Management of standard risk and high risk ALL in children

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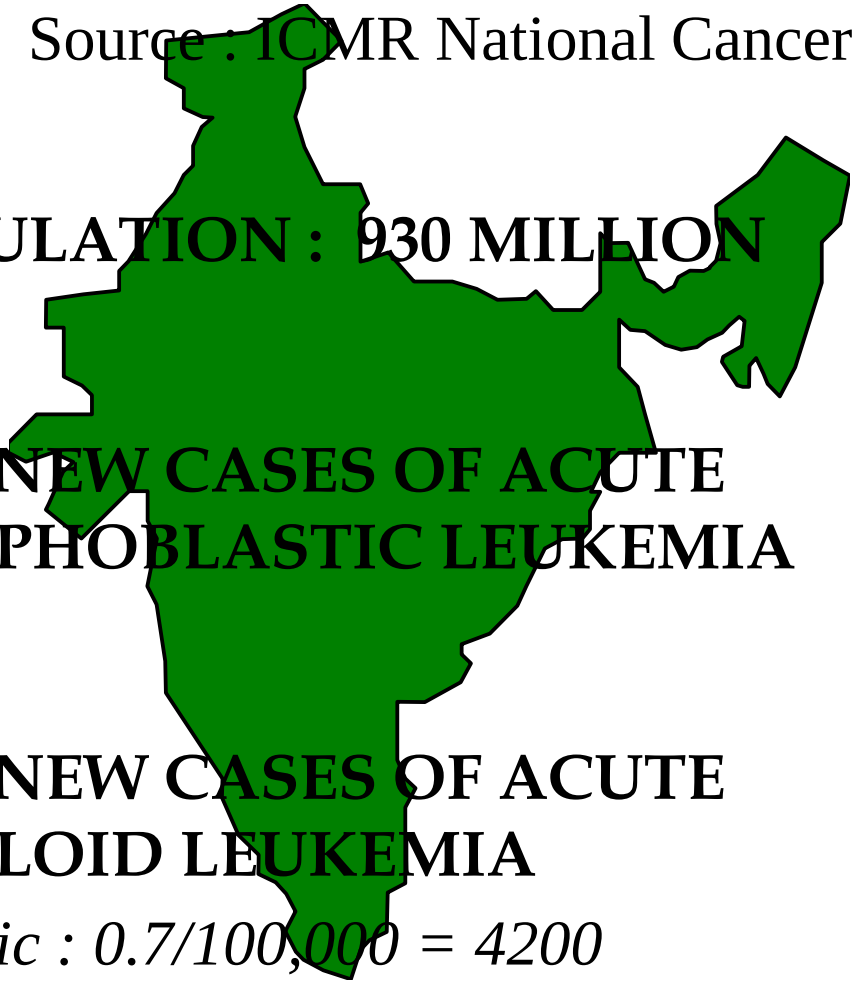
Incidence and types

Childhood Leukemia in India

Source : ICMR National Cancer Registry 1987



POPULATION : 930 MILLION

6000 NEW CASES OF ACUTE LYMPHOBLASTIC LEUKEMIA

2650 NEW CASES OF ACUTE MYELOID LEUKEMIA

Nordic : 0.7/100,000 = 4200

Age-Specific Annual Incidence of ALL (1998-2002)

- Peak incidence in childhood, followed by sharp decline in early adolescence
  - Increase in incidence during older decades

Select Age Group, Yrs	Incidence
~ 4	> 7 per 100,000
5-9	3-4 per 100,000
15-19	1-2 per 100,000
25-50	0.4-0.6 per 100,000
> 60	0.9-1.6 per 100,000

Larson MD. Acute lymphoblastic leukemia: older patients and newer drugs. ASH Education Book; 2005.

ALL: Immunophenotypic Classification

- Precursor B most frequently observed subtype

ALL Subtype, %	Frequency in Children	Frequency in Adults
B lineage		
• Precursor B	70	55
• Pro B	10	15
• B (FAB L3)	5	5
T lineage	15	25

- 20% to 30% of adults with ALL have aberrant coexpression of myeloid markers
  - Only 2% to 5% with true biphenotypic acute leukemia

Thalhammer-Scherrer R, et al. Am J Clin Path. 2002;117:380-389.

Immunophenotype in acute lymphoblastic leukaemia in children

	NO	%
• PRECURSOR B	350	71.6
• T CELL	60	12.3
• Pro B CELL	36	7.4
• BIPHENOTYPIC	10	2

Analysis of 489 patients age <15 years,1995-2007 CMCH, Vellore*

**33 patients treated prior to IPT/data not available*

Immunophenotype in acute lymphoblastic leukaemia in adults

	NO	%
• PRECURSOR B	229	53.5
• T CELL	95	22.2
• Pro B CELL	14	3.3
• BIPHENOTYPIC	18	4.2

Analysis of 428 patients age >15 years,1995-2007 CMCH, Vellore*

**72 patients treated prior to IPT/data not available*

Molecular and Cytogenetic Subtypes of B-Lineage ALL

Subtype (Favorable Cytogenetics)	Karyotype	Childhood Frequency %	Adult Frequency %	Childhood EFS %	Adult EFS %
Hyperdiploidy	> 50 chr	25	5	80-90	40-50
TEL/AML1	t(12;21)	25	3	85-90	?
MYC	t(8;14)	2	5	75-85	60-70
bcr/abl	t(9;22)	5	33	20-40	< 10
*MLL/AF4**	t(4;11)	3	6	30	15

***Most common in infant leukemia (mixed AML-ALL).**

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

Molecular and Cytogenetic Subtypes
T-Cell Lineage ALL

Subtype (Favorable Cytogenetics)	Karyotype	Childhood Frequency, %	Adult Frequency, %	Childhood EFS, %	Adult EFS, %
HOX11 expression	--	3	33	90	60
NOTCH1 mutations	--	50	50	90	--
TCR	t(14q11)	15	25	70	60
MLL-ENL	t(11;19)	2	2	95	--

Armstrong SA, Look AT. J Clin Oncol. 2005;26:6306-6315.
Graux C, et al. Leukemia. 2006;20:1496-1510.

