MANAGEMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA

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Introduction

- The management of ALL, the most common childhood malignancy (1/3rd of all malignancy), has been changing over the years.
- Multi-agent systemic chemotherapy over a prolonged duration (2–3 years) and adequate CNS-directed therapy, in addition to improved antibiotic and blood product support has improved cure rates from approximately 10% (50 years back) to nearly 90%.
- Monitoring of minimal residual disease (MRD) to refine therapy based on risk of relapse to maximize cure and minimize toxicities has improved the outcome.

DIAGNOSIS: CLINICAL

Table 2: Clinical and laboratory features at diagnosis in children with ALL

Clinical and laboratory features	Percentage of patients
Symptoms and physical findings	
Fever	60
Hepatosplenomegaly	70
Paleness	55
Bleeding (e.g., petechiae or purpura)	50
Lymphadenopathy	50
Bone pain	25
Abdominal pain	20
Weight loss	15

DIAGNOSIS: LABORATORY

Table 2: Clinical and laboratory features at diagnosis in children with ALL

Clinical and laboratory features	Percentage of patients
Laboratory features	
Leukocyte count (mm^3)	
<10,000	53
10,000–49,000	30
>50,000	17
Hemoglobin (g/dL)	
< 7.0	43
7.0 - 11.0	45
> 11.0	12
Platelet count (mm^3)	
< 20.000	28
20.000 – 99.000	47
> 100.000	25

DIAGNOSIS: LABORATORY

- Bone marrow:>25% lymphoblast
  - CSF analysis for CNS involvement
  - USG for testicular involvement
  - ECG and ECHO for baseline cardiac status
  - RFT and LFT
  - Cytogenetics

RISK STRATIFICATION

Risk stratification	Features
Low risk	Age 1-9 yrs, WBC count<50,000/cumm, pre-B ALL, trisomy 4 and 10, hyperdiploidy, t(12;21)
Standard risk	Age 1-9 yrs, WBC count<50,000/cumm, pre-B ALL, normal cytogenetics
High risk	Age<1years and >9 years, WBCcount>50,000/cumm, T-cell ALL, CNS involvement, hypodiploidy
Very high risk	t(9;22),t(4;11), induction failure

MULTIDISCIPLINARY TREATMENT TEAM

- Pediatric hemato-oncologist
- Radiation oncologist
- Nursing team
- Dietician
- Medical social worker

COMPONENTS OF MANAGEMNT

SUPPORTIVE THERAPY

SUPPORTIVE CARE

- Blood component therapy to maintain Hb>10gm/dl and TPC >1lkh/cmm before each induction.
- Cotrimoxazole prophylaxis
- Folic acid, vit B12 supplementation
- Immunization: Hepatitis B, pneumococcal, meningococcal
- Oral hygiene

CHEMOTHERAPY REGIMEN: MCP (841) : 3 PHASES

REMISSION INDUCTION: 1 (4-6 CYCLES)

- To induce remission (bone marrow blast cell < 5%)

Chemotherapy	Dose and schedule
Prednisone	40mg/m² PO days 1-28
Vincristine	1.4mg/m² IV days 1,8, 15 and 22
Methotrexate	12 mg IT, days 1,8,15 & 22
L-asparaginase	6000 µ/m² IM on alternate days *10 doses, days 2-20
Daunorubicin	30 mg/m² IV days8,15 &29

REMISSION INDUCTION : 2

- INDICATION : FAILURE OF INDUCTION 1

CHEMOTHERPY	DOSAGES AND SHEDULE
Mercaptopurine	75mg/m² PO daily 1-7days &15-21days
Cyclophosphamide	750 mg/m² IV day1& day15
Methotrexate	12mg/m² IT days 1,8,15&22
Cranial radiation	200cGy daily *9days (total 1800cGy)

CONSOLIDATION: 14 to 28 weeks

To clear residual or resistant blast cells

Chemotherapy	Dose and schedule
Cyclophosphamide	750 mg/m² IV day 1 & 15
Vincristine	1.4 mg/m² IV days 1 & day 15
Mercaptopurine	75 mg/m² PO daily days 1-7 & days 15-21
Cytarabine	100mg /m² SC every 12hrs *6hours on days 1-3 & days 15-17
Daunorubicin	30 mg/m² IV days 15

MAINTENANCE THERAPY: 2-2.5 YEAR

- Given to prevent relapse.

