ความก้าวหน้าในการดูแลผู้ป่วย โรคมะเร็งเม็ดเลือดขาวในเด็ก

พญ.พชรพรรณ สุรพลชัย
รองศาสตราจารย์ ภาควิชากุมารเวชศาสตร์
คณะแพทยศาสตร์ มหาวิทยาลัยธรรมศาสตร์

มิถุนายน **2562**

Outline

Part I

- Overview of childhood leukemia
- Management of childhood leukemia
- Outcome of childhood leukemia worldwide and in Thailand

Overview of childhood leukemia

Childhood leukemia (โรคมะเร็งเม็ดเลือดขาวในเด็ก)

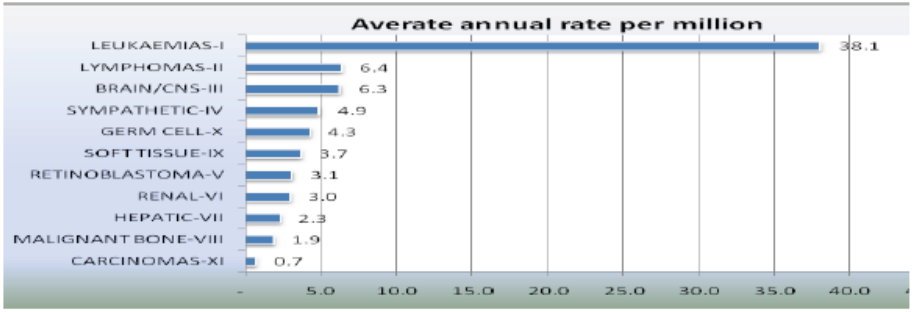
- A cancer of the white blood cells, leads to abnormal proliferation of white blood cells in bone marrow
- The most common type of cancer in children and adolescents
- The exact cause of most childhood leukemias is UNKNOWN

Overview of childhood leukemia

Incidence of Childhood leukemia

- Approx. ¼ (25-30%) of childhood cancers worldwide
- US: 2,500-3,000 children (<20 years old) diagnosed with ALL and 500 with AML each year in the US
- Thailand (ThaiPOG) during 2003-2005: 1,421 cases

- ALL 1,029 cases (72%)
- AML 328 cases (23%)



Wiangnon S, et al. Asian Pac J Cancer Prev. 2011;12(9):2215-20.
SEER Cancer Statistics Review, 1975-2015, National Cancer Institute. Bethesda, MD.

Overview of childhood leukemia

Risk factors for childhood leukemia

- Genetic risk factors: Down syndrome (trisomy 21)
- Inherited immune system disorders: Bloom syndrome, Schwachman-Diamond syndrome
- Siblings of children with leukemia, especially among identical twins
- Environmental risk factors: radiation, [illegible] chemical exposure (benzene, pesticides)
- Immune suppression: previous organ transplant

Exposure during pregnancy and early childhood

Overview of childhood leukemia

Clinical presentation of childhood leukemia

- Bone marrow failure
  - ❖ Red blood cell production: anemia
  - ❖ White blood cell production and function: infection
  - ❖ Platelets: bleeding
- Organomegaly: swollen LN, hepatomegaly, splenomegaly, gum hypertrophy
- Bone pain
- Loss of appetite and weight loss

Overview of childhood leukemia

Diagnosis of childhood leukemia

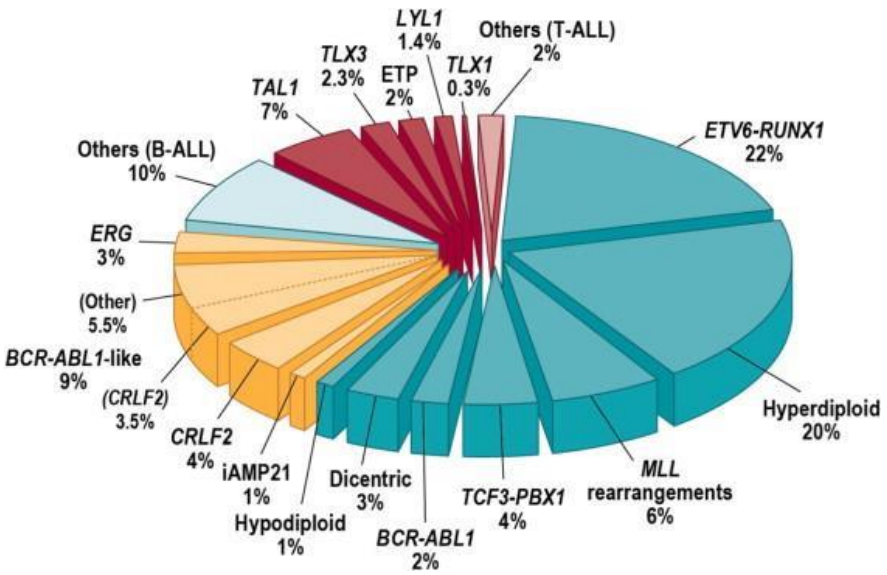
- Blood tests: CBC and smear
- Bone marrow studies
  - ❖ Morphology: marrow smear
  - ❖ Immunophenotypes: immunohistochemistry, flow cytometry
  - ❖ Chromosome and molecular genetic studies
- Lumbar puncture: CSF cell count and cytology
- Others: imaging, pleural tapping, LN or tissue biopsy

Overview of childhood leukemia

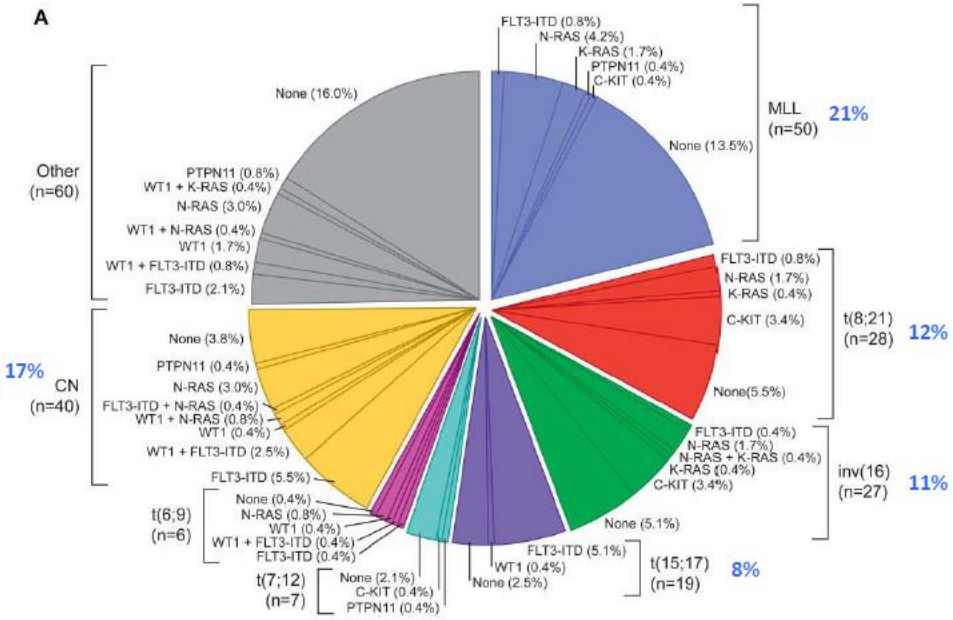
Types of childhood leukemia

- Acute leukemia (fast growing):
  - ALL: Acute lymphoblastic leukemia
  - AML/ANLL: Acute myeloid (non-lymphoblastic) leukemia
  - Rare: Acute undifferentiated leukemia, Mixed phenotype acute leukemia with t(v;11q23); *KMT2A* (*MLL*) rearranged
- Chronic leukemia (slower growing):
  - CML: Chronic myeloid leukemia
- Juvenile myelomonocytic leukemia

Subclassification of childhood ALL



Molecular genetic in childhood AML



https://www.cancer.gov/images/cdr/live/CDR775146.jpg

Creutzig U, et al. Blood. 2012;120(16):3187-205.

