzled
Hedgehog
Patched
SMO
Gli


The first molecularly targeted drug
9
22
bcr
abl
9+
22-
bcr-abl
Fusion Protein with Tyrosine Kinase Activity
Upregulate DNA, Proliferation
Faderl S et al. Oncology (Huntingt).
LLS funded research

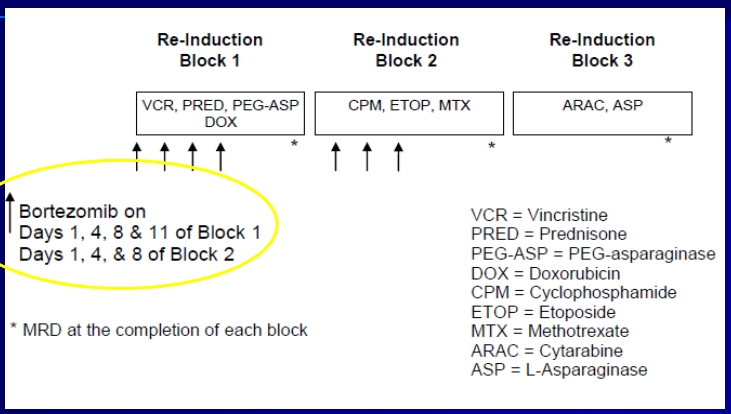
Targeted Therapy: the way of the future

Adding a single drug, Imatinib, to chemotherapy increased survival from 30% to 70%



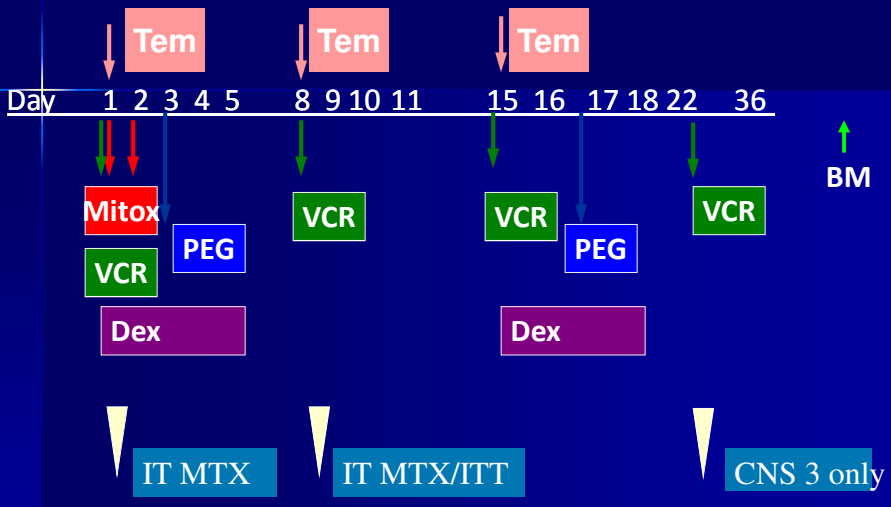


Adding New Agents into Therapy: AALL07P1



T. Horton Study Chair

ADVL1114: Temsirolimus

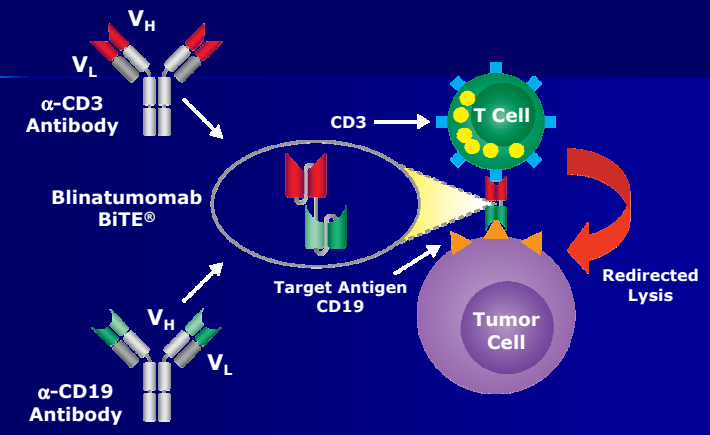


LLS funded research

Monoclonal Antibodies:
Targeting specific cancer proteins

Agent	Mechanism of Action	Target
Rituximab	antibody to CD-20	B-ALL
Epratuzamab	antibody to CD-22	B-ALL
Alemtuzumab	antibody to CD-52	B & T-ALL
Combotox	antibody to CD-19 & 22	B-ALL
Blinatumomab	Attach patient CD3 T-cells to CD19	B-ALL
Moxetumomab	antibody to CD-22	B-ALL
Inotuzumab	antibody to CD-22	B-ALL

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.