Risk stratification

Important Prognostic Factors and Their Approximate Incidences in Childhood ALL*

**Stanulla M and Schrappe M.Treatment of childhood acute lymphoblastic leukaemia. Semin Haemat. 2009; 46: 52-63.*

Factor	Favourable	Unfavourable
Age	>1 and <10 years (77%)	<1 year (3%) or >10 years (20%)
Gender	Female (45%)	Male (55%)
WBC	<50,000/L (80%)	>50,000/L (20%)
IPT	CD10- pre B-cell ALL(83%)	CD10- pre B-cell ALL (4%),T-ALL (13%) ?Myeloid markers
CNS	CNS 1 (80%)	CNS3 (3%),TLP+ 7%)
Genetic	Hyperdiploidy(20%), TEL/AML1 positivity (20%)	Hypodiploidy (1%), t(9;22) or BCR/ABL positivity (2%), t(4;11)or MLL/AF4 positivity (2%)
Prednisolone response	<1,000/cmm blood blasts (90%)	$\geq$1,000/cmm blood blasts (10%)
Early BM response	<5% blasts (M1) on day 15 of induction treatment(60%)	$\geq$25% blasts (M3) on day 15 of induction treatment (15%)
Post induction BM	<5% blasts (M1) after 4 to 5 weeks of induction treatment (98%)	$\geq$5% blasts (M2 or M3) after4 to 5 weeks of induction therapy(2%)
MRD	$<10^{-4}$ blasts after 5 weeks of induction treatment (40%)	$\geq10^{-3}$ blasts after 12 weeks of treatment (induction and consolidation) (10%)

Definition of CNS involvement

- **A mass lesion in the brain and/or meninges on CT/MRI.**
- **Cranial nerve palsy unrelated to other origin, even if the CSF is blast-free, or no circumscribed space-occupying lesion could be demonstrated within the neurocranium on MRI/CT scan**
- **Pure retinal involvement, i.e. with a blast-free CSF, and no mass on MRI/CT scan**
- **A non-traumatic LP yielding a CSF with a cell count of > 5/µL and a majority of blasts on the cytospin slide.**
  - **If contamination with blood is doubtful, the diagnosis of CNS involvement can be still made on the basis of either of the following 2 constellations of findings:**
    - **Cell count > 5/µL (chamber) + majority of blasts (cytospin) + RBC : WBC ≤ 100:1 (cytospin)**
    - **Cell count > 5/µL (chamber) + higher % of blasts in CSF than PB**

CNS status

- **CNS1 = puncture nontraumatic, no leukemic blasts in the cerebrospinal fluid (CSF) after cytocentrifugation.**
- **CNS2 = puncture nontraumatic, ≤5 leukocytes/cmm,CSF with identifiable blasts.**
- **CNS3 = puncture nontraumatic, >5 leukocytes/cmm CSF with identifiable blasts; TLP+=traumatic lumbar puncture with identifiable leukemic blasts.**
- ***TLP with no identifiable blasts is not an adverse factor.***
- ***For cytomorphological examination, CSF samples should be analyzed after cytospin preparation,a method through which cellular components within the CSF are concentrated by centrifugation.***

STANDARD-RISK GROUP (SR)

- Age > 1 yr, < 6 yrs
- WBC ≤ 20,000/cmm
- Pre B, CALLA immunophenotype (no T immunophenotype, no aberrant markers)
- No CNS disease
- No translocation t(9;22) , t(4;11), t(1;19)
- Prednisolone good response
- Post induction marrow in remission

INTERMEDIATE-RISK GROUP (IR)

- Age <1 and >6 yrs
- WBC >20,000cmm
- T cell immunophenotype (any aberrant markers)
- t(1 ;19)
- CNS disease
- Suspicious CNS disease
- Testicular disease at diagnosis
- (+prednisolne good response + marrow in remission)

HIGH-RISK GROUP (HR)

- t(9;22)
- t(4;11)
- Poor prednisolone response with any T cell, Pro B cell, WBC > 1,00,000/cmm
- Post induction marrow not in remission

BFM 2002

- SR
- PB day 8: < 1,000 blasts/µL
- and Age ≥ 1 yr – < 6 yr
- and Initial WBC < 20,000/µL
- and M1 or M2 marrow on day 15
- and M1 marrow on day 33
  All criteria must be fulfilled.

- **HR**
- **1. IR and M3 marrow on day 15 (not SR and M3 on day 15!)**
- **2. PB on day 8: ≥ 1,000 blasts/µL**
- **3. M2 or M3 marrow on day 33**
- **4. Translocation t(9;22) [BCR/ABL] or t(4;11) [MLL/AF4]**
  At least one criterion must be fulfilled

- IR
- 1. PB day 8: < 1,000 blasts/µL
- and Age < 1 yr or ≥ 6 yr and/or WBC ≥ 20,000/µL
- and M1 or M2 marrow on day 15
- and M1 marrow on day 33
- **or**:
- 2. Standard-risk criteria
- but M3 marrow on day 15
- and M1 marrow on day 33

Important Prognostic Factors and Their Approximate Incidences in adult ALL

Gokbuget N and Hoelzer D.Treatment of adult acute lymphoblasticleukaemia.Semin Haemat. 2009; 46:64-75

Factor	**Favourable**	**Unfavourable**	
		B cell	**T cell**
Age	**<35 years**	**>35 years**	
WBC	**<30,000/L**	**>30,000/L**	**>100,000/L**
IPT	**Thymic T CD10- pre B-cell ALL**	**Pro-B** (CD10-) Pre-B (CD10-)	EarlyT(CD1a-,sCD3-) **MatureT(CD1a-,sCD3+)**
Genetic	*TEL-AML1* (?) *HOX11*† (?) *NOTCH-1* (?) 9p del (?) **Hyperdiploid (?)**	**t(9;22)/BCR-ABL** **t(4;11)/ALL1-AF4** t(1;19)/E2A-PBX (?) Complex aberrations (?) Low hypodiploid/near **tetraploid (?)**	*HOX11L2*† (?) *CALM-AF4*† (?) Complex aberrations (?) Low hypodiploid/near **tetraploid (?)**
Prednisolone response	**<1,000/cmm blood blasts (90%)**	**≥1,000/cmm blood blasts (10%)**	
Time to CR	**Early**	**Late (>3-4 wk)**	
Post induction BM	**<5% blasts (M1) after 4 to 5 weeks of induction treatment**	**≥5% blasts (M2 or M3) after4 to 5 weeks of induction therapy**	
MRD	**Negative/<10^{-4}**	**Positive >10^{-4}**	