Management of childhood leukemia

Specific treatment of childhood leukemia

- Chemotherapy (chemo): “Risk-adapted therapy”
  - ❖ Induction
  - ❖ Post-induction: consolidation/internsification, maintenance
  - ❖ CNS prophylaxis
- Radiotherapy

Management of childhood leukemia

Specific treatment of childhood leukemia

- Targeted therapy:
  - ❖ Tyrosine kinase inhibitors (such as imatinib) in Philadelphia chromosome (Ph)-positive ALL
- Immunotherapy: specific natural killer (NK) cells
- Hematopoietic stem cell transplantation

Acute Lymphoblastic Leukemia (ALL)

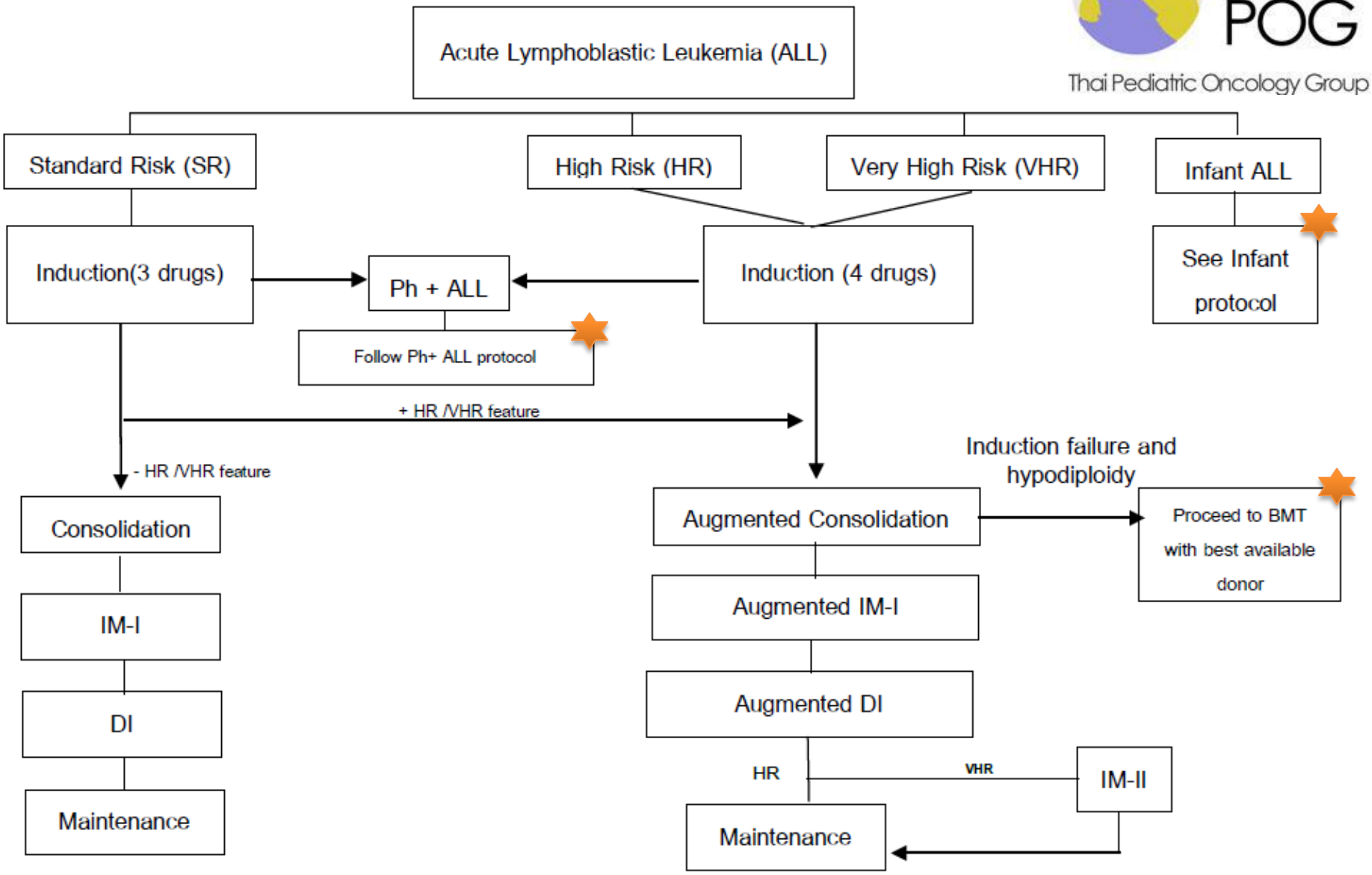
Management guideline

Risk stratification for ALL

Thai Pediatric Oncology Group

Standard Risk (SR)	High Risk (HR)	Very High Risk (VHR)
Clinical criteria ■ Pre-B ALL ○ Age 1-9 and ○ WBC <50,000 ■ Down Syndrome Molecular criteria (optional) ■ Day 29 BM MRD <0.01% ■ No unfavorable molecular feature	Clinical criteria ■ T-ALL ■ Pre-B ALL ○ Age 10-13 or ○ WBC ≥50,000 ■ Testicular disease ■ Steroid pretreatment Molecular criteria (optional) ■ Day 29 BM MRD ≥0.01% with favorable cytogenetic: ETV-6/RUNX-1 or double trisomy 4,10	Clinical criteria ■ Pre-B ALL ○ Age ≥14 ■ CNS-3 ■ Induction failure (M2 or M3 at day 29) Molecular criteria (optional) ■ Day 29 BM MRD ≥0.01 with no favorable cytogenetic ■ Unfavorable molecular feature ○ iAMP 21 ○ MLL rearrangement ○ Hypodipliody (<44 chromosome or DNA index <0.81) ○ Ph-chromosome (follow Ph-ALL protocol)

*Patient with Burkitt leukemia (stage IV mature B cell lymphoma with bone marrow involvement >25%) will be treated with high risk mature B-cell lymphoma protocol (ThaiPOG-BL-13HR)