Adult phase 1 Blinatumomab Trial: Best Response During First 2 Cycles

	Cohort 1 15 µg/m²/d (n = 7)	Cohort 2a 5-15 µg/m²/d (n = 5)	Overall (N = 12)
CR/CRh*, n (%)	5 (71)	4 (80)	9 (75)
CR	2 (29)	4 (80)	6 (50)
CRh*	3 (43)	0	3 (25)
Non-responder	1 (14)	1 (20)	2 (17)
Not available	1 (14)	0	1 (8)
MRD response ($<10^{-4}$), n (%)			
MRD response	5 (71)	4 (80)	9 (75)
No response or progression	1 (14)	1 (20)	2 (17)
Not available	1 (14)	0	1 (8)

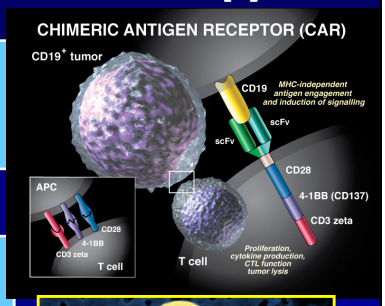
CRh*: CR with only partial hematologic recovery: ≤ 5% blasts in the bone marrow, no evidence of circulating blasts or extramedullar disease, partial recovery of peripheral blood counts.

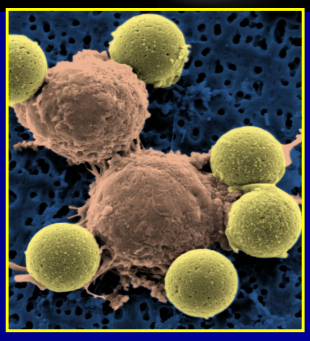
What is CART-19 (CTL019) Immunotherapy?

Immunotherapy reprograms a patient's own immune system to better fight cancer.

T cells are workhorses of the immune system. They recognize cells that don't belong and attack them. However, T cells are blind to cancer cells, which fly under the radar.

Custom-designed T cells engineered to seek out the CD 19 + B-ALL cells in the body. These specialized T cells can target the B cell leukemia, attach to its CD19 protein and then kill off the leukemia cell.





LLS funded research

Clinical Update of Pediatric and Adult ALL Patients treated with CART19

5 Children
- -Refractory or 3rd+ Relapse
- -3 to 8+ prior therapies
- -4 with prior all BMT
- 4 CR, 3 A&W up to 1 year out
  - •1 relapsed with CD 19 (-) leukemia
  - Now Infusing 2-3/month (over 16 total)

•1 Adult
- •1 CR

Barrett, D et al. AACR 2013

Take Home Message

1) We are curing more and more children with ALL
2) Conventional chemotherapy is not going to make much more of a difference
3) Targeted therapy is much more specific and often less toxic
4) Todays experimental therapy (Phase 1) is tomorrows cure
5) Adolescents and Young adults should be treated like Children (when it comes to ALL)

Side Effects of Treatment

- Can occur after chemotherapy, radiation therapy, or supportive care therapy
- Type of cancer, its location and age of the child will affect the severity of the side effects
- Side effects can encompass all body symptoms

LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers | someday is today

LLS has top notch resources

CureSearch® for Children's Cancer

- Curesearch.org is a also a great pediatric reference for parents and families newly diagnosed, in treatment, at the end of treatment and after treatment

Most common side effects of ALL treatment

- Hair loss
- Bone marrow suppression
- Impairment of the immune system
- Central nervous system complications
- Musculoskeletal complications
- Gastrointestinal complications
- Growth and development
- Pain

Hair Loss

- Also called alopecia
- Some chemotherapy causes loss or thinning of hair
- Typically starts 14 days after treatment is started
- Hair grows back when treatment is finished or treatment becomes less intensive