Investigations

Investigations

- Immunophenotyping (peripheral blood or bone marrow) ,BM cytogenetics and RT-PCR samples for Ig H/ TCR rearrangenments to be sent at diagnosis.
- RT PCR (BCR ABL, TEL AML, E2A PBX, MLL AF4) to be sent before initiation of treatment in B lineage ALL. DNA PCR for t(8;14) to be sent for mature B ALL.
- CSF analysis (counts,cytospin) with intrathecal methotrexate instillation to be done prior to initiation of steroids (Target platelet count – 20,000/cmm).
- Chest X ray to document mediastinal mass/ pleural effusion. Central venous access insertion to be postponed in event of mediastinal mass.
- Investigations to assess tumor lysis (Na, K, Creatinine, Ca, P, LDH, Uric acid, blood counts) to be done 12-24 hours after initiation of steroids and to be repeated as deemed necessary.

Investigations

- **Prednisolone Response – to be assessed on basis of day 8 counts.**
- **Post Induction phase I bone marrow to be done for remission assessment. DNA samples for Ig H/ TCR rearrangements for assessment of minimal residual disease to be sent. To repeat if MRD positive prior to re-induction.**
- **BM with residual disease(patient enters high risk group) – However if patient cannot opt for high dose chemotherapy and continues with intermediate risk BFM based therapy to repeat marrow after phase II induction to document disease response .**
- **In case of mediastinal mass at diagnosis an X ray chest needs to be repeated post induction phase I to document resolution.**
- **Bone marrow to be repeated prior to initiation of re-induction for assessment of minimal residual disease.**

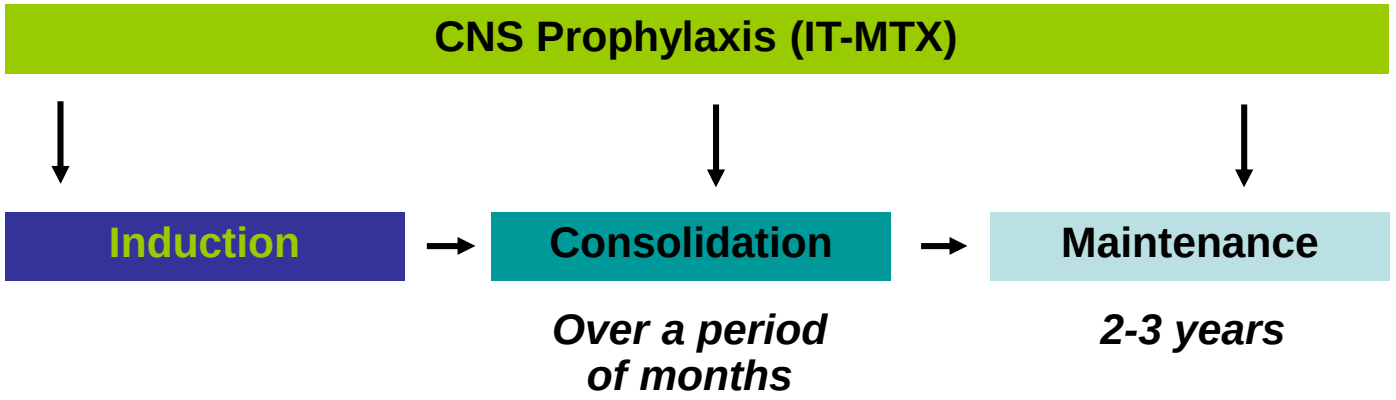
Investigations

- No consensus data exists regarding monitoring of coagulation parameters for patients on L asparaginase.
- Blood counts to be monitored once in 15 days on final maintenance
- LFT/SGPT to be monitored at least once in 3 months during maintenance.

Treatment in children

ALL: Typical Treatment

- Induction, consolidation, maintenance phases
  - CNS prophylaxis with IT-MTX



Treatment of ALL: BFM-Based Model

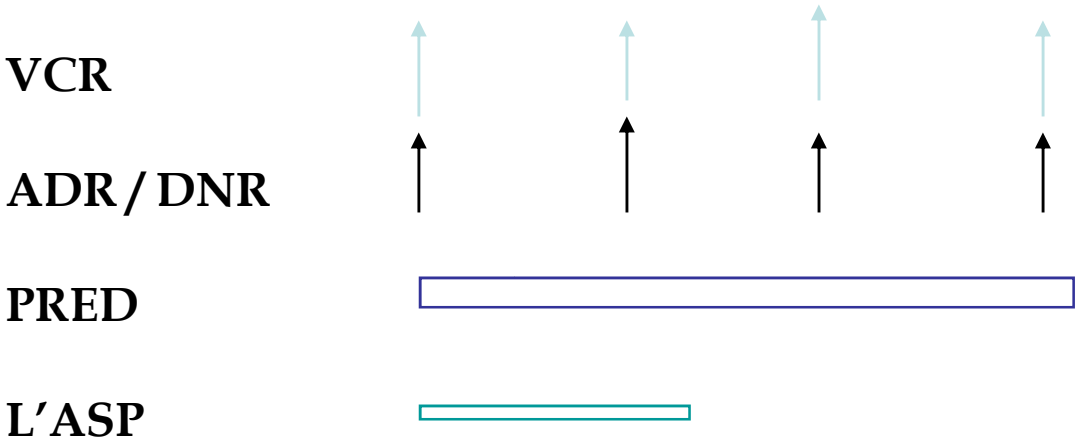
- Induction phase I (4 weeks)
  - Prednisone, vincristine, daunorubicin, L-asparaginase
  - No benefit to adding cyclophosphamide, high-dose cytarabine, or high-dose anthracycline
- Induction phase II (4 weeks)
  - Cyclophosphamide, cytarabine, 6-mercaptopurine
- Consolidation
  - 4-7 cycles of intensive multiagent chemotherapy
  - Delayed reinduction