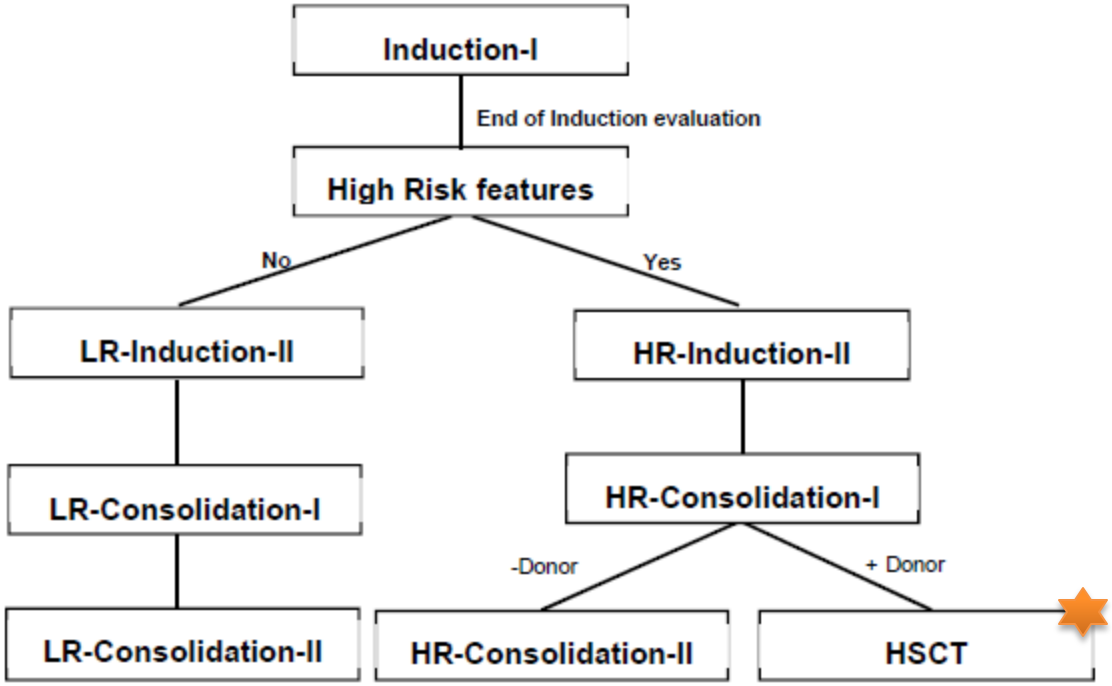

Protocol assignment and treatment schema for new ALL patient
Acute Lymphoblastic Leukemia (ALL)
Standard Risk (SR)
High Risk (HR)
Very High Risk (VHR)
Infant ALL
Induction(3 drugs)
Ph + ALL
Induction (4 drugs)
See Infant protocol
Follow Ph+ ALL protocol
+ HR /VHR feature
- HR /VHR feature
Induction failure and hypodiploidy
Consolidation
Augmented Consolidation
Proceed to BMT with best available donor
IM-I
Augmented IM-I
DI
Augmented DI
HR
VHR
IM-II
Maintenance
Maintenance

Acute Myeloid Leukemia (AML)

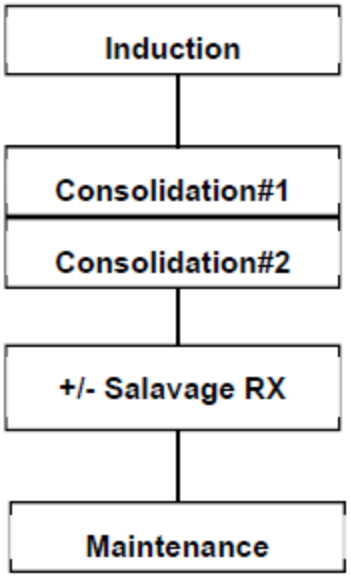
Risk stratification for AML

Low Risk (LR)	High Risk (HR)
▪ Presence of low risk molecular marker: Inv 16 or t(8,21) without high risk features ▪ MRD < 0.1% or M1 status at the end of induction-I ▪ AML patient who has no molecular marker and cytogenetic information available	▪ FLT3/ITD positive with high allelic ratio >0.4 regardless of low risk features ▪ Presence of monosomy 5, monosomy 7, -5q or MLL rearrangement regardless of low risk features ▪ MRD $\geq$ 0.1% or M2/M3 status at the end of induction-I regardless of low risk features

Treatment schema for AML protocol:



Treatment schema for APL protocol:



อายุ (เดือน)	Methotrexate (mg)	Hydrocortisone (mg)	Cytarabine (mg)
<12	6	12	18
12-23	8	16	24
24-35	10	20	30
≥36	12	24	36

Triple IT

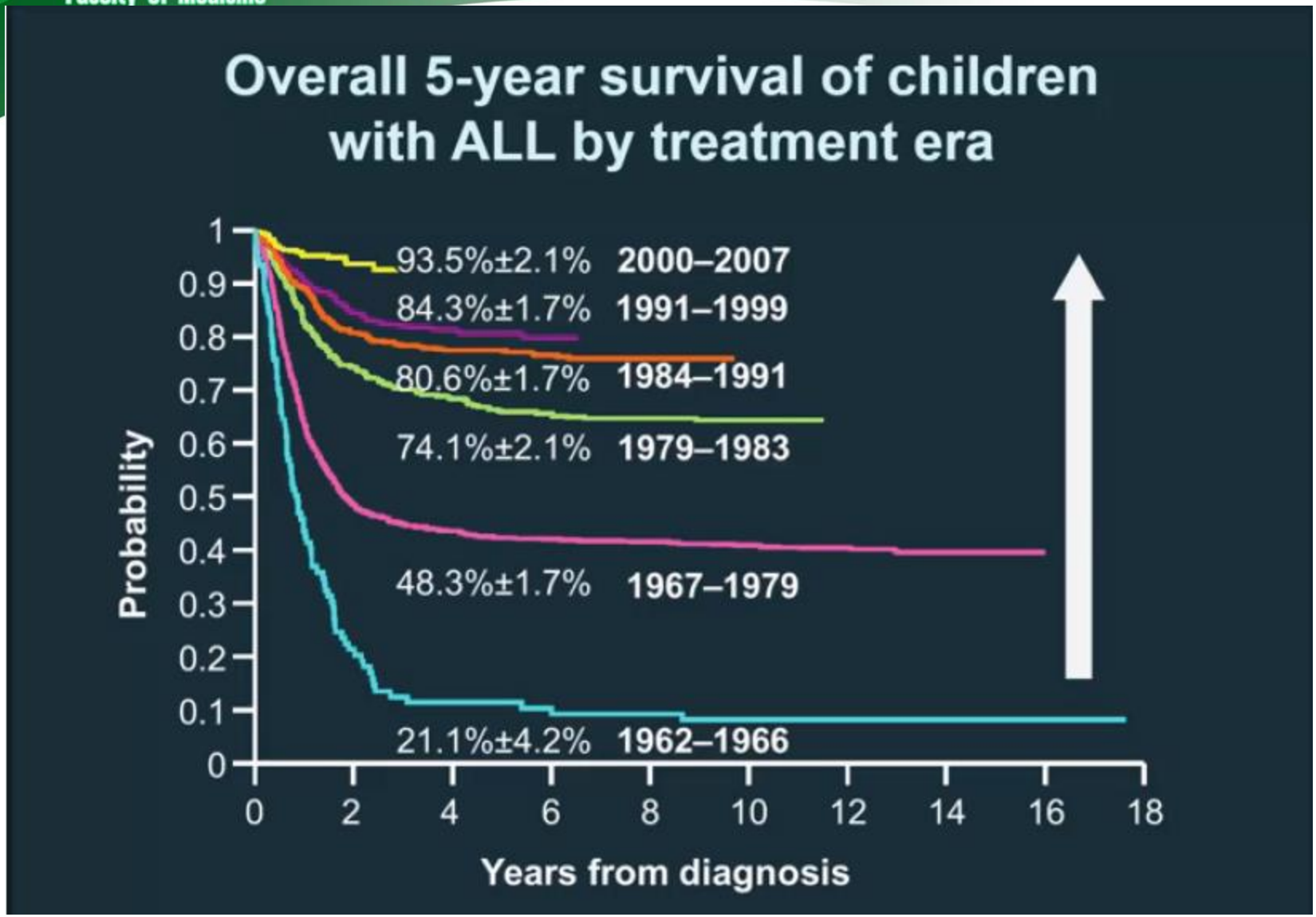
Management of childhood leukemia

Supportive treatment of childhood leukemia

- Multidisciplinary supportive care team
- Parent/caregiver advocacy
- Funding support