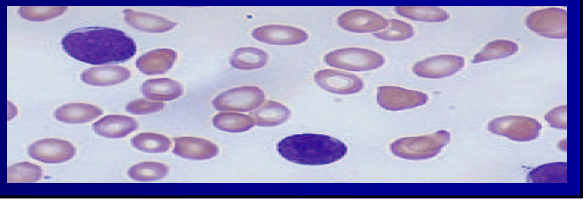
Side Effects of Treatment

- Bone marrow suppression
  - Most common dose-limiting component of cancer therapy
  - Bone marrow provides environment for formation of red blood cells, white blood cells and platelets

Bone marrow suppression

Anemia

- Also means low red blood cell count
- Red blood cells carry oxygen throughout the body
- May cause shortness of breath, headache, feeling tired, fast heart rate, pale skin



Bone marrow suppression

Thrombocytopenia

- Also means low platelet count
- Platelets stop bleeding by forming clots
- Risk of bleeding when platelet count is low
- Signs of low platelets: bruising or petechiae, bleeding, black stools

Bone Marrow Suppression

Neutropenia

- Reduction in circulating neutrophils
- Absolute Neutrophil Count (ANC)
- Severity can be mild, moderate or severe
- Can be asymptomatic, fevers can occur
- Increases risk for serious infection, risk increases with prolonged neutropenia

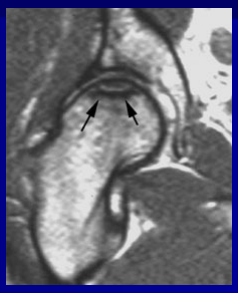
Side Effects of Treatment

- Impairment of the immune system
  - Increased risk for infection
  - PCP prophylaxis- bactrim, pentamidine, atovaquone
  - Routine immunizations are held during treatment and for a time after therapy has ended
  - Yearly Flu vaccine recommended

Central Nervous System

- Central nervous system complications
  - Cognitive deficits
  - Behavioral changes
  - Neuropathic pain, Flat Footed Gait
- Rare
  - Seizure
  - Stroke
  - Change in Mental Status

Musculoskeletal Concerns



- Steroid Myopathy
- Weakness
- Osteonecrosis
- Osteopenia
- Increased risk of Bone Fractures
- Pain at bone marrow sites

Gastrointestinal

- Mucositis
- Nausea/vomiting
- Diarrhea/constipation
- Perirectal cellulitis
- Chemical or reactive hepatitis
- Pancreatitis
- Veno-occulsive disease

Side Effects of Treatment

- Growth and development
  - Monitor throughout treatment
  - Intervene early
- Pain
  - Can be acute and/or chronic
  - May be from disease and/or treatment
  - Treat underlying cause of pain
  - Pharmacologic and non-pharmacologic treatment of pain

Psychosocial Effects

- Fear
  - Fear of unknown
  - Treatment and procedures
- Guilt
  - Parents often feel guilty for not knowing that their child was sick
  - Siblings may feel guilty that they are healthy
  - Something they did caused this

LLS Care for the Caregivers

Psychosocial Effects

- Anger
  - Feeling angry is a normal reaction
  - Steroid behavior
- Depression
  - Feeling sad or blue is normal reaction to diagnosis and treatment
  - The changes in family routine may bring feelings of social isolation and loss

No Stigma for seeking therapy/support

Quality of life (QOL)

- Numerous studies on treatment of ALL and QOL
  - QOL impaired during treatment
  - QOL can be affected both on therapy and after therapy
  - Children/adolescents with ALL have decreased QOL when compared to norms

Survivorship

- Patients should be followed annually, even when years off therapy
- Late effects need to be screened
  - Cardiovascular
  - Growth/ Development
  - School Performance
  - Liver and renal function
  - Radiation field second cancer screen

Pediatric ALL
Update on Treatment and Follow-Up Care

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Question and Answer Session

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

Pediatric ALL

Update on Treatment and Follow-Up Care

someday is today | LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers

For more information about pediatric ALL and other programs from The Leukemia & Lymphoma Society (LLS), please contact an LLS Information Specialist.

- **TOLL-FREE PHONE: (800) 955-4572**
- **EMAIL: infocenter@LLS.org**
- **LIVE ONLINE CHAT: www.LLS.org/informationspecialists**