PRE-INDUCTION

- CONCEPT : reduce tumour load with non myelosupressive chemotherapy
- DRUG : PREDNISOLONE
- ADVANTAGES : indicates chemosensitivity and prognosis
- DISADVANTAGE : delay in starting therapy

INDUCTION CHEMOTHERAPY FOR ACUTE LYMPHOBLASTIC LEUKAEMIA

- VINCRISTINE
- PREDNISOLONE
- L' ASPARAGINASE
- ADRIAMYCIN / DAUNORUBICIN



CONSOLIDATION OR INTENSIFICATION THERAPY IN ACUTE LEUKAEMIA

CONCEPT : GIVE ADDITIONAL DRUGS AT HIGHER DOSES THAN DURING INDUCTION TO KILL RESIDUAL LEUKAEMIA

- 1.REPEAT VINCRISTINE, STEROID AND DAUNORUBICIN USED IN INDUCTION.
- 2.USE ALTERNATE DRUGS LIKE CYTOSINE, CYCLOPHOSPHAMIDE AND VP16.
- USE HIGH DOSE METHOTREXATE

MAINTENANCE

BASED ON THE CONCEPT THAT THERE ARE RESIDUAL LEUKAEMIC CELLS AT THE END OF INDUCTION AND CONSOLIDATION WHICH CAN BE KILLED AS SOON AS THEY BEGIN TO CYCLE IF THERE IS A CONSTANT LOW LEVEL OF CHEMOTHERAPY

- 6 MERCAPTOPURINE
- METHOTREXATE

Central Nervous System Prophylaxis

- IT-MTX and systemic high-dose MTX
- Cranial irradiation
  - Probably not necessary with systemic high-dose treatment (MTX, ARA-C) and extended IT-MTX

Intrathecal therapy in CNS disease

Six doses of triple intrathecal at twice weekly intervals during induction Phase I

	Adult	**<1**	**1-2**	**2-3**	**>3**
METHOTREXATE:	12.5mg	6	8	10	12.5
CYTARABINE:	40 mg	8	10	13	15
HYDROCORTISONE:	50 mg	10	15	20	25

Repeat CSF analysis at 4th LP for intrathecal during Phase I

All Intrathecal during Phase II to be given as triple

Triple intrathecal once in 3 months during maintenance

PROPHYLACTIC CNS THERAPY (CNS STATUS 1) - No tCRT

- SR and IR patients
  - BCP-ALL: MD MTX; no CRT
  - T-ALL: HD MTX; 12 Gy (pts aged ≥ 1 year)

- HR patients (all- independent of immunophenotype):
- HD MTX + HD ARA-C; 12 Gy (pts aged ≥ 1 year)

- All patients: prophylactic shots of single/triple IT therapy (by risk group & arm)

PROPHYLACTIC CNS THERAPY (CNS STATUS 2) - No tCRT

- The same as for CNS status 1
- **2** additional **IT MTX** doses on days **18** & **27.**

CNS THERAPY IN CNS STATUS 3 - all patients undergo tCRT

- **Patients aged ≥1 < 2 years: 12 Gy**
- **Patients aged ≥ 2 years: 18 Gy**
- **Locoregional therapy:**
  - **• Prophylactic shots of single/triple IT therapy (by risk group & arm) +**
  - **• Additional doses of IT MTX in Protocol I/I'/II/III**
  - **• Additional TIT in block HR-2'**
- **Systemic chemotherapy:**
- **SR/IR BCP-ALL: MD MTX**
- **SR/IR T-ALL: HD MTX**
- **HR: HD MTX + HD ARA-C**

TIMING OF CRT

- Upon the conclusion of the first or single intensive therapeutic element of reinduction therapy in all but:

- Option HR-2B, where CRT is delivered after the last intensive therapeutic element of reinduction therapy (Protocol II), as was the case in ALL-BFM 95

- Prior to allogeneic SCT:

  – TBI within the conditioning regimen, if indicated

  – Local RTX pre-conditioning, if indicated

Testicular Involvement at Diagnosis

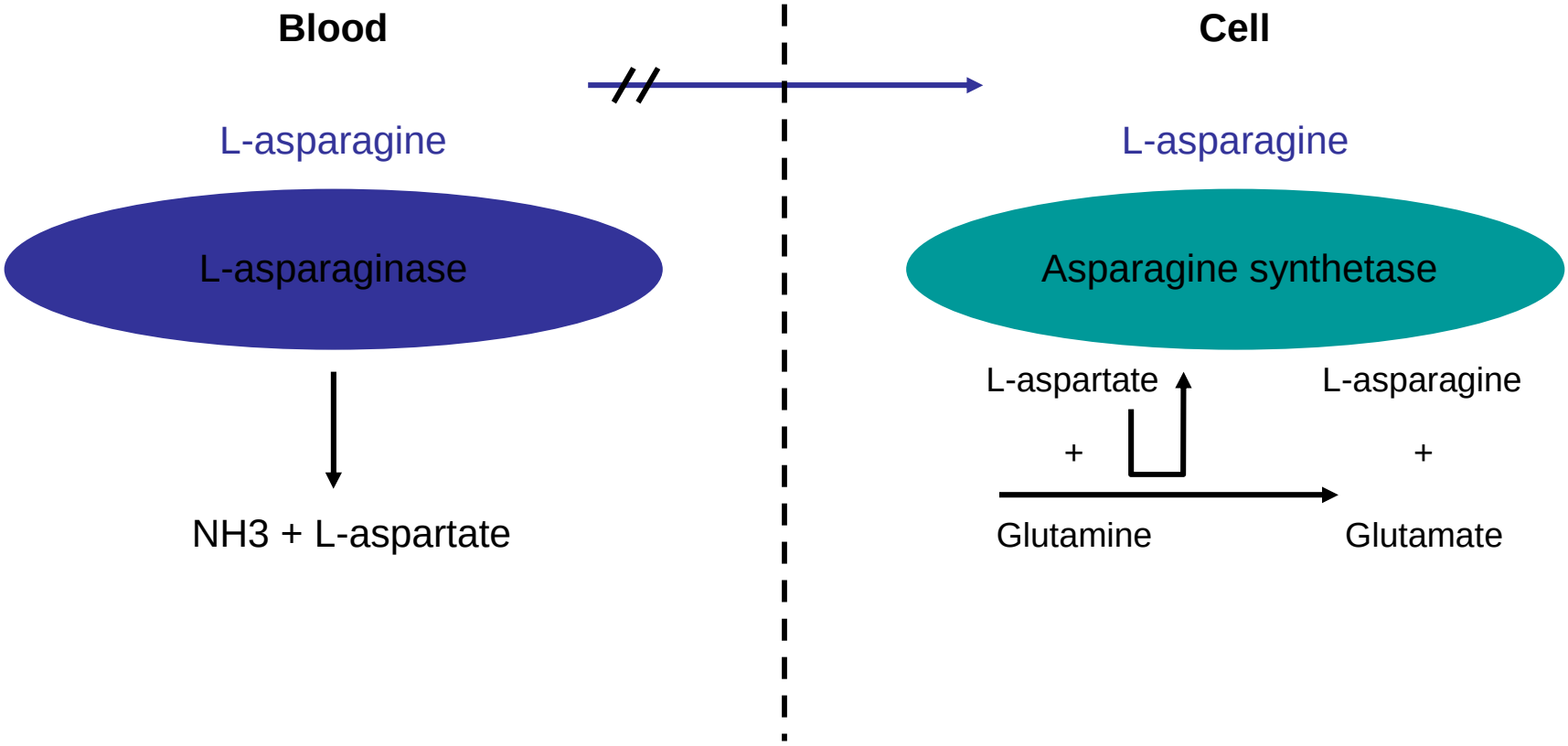
- Intermediate Risk protocol + High dose Methotrexate or testicular RT (24Gy) based on affordability (High dose Methotrexate protocol M in interim maintenance)
- Testicular RT to be administered concomitantly with CNS RT

Drugs in ALL

L-asparaginase

- Used only in ALL
- Enzyme that depletes serum L-asparagine
- Activity related to serum L-asparagine depletion
- No myelosuppression
- No late effects
- Unique adverse effects

L-asparaginase: Mechanism of Action*



***Sensitivity of ALL cells to asparaginase due to low asparagine synthetase in leukemic cells.**

L-asparaginase: Toxicity

- Hypersensitivity
  - Neutralizing antibodies
- Liver dysfunction
  - Liver enzymes, bilirubin, low albumin
- Hemostasis
  - Bleeding: low clotting factors
  - Clotting: low antithrombin III, protein S
- Pancreatitis, diabetes mellitus, CNS effects (lethargy, somnolence)

Pegylated Asparaginase

- Pegylated *E. coli* L-asparaginase
- Less immunogenic
- Long half-life
  - Less frequent dosing
  - Continuous asparagine depletion
- In children
  - More rapid reduction in marrow blasts during induction
  - Lower incidence of neutralizing antibodies
  - Similar safety profile as native form
- In adults
  - Similar toxicity to native form after single and multiple doses

Avramis VI, et al. Blood. 2002;99:1986-1994.
Panosyan EH, et al. J Pediatr Hematol Oncol. 2004;26:217-226.

ALL: New Chemotherapies

- Antimetabolites
  - Nelarabine (relapsed T-ALL)
  - Clofarabine
  - Trimetrexate (dihydrofolate reductase inhibitor)
- Liposomal or pegylated agents
  - Pegylated L-asparaginase
  - Liposomal daunorubicin
  - Liposomal vincristine
- Cytarabine liposome injection (IT)

Clofarabine in ALL

- Children (N = 61)[1]; median of 3 prior regimens
- 52 mg/m^2 on Days 1-5
  - CR + CRp in 12 patients (20%); PR in 6 patients (10%)
  - Median survival:13 weeks
  - 9 responders proceeded to SCT
- Adults (N = 12)[2]
  - Dose 40 mg/m^2 on Days 1-5
  - CR in 2 patients (17%)

1. **Jeha S, et al. J Clin Oncol. 2006;24:1917-1923.**
2. Kantarjian H, et al. Blood. 2003;102:2379-2386.

ALL: Targeted Treatments

ALL Subtype	Target	Treatment
Ph+	BCR/ABL	Imatinib, dasatinib, nilotinib
T cell	NUP214-ABL1 NOTCH1 mutation	Imatinib, dasatinib, nilotinib Gamma secretase inhibitor
Mature B cell	CD20	Rituximab
Precursor B cell	CD20	Rituximab
All subtypes	CD52	Alemtuzumab
MLL and hyperdiploidly	FLT3 overexpression	CEP701, PKC 212

T-Cell ALL: Gamma Secretase Inhibitor MK 0752

- NOTCH 1 gain-of-function mutations in 50% of T-ALL
- Gamma secretase inhibitors abrogate stimulatory effects of NOTCH 1
- Phase I trial
  - Gamma secretase inhibitor MK-0752
  - 4 patients: NOTCH1 activated mutations
  - 1 patient: decrease in size of mediastinal mass

DeAngelo D, et al. ASCO 2006. Abstract 6585.

Treatment in adults

Subtype Oriented Strategies for Treatment of Patients With Adult T-ALL

- Largest adult T-ALL cohort (N = 744); age range: 15-55 yrs
  - Treated in 3 consecutive GMALL studies that included B-cell

Immunophenotype	Markers	Frequency, %
T-lineage	TdT+, cyCD3+, CD7+	24
•Early T-ALL	CD2-, sCD3-, CD1a-	6
•Thymic T-ALL	sCD3±, CD1a+	12
•Mature T-ALL	sCD3+, CD1a-	6

Subtype Oriented Strategies for Treatment of Patients With Adult T-ALL

- GMALL 05/93; no SCT, no risk stratification by subtype
- GMALL 06/99 + 07/03; thymic T treated as standard risk, early and mature as high risk, SCT in CR1

Outcome, %	Thymic T		Early T		Mature T	
Study	05	06, 07	05	06, 07	05	06, 07
OS*	51	63	30	37	21	45
CR	93	92	72	84	84	77
SCT in CR1	--	11	--	84	--	68
• CCR	--	79	--	47	--	61
• OS (SCT)	--	87	--	44	--	59

*10-yr OS for Study 05, 8-yr OS for Studies 06 and 07.