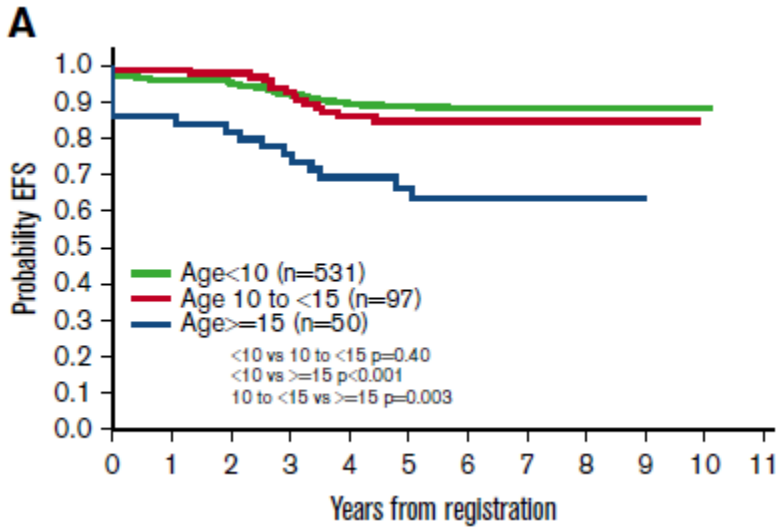
OUTCOME OF CHILDHOOD LEUKEMIA

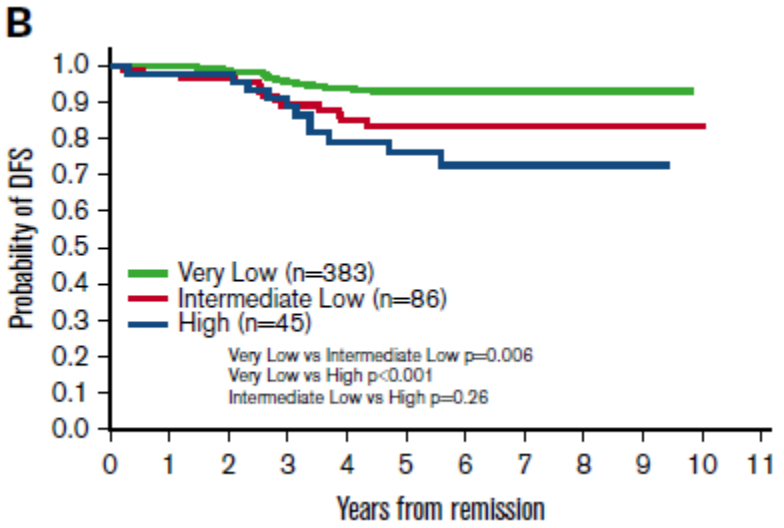
CHILDHOOD LEUKEMIA

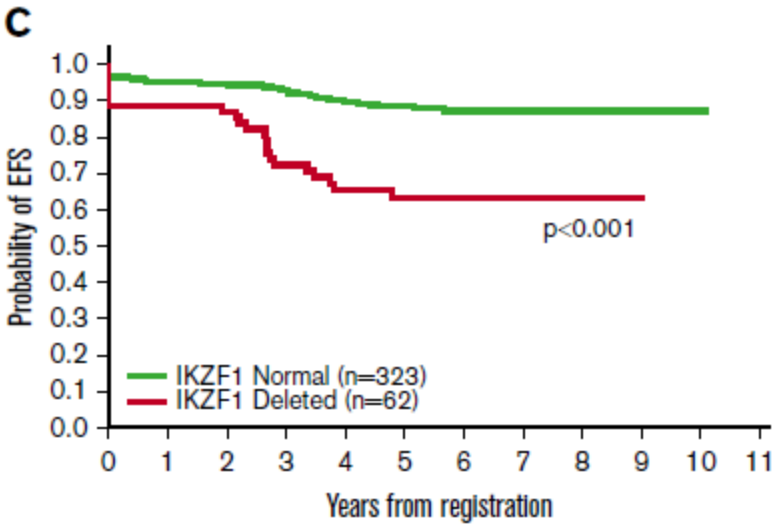


Pui CH, Evans WE. N Engl J Med. 2006;354(2):166-78.

Outcome of childhood ALL treated with DFCI 05-001



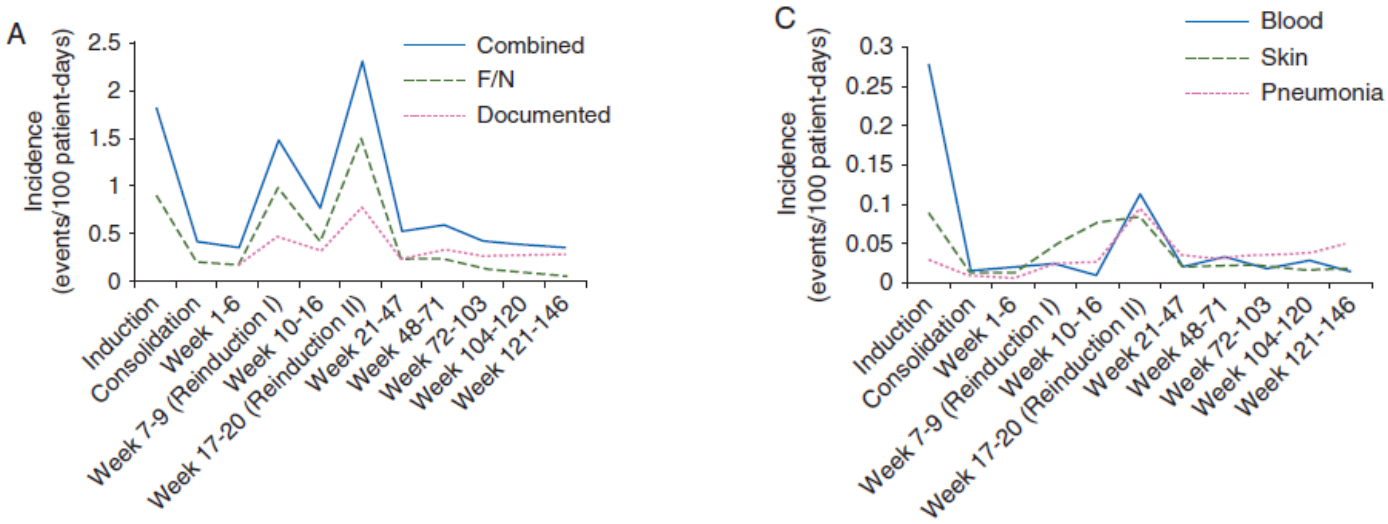




- In 678 patients, 5-year EFS was 87% and OS 93%
- Age >15 years, WBC >50,000/mm^3, *IKZF1* deletion, and MRD >10^{-4} conferred inferior outcome

Vroonman S, et al. Blood. 2018;2(12):1448-58.