Chemotherapy	Dose and schedule
Prednisone	40 mg/m² PO days 1-7
Vincristine	1.4 mg/m² IV on day 1
Daunorubicin	30mg/m² IV on day 1
L-asparaginase	6000 /m² IM days 1,3,5 &7
Mercaptopurine	15 mg/m² PO once a week, missing every 4th for a total of 12 weeks, begin on day 15 75mg/m² PO daily, 3 weeks out of every 4 for total

TREATMENT OF RELAPSE

- Combination chemotherapy
- Total body radiation therapy
- Bone marrow transplantation

NEWER TARGET THERAPY

Table III. Examples of targeted therapy in childhood ALL[87,88]

Agent	Target	ALL subtype
Monoclonal antibodies		B-precursor ALL
Rituximab	CD20	
Epratuzumab	CD22	
Blinatumomab	CD19	
Alemtuzumab	CD52	
Tyrosine kinase inhibitors	BCR/ABL	Ph^+ ALL
Imatinib	Other tyrosine kinases	
Dasatinib		
Nilotinib		
FLT3 inhibitors	FLT3 receptor tyrosine kinase	Infant ALL; hyperdiploid ALL
Gamma secretase inhibitors	NOTCH	T-ALL

ALLOGENIC HSCT

Table 1
Common indications for allogeneic HSCT in childhood leukemias

Disorder	Disease state	Comments
ALL	CR1: hypodiploid karyotype	
	CR1: following primary induction failure	
	CR1: infant ALL (HR subgroup)	<3 mo old at dx; WBC>300 k/mm^3, MLL+
	CR1: increased MRD after induction?	
	CR2: T-cell ALL	Relapse in marrow or any other site; any timing
	CR2: Ph^+ ALL	Relapse in marrow or any other site; any Timing
	CR2: precursor B-cell ALL	Marrow relapse while on or within 1 y of completing primary therapy
	CR2: precursor B-cell ALL	Extramedullary (CNS, testis, eye) relapse within 18 mo of initial diagnosis

RADIOTHERAPHY

- **Indications**: Induction failure, CNS and bone marrow relapse
- **Dose**: 200cGY
- **Complication:** Neurocognitive deficits, Obesity, Cardiomyopathy, Avascular necrosis, Secondary leukemia and osteoporosis, Growth hormone deficiency and brain tumors.

MONITORING

Clinical

- Vital signs
- Weight
- Organomegaly
- Neurocognitive defects
- Gonads
- Ophthalmic
- Growth

Laboratory

- CBC
- Bone marrow Studies
- Chest x ray
- USG
- RFT
- LFT
- ECG
- LDH
- MRD

PROGNOSIS

Table 1
Prognostic factors in childhood acute lymphoblastic leukemia

Factor	Favorable	Intermediate	Unfavorable
Age (years)	1 to 9	≥10[a]	<1 and *MLL*+
White blood cell count ($\times 10^9$/L)	<50	≥50[a]	
Immunophenotype	Precursor B cell	T cell[a]	
Genetics	Hyperdiploidy >50 or DNA index >1.16 Trisomies 4,10, and 17 t(12;21)/*ETV6-CBFA2*	Diploid t(1;19)/*TCF3-PBX1*[a]	t(9;22)/*BCR-ABL1* t(4:11)/*MLL-AF4* Hypodiploid <44
CNS status	CNS1	CNS2[a] Traumatic with blasts	CNS3
MRD (end of induction)	<0.01%	0.01% to 0.99%	≥1%

[a] These factors used to carry an unfavorable prognosis; however, outcome has improved with risk-directed contemporary therapy.