Hoelzer D, et al. ASH 2009. Abstract 324.

Stem Cell Transplantation (SCT): CIMBTR Recommendations

- First CR
  - Allo SCT or MUD in high-risk patients
  - Role in standard-risk patients unclear but not recommended
  - Auto SCT: no benefit over chemotherapy
- Second CR
  - Allo SCT

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

Table 7: Indications for Allogeneic SCT in ALL IC-BFM 2002

INDICATION		MFD† SCT
NR d33		+
PPR	+ T-ALL	+
	+ pro B-ALL	+
	+ WBC > 100,000/µL	+
	+ t(9;22) or BCR/ABL	+
	+ t(4;11) or MLL/AF4*	+
PGR	+ t(9;22) or BCR/ABL	+
HR	+ M3 d15	+

† MFD **m**atched **f**amily **d**onor

* Infants < 1 yr only

Philadelphia Chromosome (Ph+) ALL

- t(9;22) bcr/abl translocation
- Precursor B cell
- Incidence continuously increasing with age
  - Rare in children; 50% incidence in ALL patients older than 55 years of age
- Associated with very poor outcome
  - No cure with intensive ALL chemotherapy (all ages)
  - Cure with SCT
    - Lower cure rate than other ALL subtypes

Imatinib in Ph+ ALL

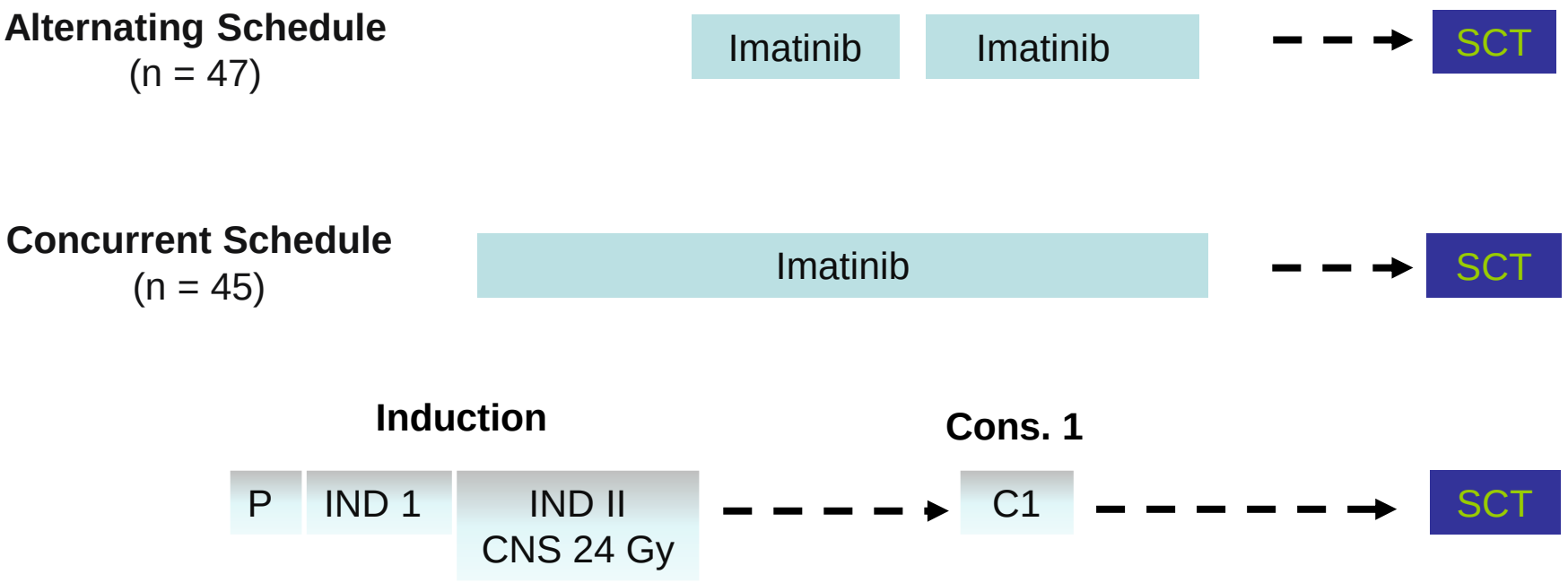
- Induces high response rate as single agent
  - Response generally not durable
- In combination with ALL chemotherapy
  - Higher CR rate: 90% to 97% and improved outcome compared with chemotherapy alone[1,2]
  - Increased access to transplantation for more patients[3]
  - Improves outcome of subsequent SCT[3]
  - Concurrent administration of imatinib + chemotherapy superior to alternating schedule[4]

1. Thomas DA, et al. Blood. 2004;103:4396-4407. 2. Yanada M, et al. J Clin Oncol. 2006;24:460-464. 3. Lee S, et al. Blood. 2005;105:3449-3457. 4. Wassmann B, et al. Blood. 2006;108:14691477.