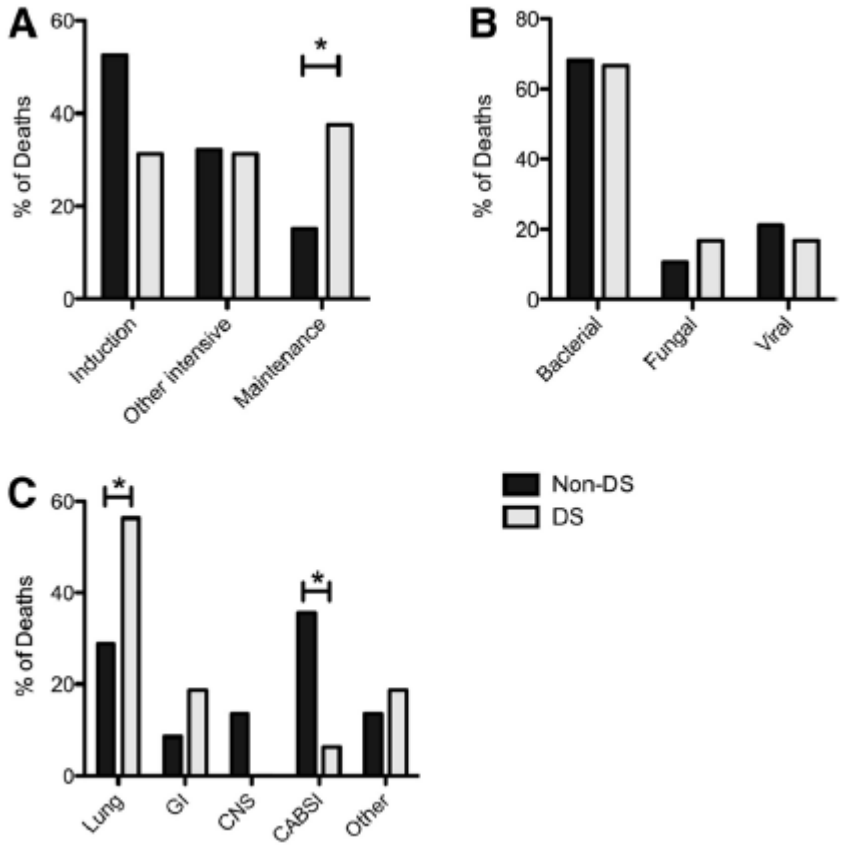
Infection-related complications during ALL therapy



- 409 children with ALL treated with Total XV study 2000-2010
- Infection-related complications are associated with young age, white race, intensive chemotherapy
- These findings can devise future therapeutic interventions, such as close monitoring of patients, use of prophylactic antibiotics, modifications of chemotherapy dosing and regimen intensity

Inaba H, et al. Ann Oncol. 2017;28:38-92..

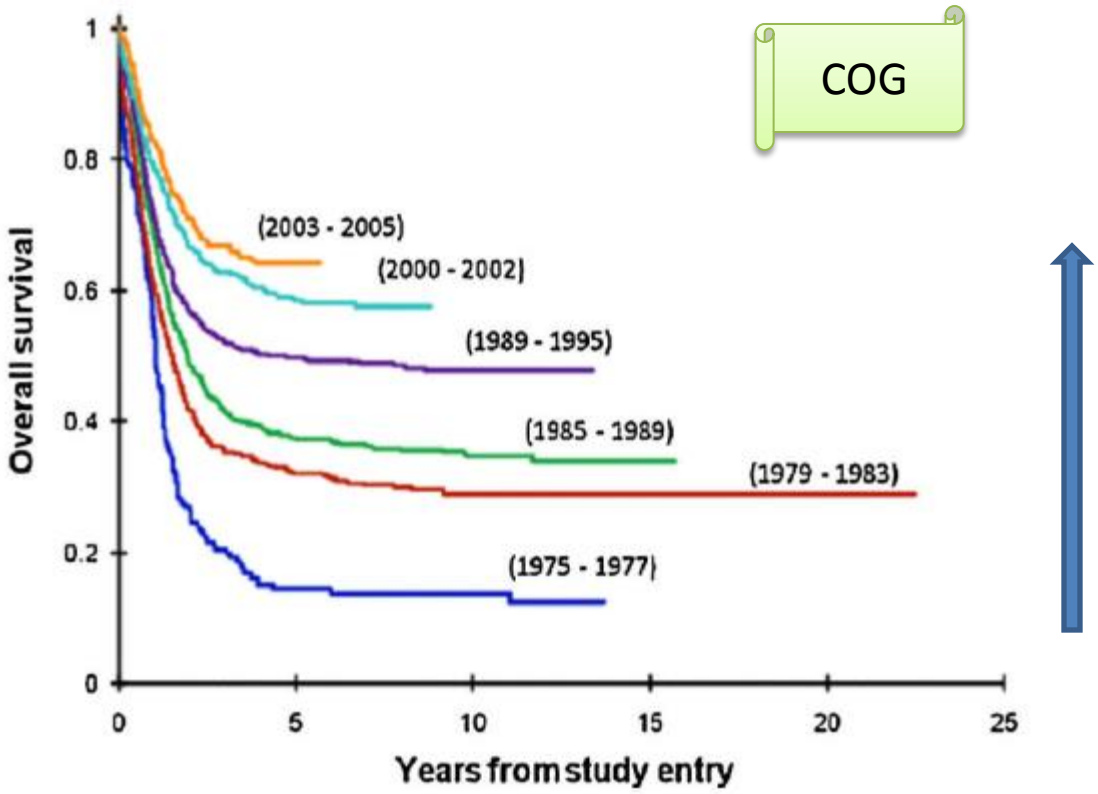
Infection-related mortality during ALL therapy



- 75 cases in UKALL2003 trial
- 5-year cumulative incidence of Infection-related mortality (IRM) 2.4%
- For such a high-risk cohort (eg. DS, high intensity regimen), consideration should be given to the use of enhanced supportive care and increased antibiotic prophylaxis

O'Connor D, et al. Blood. 2014;124(7):1056-61.

Overall survival of childhood AML: incremental improvement over the last 40 years



Gamis AS, et al. Pediatr Blood Cancer. 2013;60(6):964-71.