MINIMAL RESIDUAL DISEASE (MRD)

- MRD an excellent prognostic marker
- PCR assay or Flow cytometry can detect one leukemic cell in 10,000 to 100,000 normal cells.
- MRD at the end of induction
  - < 0.01%: Favorable prognosis
  - > 1: Unfavorable prognosis

OVERALL SURVIVAL IS IMPROVING OVER YEARS

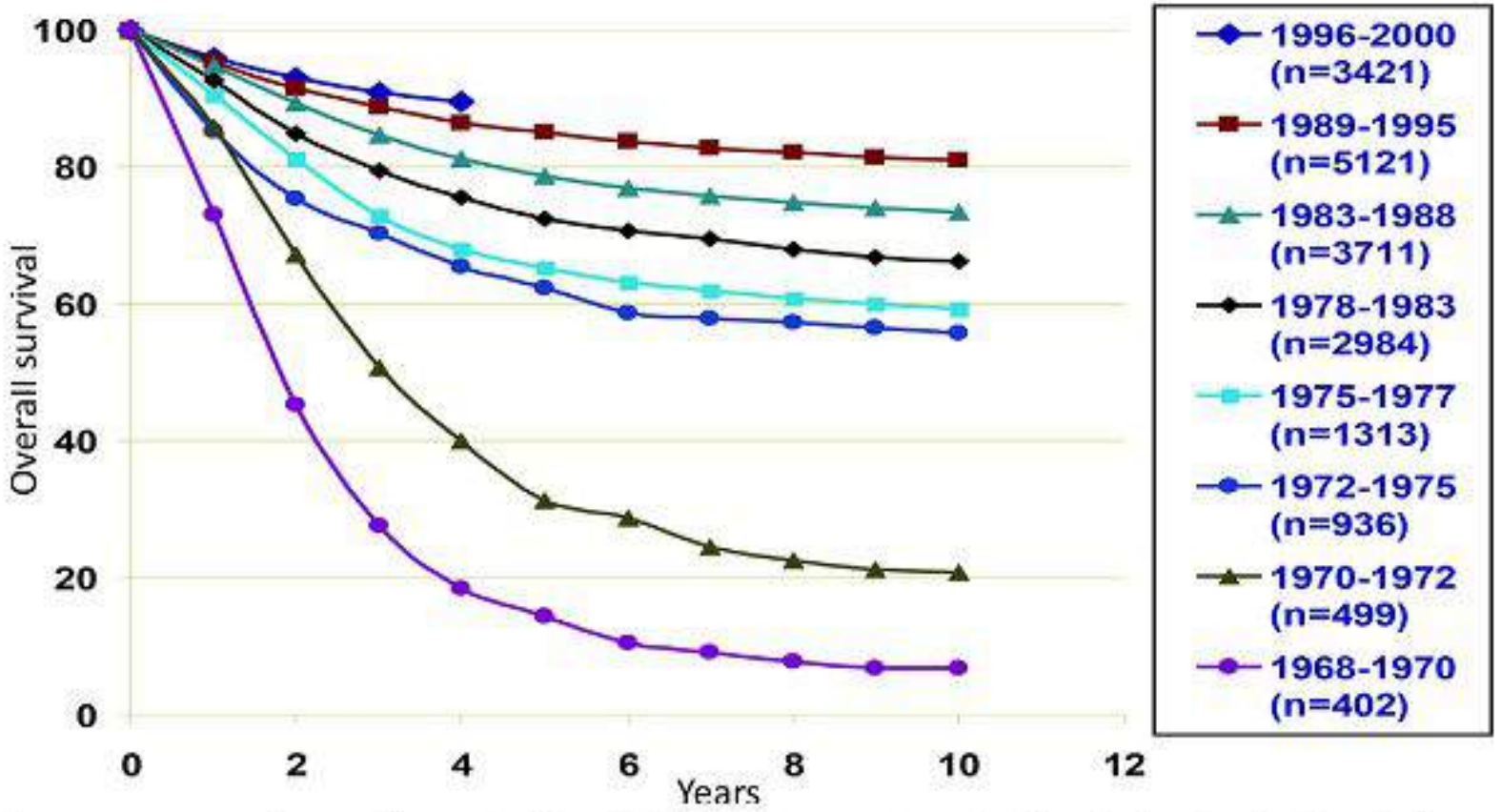

Fig. 1. Improved overall survival in childhood acute lymphoblastic leukemia (ALL). (*From* Hunger SP, Winick NJ, Sather HN et al. Therapy of low-risk subsets of childhood acute lymphoblastic leukemia: when do we say enough? Pediatr Blood Cancer 2005;45(7):876–80; with permission.)