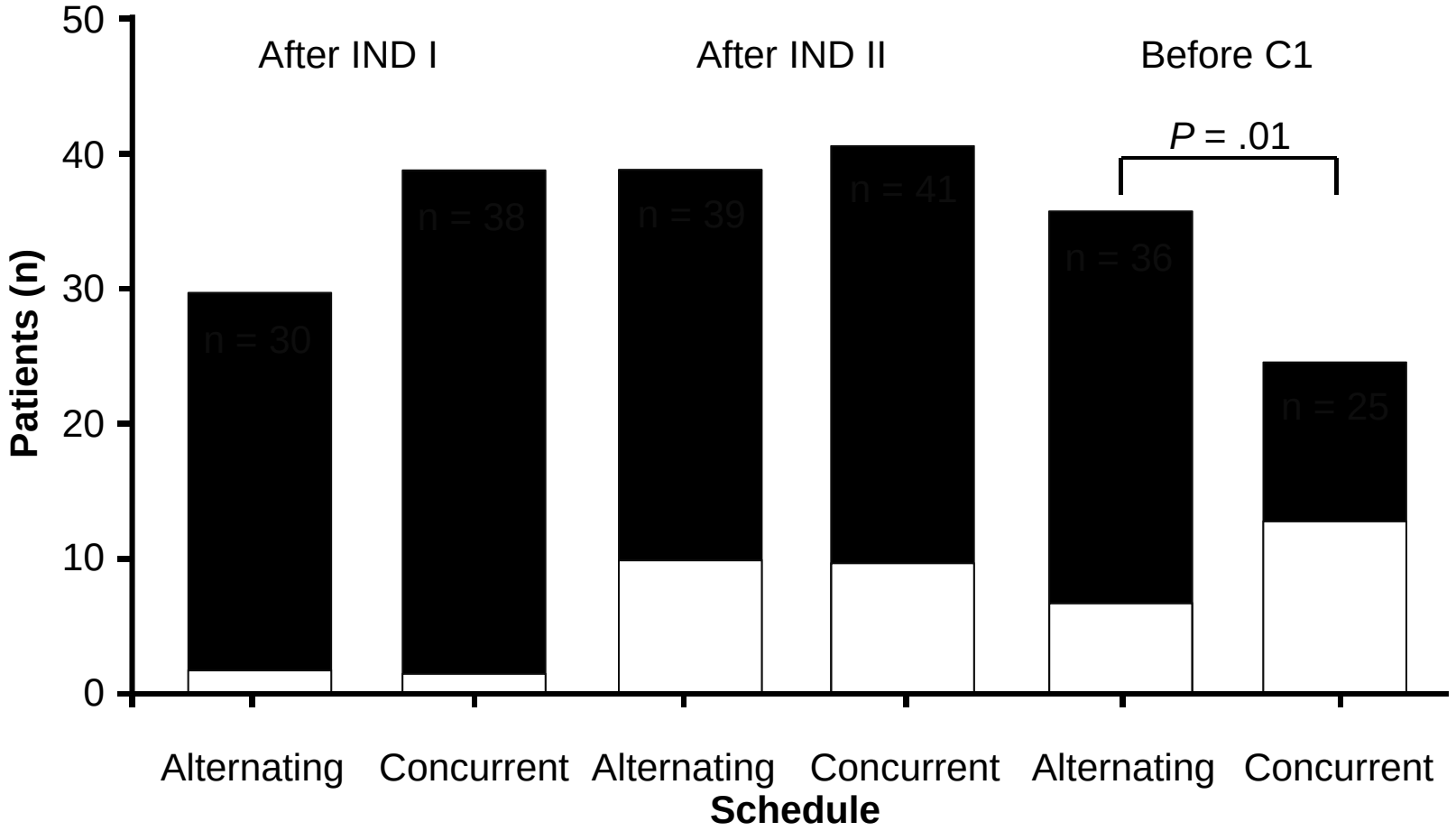
Ph+ ALL in the Imatinib Era

- Despite improvement in long-term survival with imatinib and chemotherapy, Ph+ ALL remains a high-risk disease
  - No longer the “initially rapidly fatal” disease of a decade ago
- Allogeneic HSCT whenever possible
  - Related
  - Unrelated donor
- Major unresolved investigative issue is the role of reduced-intensity HSCT in older patients, in whom disease is relatively common

Alternating vs Concurrent Imatinib With Chemotherapy



Alternating vs Concurrent Imatinib With Chemotherapy



Imatinib-Resistant Ph+ ALL

- Dasatinib
  - Substantial data
- Nilotinib
  - More limited data
- Others
  - Bosutinib
  - INNO-406
  - MK-0457 (also active against T315I Bcr-Abl mutation)

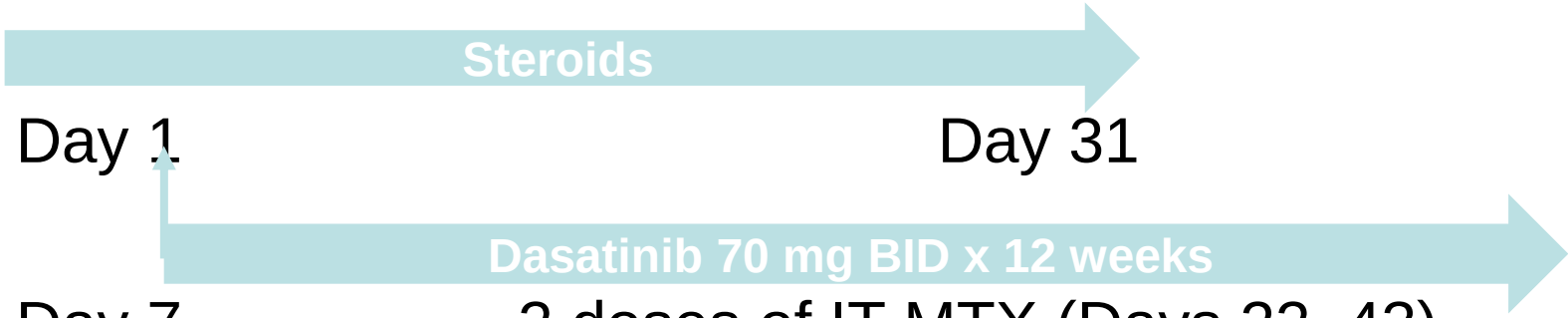
Treatment of Relapsed Ph+ ALL: Dasatinib

	Ph+ ALL	CML (Chronic Phase)
Patients, N	36	186
Imatinib status, %		
• Resistant	94	68
• Intolerant	6	32
Response, %		
• CHR	31	90
• NEL	11	
• McyR	58	45
• CcyR	58	33
Median duration of response, mos	4.8	> 6.0

Coutre S, et al. ASCO 2006. Abstract 6528

GIMEMA LAL1205: Dasatinib for Newly Diagnosed Adult Patients With Ph+ ALL

- 48 pts, Ph+ ALL; median age: 54 years (range: 24-76)



- Day 1 — Day 31
- Day 7 — 2 doses of IT MTX (Days 22, 43)
  Frequent monitoring of MRD
- 34 evaluable pts
  - Hematologic CR: 100%
  - Rapid achievement of MRD, typically by Day 22

Foà R, et al. ASH 2008. Abstract 305.