Outcomes of pediatric AML in recent collaborative studies

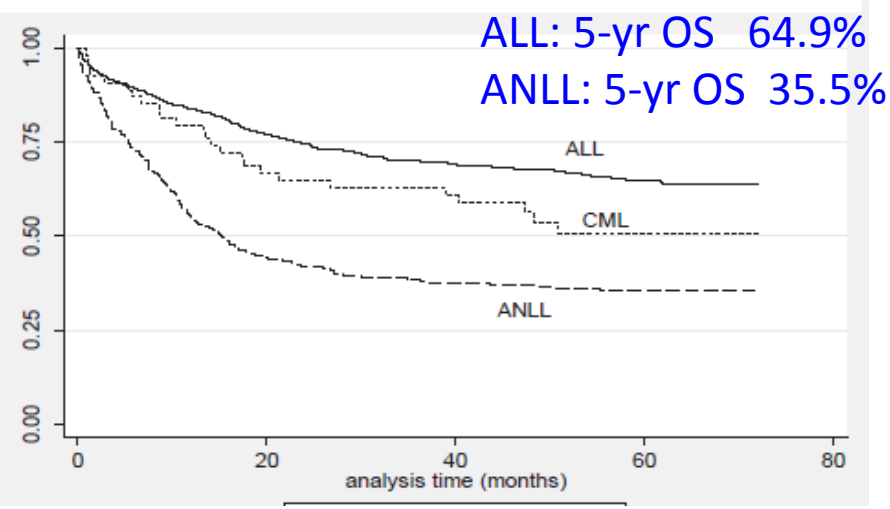
Study Group and Source	Study Acronym and Inclusion Time	No. of Patients	No. (%) of Patients Treated With SCT	Median ± SD EFS (%)	Median ± SD OS (%)	Relapse (%)	Source
AIEOP	AML2002/01 (2002-2011)	482	Allo-SCT: 141 (29) Auto-SCT: 102 (21)	8-year: 55 ± 3	8-year: 68 ± 2	24	Pession et al 2013[11]
BFM-AML SG	AML-BFM 2004 (2004-2010)	521	42 (8)	5-year: 55 ± 2	5-year: 74 ± 2	29	Creutzig et al 2013[6]
COG	AAML03P1 (2003-2005)	340	73 (21)	3-year: 53 ± 6	3-year: 66 ± 5	33 ± 6	Cooper et al 2012[5]
	AAML0531 (2006-2010)	1,022 (ages 0-29 years)	NA	3-year: 53 *v* ≥ 47	3-year: 69 *v* 65	33 *v* 41	Gamis et al 2014[9]
Japan	AML99 (2000-2002)	240	Allo-SCT: 41 (17) Auto-SCT: 5 (2)	5-year: 62 ± 7	5-year: 76 ± 5	32	Tsukimoto et al 2009[15]
JPLSG	AML-05 (2006-2010)	443	54 (12)	3-year: 54 ± 2	3-year: 73 ± 2	30	Tomizawa et al, Leukemia 2013[14] and Int J Hematol 2013[13]
MRC	MRC AML12 (1995-2002)	564	64 (11)	10-year: 54	10-year: 63	35	Gibson et al 2011[10]
EORTC-CLG	EORTC 58,921 (1993-2002)	177	Allo-SCT: 39 (27)	7-year: 49 ± 4	7-year: 62 ± 4		Entz-Werle et al 2005[8]
NOPHO	NOPHO AML 2004 (2004-2009)	151	22 (15)	3-year: 57 ± 5	3-year: 69 ± 5	30	Abrahamsson et al 2011[4], Hasle et al 2012[16]
PPLLSG	PPLLSG AML-98 (1998-2002)	104	Allo-SCT: 14 (13) Auto-SCT: 8 (8)	5-year: 47 ± 5	5-year: 50 ± 5	24	Dluzniewska et al 2005[7]
SJCRH	AML02 (2002-2008)	216	59 (25)	3-year: 63 ± 4	3-year: 71 ± 4	21	Rubnitz et al 2010[12]

Abbreviations: AIEOP, Italian Association for Pediatric Hematology and Oncology; Allo, allogeneic; AML, acute myeloid leukemia; Auto, autologous; BFM SG, Berlin-Frankfurt-Munster Study Group; CLG, Children's Leukemia Group; COG, Children's Oncology Group; EFS, event-free survival; EORTC, European Organisation for Research and Treatment of Cancer; Japan, Japanese Childhood AML cooperative study; JPLSG, The Japanese Pediatric Leukemia/Lymphoma Study Group; MRC, Medical Research Council; NA, not available; NOPHO, Nordic Society for Pediatric Hematology and Oncology; OS, overall survival; PPLLSG, Polish Pediatric Leukemia/Lymphoma Study Group; SD, standard deviation; SCT, stem-cell transplantation; SJCRH, St Jude Children's Research Hospital.

Zwaan CM, et al. J Clin Oncol. 2015;33(27):2949-62.

Childhood Cancer Incidence and Survival 2003-2005, Thailand: Study from the Thai Pediatric Oncology Group

Surapon Wiangnon[1]*, Gavivann Veerakul[2], Issarang Nuchprayoon[3], Panya Seksarn[3], Suradej Hongeng[4], Triroj Krutvecho[5], Nintita Sripaiboonkij[6]

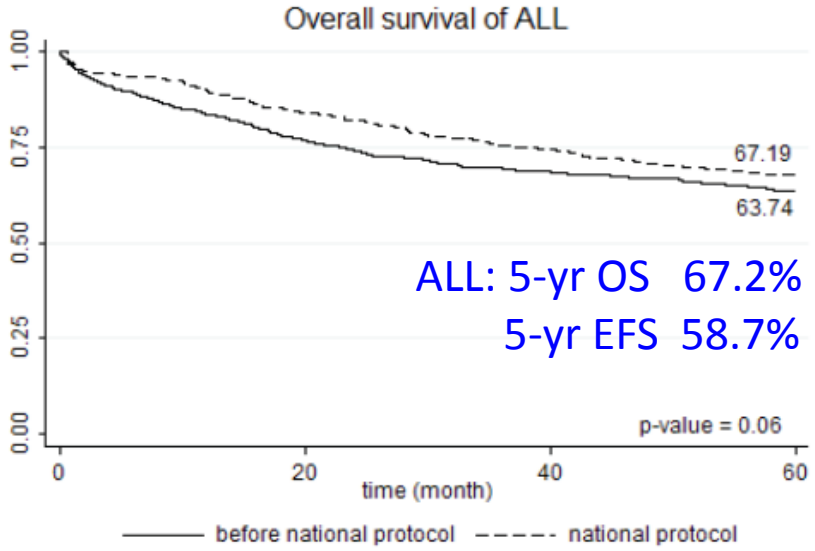


Survival of leukemia children, 2003-2005

5-year OS for all cancer = 54.9%

Outcome of Childhood Acute Lymphoblastic Leukemia Treated Using the Thai National Protocols

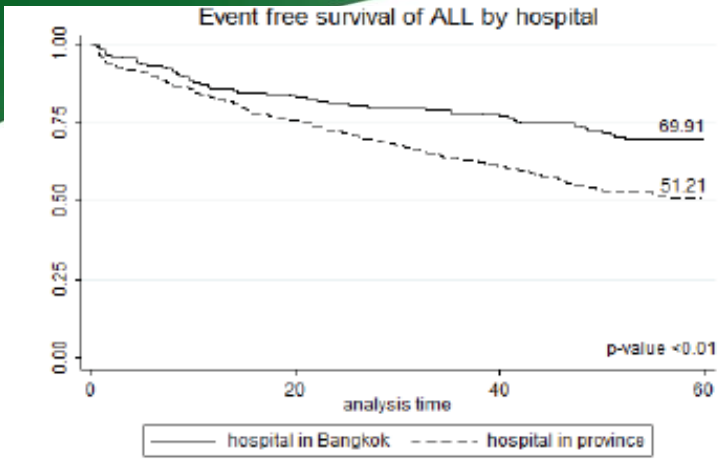
Panya Seksarn[1]*, Surapon Wiangnon[2], Gavivann Veerakul[3], Thirachit Chotsampancharoen[4], Somjai Kanjanapongkul[5], Su-On Chainansamit[6]

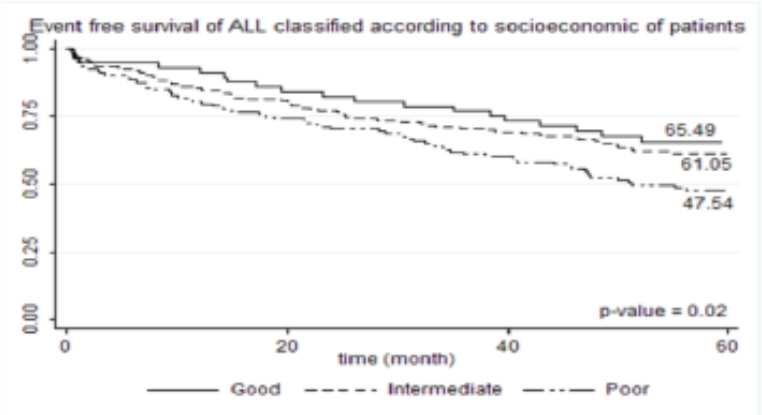


Survival in children with ALL, 2006-2008

Wiangnon S, et al. Asian Pac J Cancer Prev. 2011;12(9):2215-20.
Seksarn P, et al. Asian Pac J Cancer Prev. 2015;16(11):4609-14.