Table 1
Outcomes for newly diagnosed childhood acute lymphoblastic leukemia

Cooperative Group	Study	Years	Patients	5-y EFS (%)
Berlin-Frankfurt-Münster[52]	ALL-BFM-95	1995–2000	2169	79.6[a]
Children's Oncology Group[52]	Multiple	2000–2005	7153	90.4
Dana Farber Cancer Institute Consortium[52]	DFCI 95-01	1996–2001	491	82.0
Nordic Society of Pediatric Hematology and Oncology[52]	NOPHO	2002–2007	1023	79.0
St Jude Children's Research Hospital[52]	TOTXV	2000–2007	498	85.6
United Kingdom Acute Lymphoblastic Leukaemia[52]	UKALL 2003	2003–2011	3126	87.2

Abbreviation: EFS, event-free survival.

[a] 6-Year EFS used in ALL-BFM-95.

TREATMENT OF EARLY COMPLICATION

- Tumour lysis syndrome: hyperuricimia, hyperkalemia, hyperphosphatemia.

- Rx: Bicarbonate, allopurinal, and dialysis

Table IV. Screening and prevention of late effects in childhood ALL survivors

Late effect	Exposure risk	Screening	Prevention
Neurocognitive	• CRT • Intrathecal methotrexate • High-dose systemic methotrexate • Young age at exposure	• Baseline neuropsychological assessment • Neuropsychological assessment at educational transitions • Yearly evaluation	• Special education services • Education accommodations • Cognitive rehabilitation • Stimulant medications (investigational)
Cardiac	• Anthracyline dose >300 mg/m^2 • Chest irradiation	• Baseline eletrocardiogram and echocardiogram • Echocardiogram at 5 years and/or based on risk	• Avoidance of isometric exercise
Musculoskeletal	• Steroids	• Magnetic resonance imaging • Bone mineral density analysis	• Statins (investigational) • Weight-bearing exercise • Adequate calcium and vitamin D
Second malignancy	• Alkylating agents • Topoisomerase II inhibitors • Radiation	• Yearly complete blood count • Yearly physical examination	• Risk-stratified therapy to avoid exposure in lower-risk patients
Obesity/metabolic syndrome	• Steroids • Inactivity	• Yearly evaluation	• Exercise

Adapted from Neglia et al.[107]

CONCLUSION

Management steps include

- 1. Confirmation of diagnosis
- 2. Risk stratification
- 3. Combination Chemotherapy +/- radiotherapy
- 4. Supportive therapy
- 5. Treatment of complications
- 6. Follow up for 5-6 event free years.

THANK YOU

Table 4
New targeted therapies for childhood and adolescent acute lymphoblastic leukemia

Drug	Target	Type of ALL
Imatinib	*ABL* tyrosine kinase	*BCR-ABL* fusion, *NUP214-ABL1* fusion
Dasatinib, nilotinib	*ABL* tyrosine kinase (also many mutations), *SRC* kinases	*BCR-ABL* fusion
PKC412, CEP701, other *FLT3* inhibitors	Mutated *FLT3*, wild type over-expressed *FLT3*	*MLL* gene–rearranged ALL, hyperdiploid ALL
Demethylating agents	Hypermethylation	*MLL* gene–rearranged ALL, other subtypes?
Rituximab	CD20	CD20 + (B-lineage) ALL
Epratuzumab	CD22	CD22 + (B-lineage) ALL
Gemtuzumab ozogamicin	CD33	CD33 + ALL
Alemtuzumab	CD52	CD52 + ALL
Forodesine	PNP (purine nucleoside phosphorylase)	T-ALL
Nelarabine		T-ALL