Protocol development for Leukemia

By:

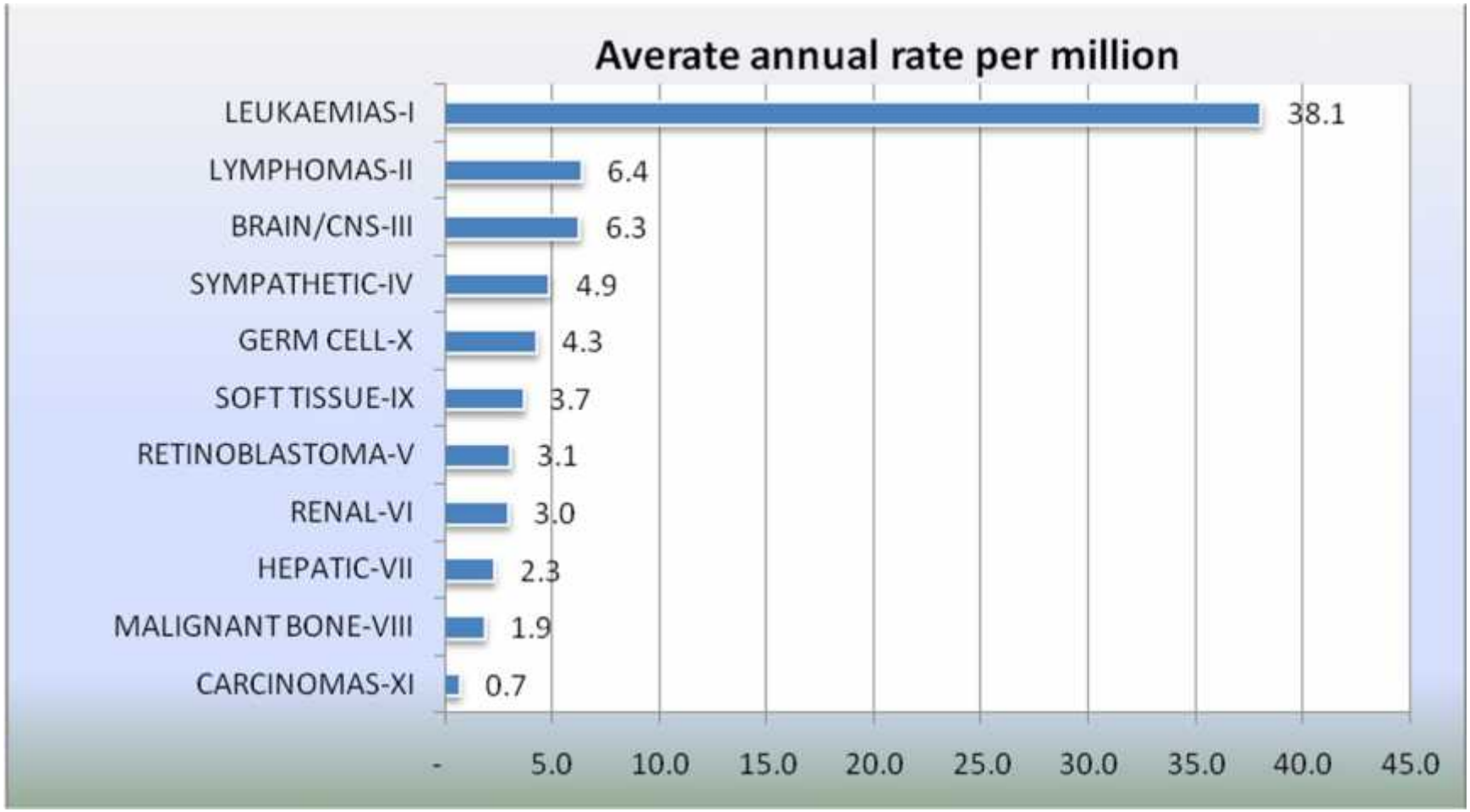
Sonephet SAYSOULIGNO. MD

Pediatric Hemato – Oncologist

Hematology department

National Children hospital, Vientiane, Lao PDR

Incidence in Thailand