CHILDHOOD LEUKEMIA





Outcome of Childhood Acute Lymphoblastic Leukemia Treated Using the Thai National Protocols

Panya Seksarn[1]*, Surapon Wiangnon[2], Gavivann Veerakul[3], Thirachit Chotsampancharoen[4], Somjai Kanjanapongkul[5], Su-On Chainansamit[6]

- 486 cases from 12 hospitals (2006-2008)
- There were discrepancies in EFS between centers in Bangkok and up-country provinces (69.9 vs 51.2%)
- Socioeconomics and patient compliance were key elements in determining the outcome (65.5 vs 47.5%)

Survival in children with ALL, 2006-2008

Wiangnon S, et al. Asian Pac J Cancer Prev. 2011;12(9):2215-20.
Seksarn P, et al. Asian Pac J Cancer Prev. 2015;16(11):4609-14.

CLINICAL LYMPHOMA, MYELOMA & LEUKEMIA

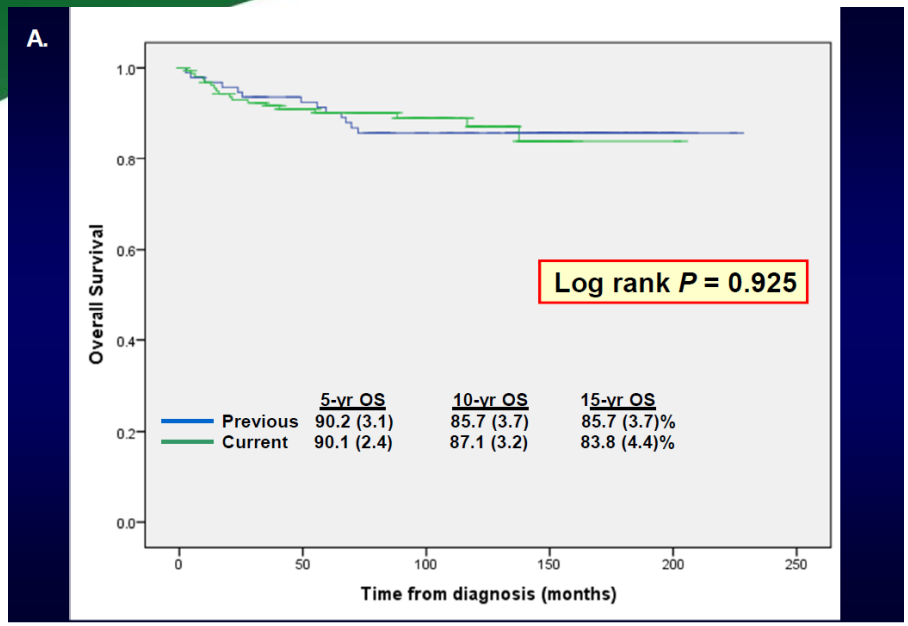
Original Study

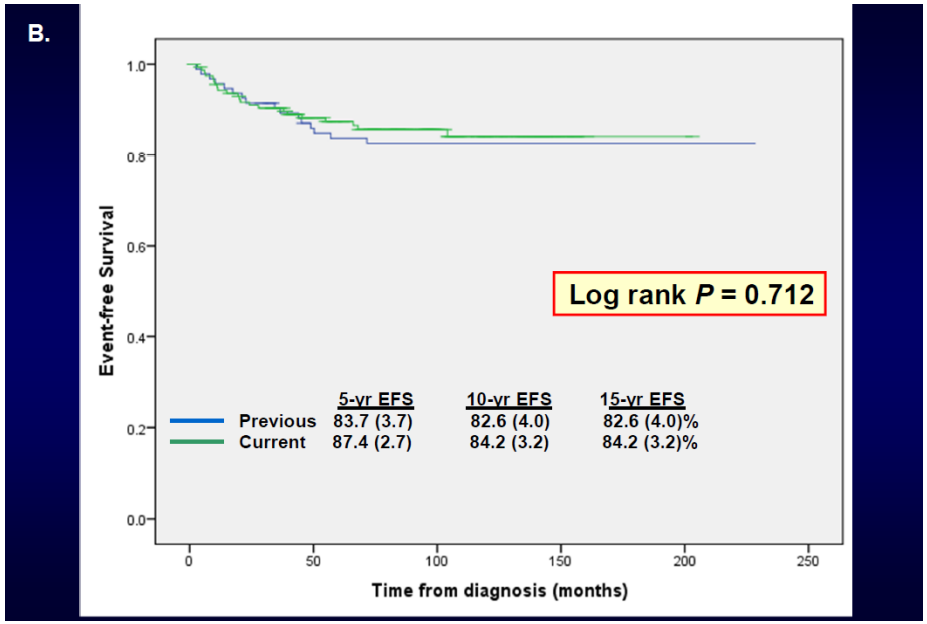
Long-Term Outcomes of Modified St Jude Children's Research Hospital Total Therapy XIIIB and XV Protocols for Thai Children With Acute Lymphoblastic Leukemia

Pacharapan Surapolchai,[1] Usanarat Anurathapan,[2] Arpatsorn Sermcheep,[2] Samart Pakakasama,[2] Nongnuch Sirachainan,[2] Duantida Songdej,[2] Pongpak Pongpitcha,[2] Suradej Hongeng[2]

- Long-term outcomes and prognostic features of 250 Thai children with ALL treated with modified St Jude Children's Research Hospital (SJCRH) protocols (Total Therapy XIIIB and XV) during 1997-2014

Surapolchai P, et al. Clin Lymphoma Myeloma Leuk. 2019. (in press)





- Patients with WBC >100,000/mm^3 and classified as high-risk conferred inferior EFS in modified Total XIIIB; MRD positivity was a prognostic factor of inferior OS only for modified Total XIIIB patients
- Favorable outcomes of childhood ALL occurred using adapted SJCRH protocols, up to 80% perhaps because of multidisciplinary team and parent advocacy

Surapolchai P, et al. Clin Lymphoma Myeloma Leuk. 2019. (in press).