Single-Agent Dasatinib in Imatinib-Resistant Ph+ ALL

- Phase I dose-escalation study
- N = 84
- 10 pts with CML in lymphoid blast crisis or Ph+ ALL
  - Major hematologic response: 70%
  - All except 1 responders

➔Relapse at median of 4 months (range: 1-8)

Talpaz M, et al. N Engl J Med. 2006;354:2531-2541.

Single-Agent Nilotinib in Imatinib-Resistant Ph+ ALL

- Phase I dose-escalation study
- N = 119
- 13 pts with imatinib-resistant Ph+ ALL
  - 2 responders
    - 1 partial hematological response
    - 1 complete molecular remission

Kantarjian H, et al. N Engl J Med. 2006;354:2542-2551.

Relapsed Ph+ ALL

- Dismal outcome irrespective of any previous therapy
- If no previous transplant
  - Reinduction (1 attempt only)
  - Allogeneic transplant from alternative donor (MUD, cord, haplo)
- Postallogeneic transplant options include
  - No role for DLI
  - Dasatinib or other TKI plus best supportive care

ALL: Novel Management Approaches

- Minimal residual disease evaluation
  - Define prognostic groups for treatment selection
- Microarray analysis (gene expression profiles)
  - Prognosis
  - Identify new targets

REMISSION IN ACUTE LEUKAEMIA

- NO CLINICAL EVIDENCE OF LEUKAEMIA
- NORMAL PERIPHERAL BLOOD
  - NORMAL TOTAL AND DIFFERENTAL WBC
  - NO BLASTS
  - NORMAL PLATELET COUNT
- BONE MARROW
  - NORMOCELLULAR
  - LESS THAN 5% MYELOBLASTS
  - NO LYMPHOBLASTS

When the patient is in clinical remission with no detectable leukaemic cells there could be over 100 million leukaemic cells remaining .

Minimal Residual Disease

- Methods
  - Multicolor flow cytometry or PCR
  - Fusion transcripts
  - Rearranged immunoglobulin and T-cell receptor genes
  - Prognostic levels defined for children; prognostic time points and levels yet to determined for adults

Time of Evaluation	Minimum Residual Disease	Prognosis
Children		
• At CR	< 0.01%	Excellent outcome
• After CR	> 0.1%	High relapse risk

GRAALL: Early MRD Strong Predictor of Outcome in Adults With Ph-Negative ALL

- Nonrandomized multivariate analysis of patients on 2 trials[1]
  - N = 212
  - Adults with Ph-negative ALL treated within GRAALL-2003[2] or ongoing GRAALL-2005 trials
    - Pediatric-based treatment regimen[2]
- MRD detected by IgH and TCR gene rearrangements
  - RQ-PCR in centralized laboratories
- Wk 6: MRD1 evaluated in patients with CR after first induction (n = 212)
- Wk 12: MRD2 evaluated following consolidation in GRAALL trial (n = 163)

1. Beldjord K, et al. ASH 2009. Abstract 577. 2. Huguet F, et al. J Clin Oncol. 2009;27:911-918.

GRAALL: Early MRD Strong Predictor of Outcome in Adults With Ph-

MRD Classification Levels			
Level	**Classification**	**RQ-PCR Result**	**Transcript vs Baseline**
0	Favorable	Negative	--
1	Favorable	Positive	$< 10^{-4}$
2	Intermediate	Positive	$\geq 10^{-4}$ and $< 10^{-3}$
3	Unfavorable	Positive	$\geq 10^{-3}$ and $< 10^{-2}$
4	Unfavorable	Positive	$\geq 10^{-2}$

- CIR, DFS, and OS predicted by MRD1 level by multivariate analysis ($P < .0001$)

Outcome, %	MRD1 = 0-1	MRD1 = 2	MRD1 = 3-4
3-yr CIR	13	38	56
3-yr DFS	80	40	
3-yr OS	82	49	
High-risk ALL	50	86	
Allogeneic SCT	24	47	

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CME article

Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study

The Associazione Italiana di Ematologia Oncologia Pediatrica and the Berlin-Frankfurt-Münster Acute Lymphoblastic Leukemia (AIEOP-BFM ALL 2000) study has for the first time introduced standardized quantitative assessment of minimal residual disease (MRD) based on immunoglobulin and T-cell receptor gene rearrangements as polymerase chain reaction targets (PCR-MRD), at 2 time points (TPs), to stratify patients in a large prospective study. Patients with precursor B (pB) ALL (n = 3184) were considered MRD standard risk (MRD-SR) if MRD was already negative at day 33 (analyzed by 2 markers, with a sensitivity of at least 10^{-4}); MRD high risk (MRD-HR) if 10^{-3} or more at day 78 and MRD intermediate risk (MRD-IR): others. MRD-SR patients were 42% (1348): 5-year event-free survival (EFS, standard error) is 92.3% (0.9). Fifty-two percent (1647) were MRD-IR: EFS 77.6% (1.3). Six percent of patients (189) were MRD-HR: EFS 50.1% (4.1; $P < .001$). PCR-MRD discriminated prognosis even on top of white blood cell count, age, early response to prednisone, and genotype. MRD response detected by sensitive quantitative PCR at 2 predefined TPs is highly predictive for relapse in childhood pB-ALL. The study is registered at http://clinicaltrials.gov: NCT00430118 for BFM and NCT00613457 for AIEOP. (*Blood*. 2010;115(16):3206-3214)

B-Cell ALL (FAB L3): Burkitt's Leukemia

- Rapid cell proliferation and very high LDH
- t(8;14), t(2;8), t(8;22)
  - Rearrangement of *myc* protooncogene (ch 8) with Ig heavy chains (ch 14) or light chains (ch 2 or 22)
- Short intensive chemotherapy
  - High-dose MTX and cyclophosphamide
- Intensive CNS prophylaxis
- No maintenance
- Cure rate: 60%; relapse rare 6 months after CR