Wiangnon, 2011

Incidence in Thailand

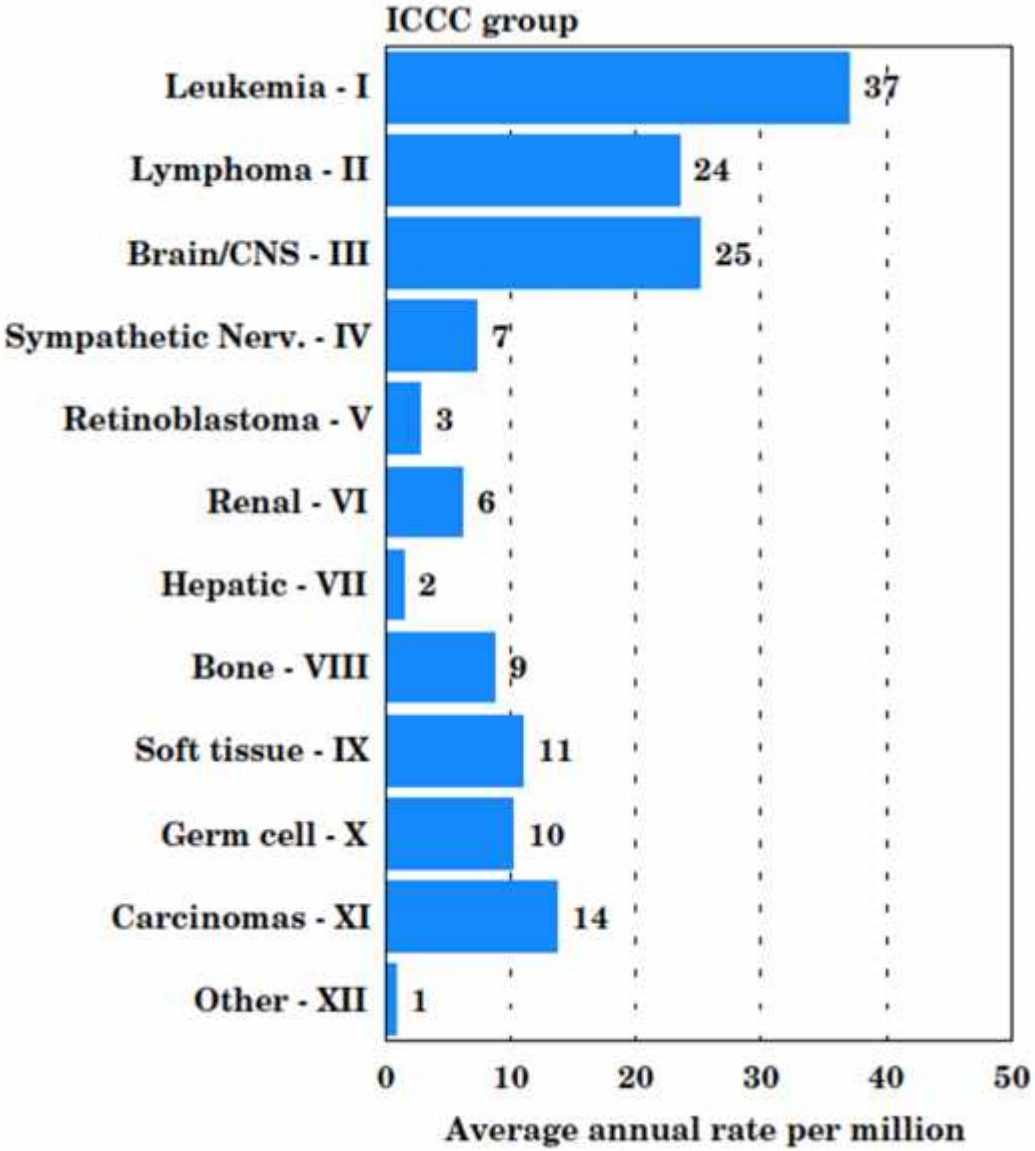
Childhood Cancer Incidence and Survival 2003-2005, Thailand

Table 1. Incidences of Cancers in Childhood, Both Sexes Combined, Thailand 2003-2005