Late effects in survivors of childhood acute lymphoblastic leukemia: a study from Thai Pediatric Oncology Group

Late effects	Number (%)
Endocrine/metabolic	64 (24.8)
Psychosocial	28 (10.9)
Cardiovascular	9 (3.5)
Dental	5 (1.9)
Nervous system	4 (1.5)
Dermatologic	2 (0.8)
Immune	2 (0.8)
Pain	2 (0.8)
Auditory	2 (0.8)
Gastrointestinal/hepatic	1 (0.4)
Ocular	1 (0.4)
Musculoskeletal	1 (0.4)
Pulmonary	0
Urinary	0

Endocrine and metabolic complication	Number (%) ($n = 64$)
Obesity (BW >120% of weight for height)	28 (43.8)
Overweight (BW 110–120% of weight for height)	15 (23.4)
Short stature (height <3rd percentile)	13 (20.3)
Underweight (BW <3rd percentile)	7 (10.9)
Delayed puberty	6 (9.4)
Hyperthyroidism	2 (3.1)
Hypothyroidism	1 (1.6)
Dyslipidemia	2 (3.1)
Type 2 diabetes mellitus	2 (3.1)
Type 1 diabetes mellitus	1 (1.6)
Insulin resistance	1 (1.6)
Adrenal insufficiency	1 (1.6)
Growth hormone deficiency	1 (1.6)

- 258 survivors, follow up 7.2 years with 47.3% had ≥1 late effect
- Overweight/obesity was the most common late effect, which CNS radiation was a significant risk factor (OR 1.97, 95% CI 1.02–3.81)

Pakakasama S, et al. Int J Hematol. 2010;91(5):850-4 .

Impaired Glucose Tolerance and Insulin Resistance in Survivors of Childhood Acute Lymphoblastic Leukemia: Prevalence and Risk Factors

Pacharapan Surapolchai, MD,† Suradej Hongeng, MD,* Pat Mahachoklertwattana, MD,* Samart Pakakasama, MD,* Angkana Winaichatsak, MD,‡ Nittaya Wisanuyothin, MD,‡ Ekawat Pasomsub, PhD,§ Surakameth Mahasirimongkol, MD,‖ and Nongnuch Sirachainan, MD**

- Ten out of 131 ALL survivors (7.6%) had impaired glucose tolerance (IGT) whereas 40 out of 131 (30.5%) had insulin resistance (IR) and showed characteristics of the metabolic syndrome
- The *PAX4* variant (rs2233580) might impact individual susceptibility against IGT and diabetes, when adjusted for age

Surapolchai P, et al. J Pediatr Hematol Oncol. 2010;32:383–9.

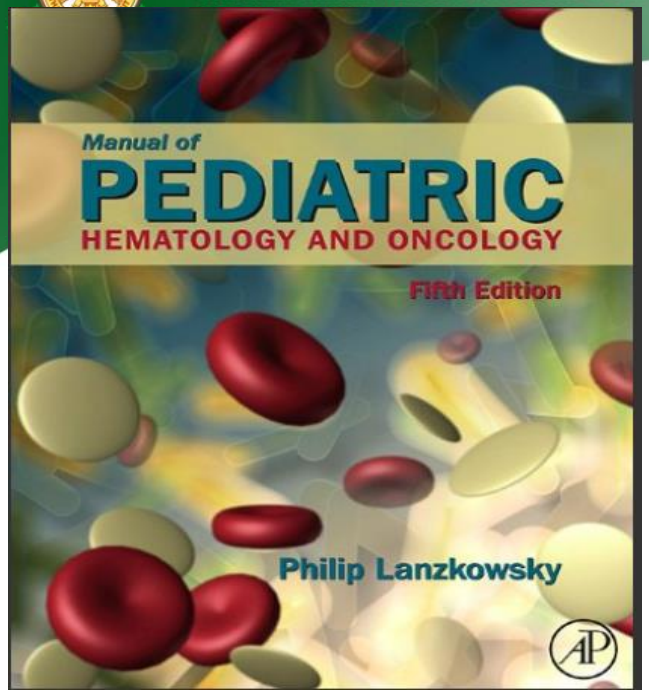
Clinical practice points

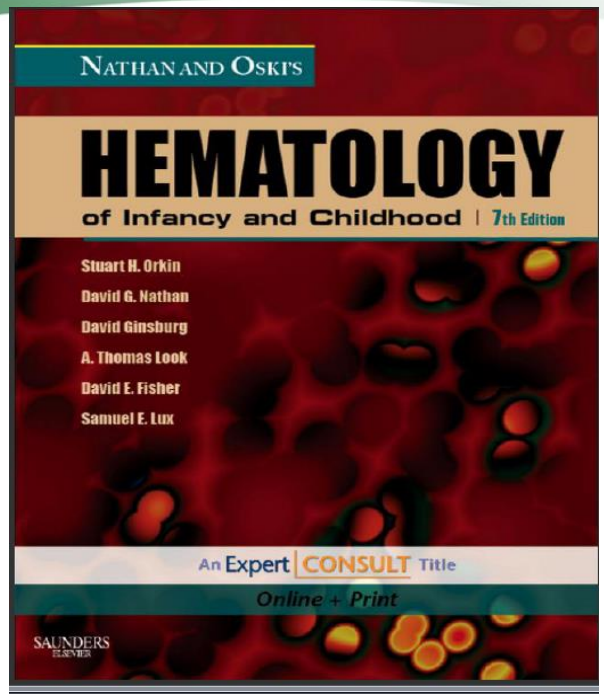
- Strategies for advance improvement in survival outcome in childhood leukemia:

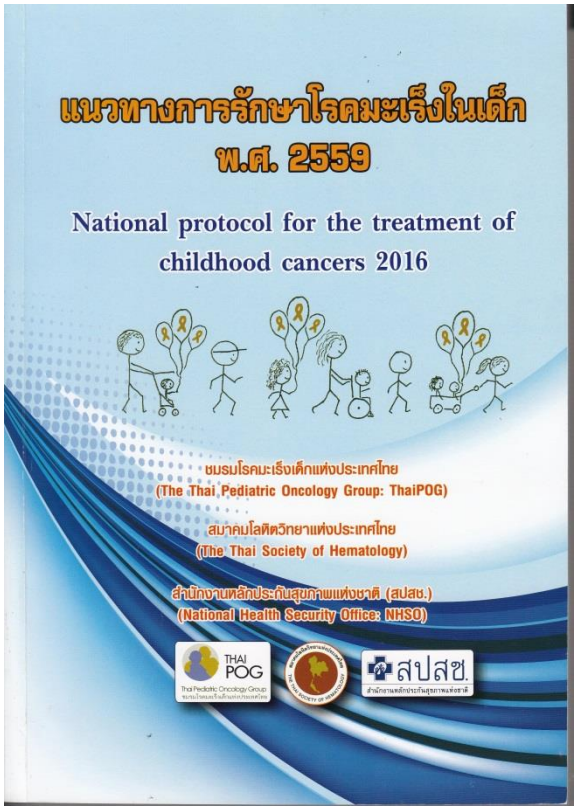
1. Effective treatment administration
2. Precise diagnosis and risk stratification
3. Improved supportive care

- Follow-up for leukemia survivors with “standardized survivorship care plan” is crucial for individual formulation, based on disease, age and history of treatment

CHILDHOOD LEUKEMIA







Acknowledgements

- Health care practitioners, childhood leukemia patients and legal guardians
- ชมรมโรคมะเร็งในเด็กแห่งประเทศไทย (The Thai Pediatric Oncology Group; ThaiPOG)
- สมาคมโลหิตแห่งประเทศไทย (Thai Society of Hematology)
- สำนักงานหลักประกันสุขภาพแห่งชาติ (สปสช.) (National Health Security Office; NHSO)
- กองทุนโรคมะเร็งในเด็ก ในพระอุปถัมภ์ พระเจ้าวรวงศ์เธอ พระองค์เจ้า โสมสวลี พระวรราชาทินัดดามาต (The Children Cancer Fund under the Patronage of HRH Princess Somsawali)

ขอขอบพระคุณ