Type of Cancer	Number of cases					Rel. freq.(%)				Rate per million					
	< 1	1-4	5-9	10-14	All	M/F	Overall	Group	0-4	5-9	10-14	Crude	ASR	Cum.	%MV
I. Leukemias	82	576	418	345	1421	1.3	50.9	100	55.5	30	24	35.4	38	547	100
Lymphoid	42	451	330	206	1029	1.4	36.9	72.4	41.6	24	14.3	25.6	28	397.5	100
Acute non-lymphocytic	35	109	73	111	328	0.9	11.7	23.1	12.1	5.2	7.7	8.2	8.6	125	100
Chronic myeloid	4	11	12	24	51	1.6	1.8	3.6	1.3	0.9	1.7	1.3	1.3	19.5	100
Other specified	1	5	3	4	13	0.9	0.5	0.9	0.5	0.2	0.3	0.3	0.3	5	100

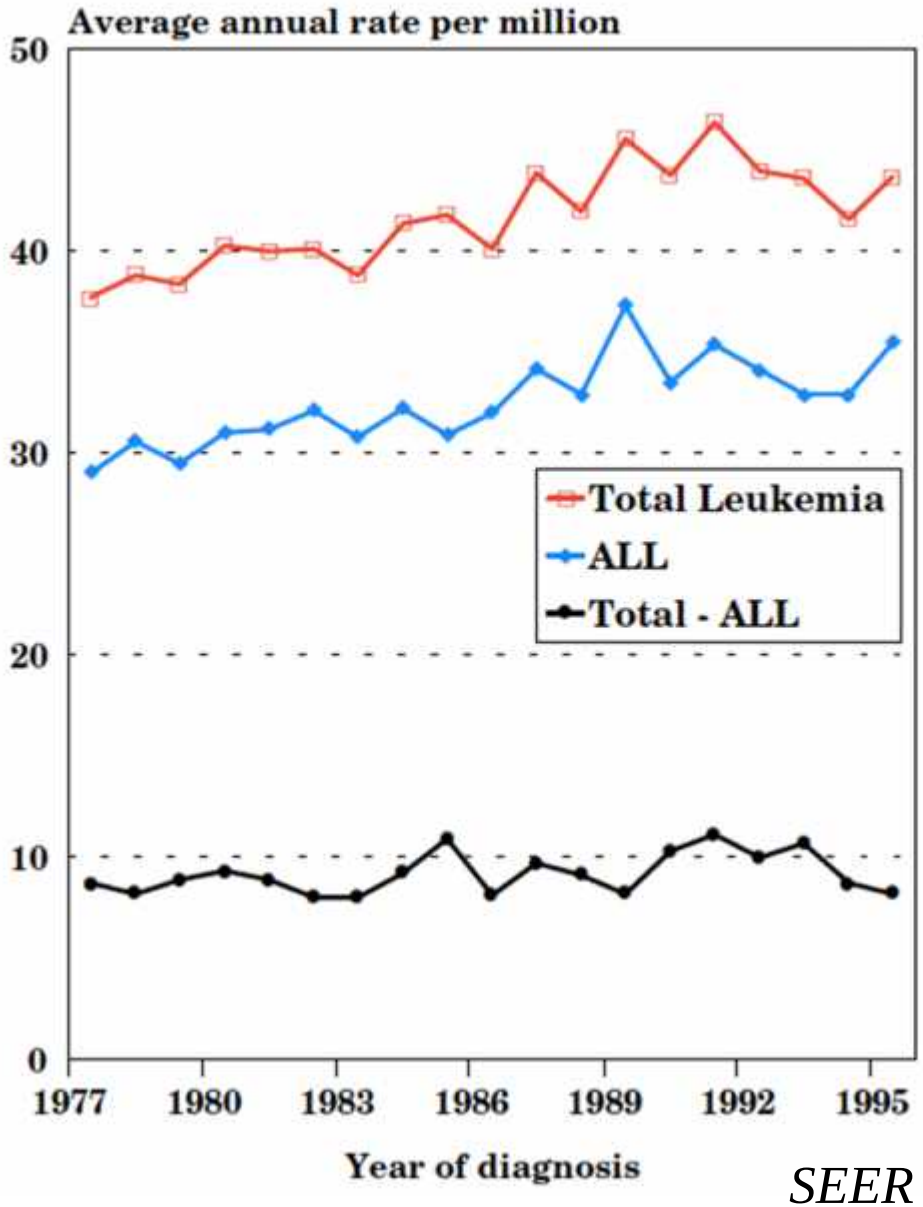
Wiangnon, 2011

Incidence in USA



SEER Pediatric Monograph

Incidence in USA



SEER Pediatric Monograph

Expectation in Lao PDR

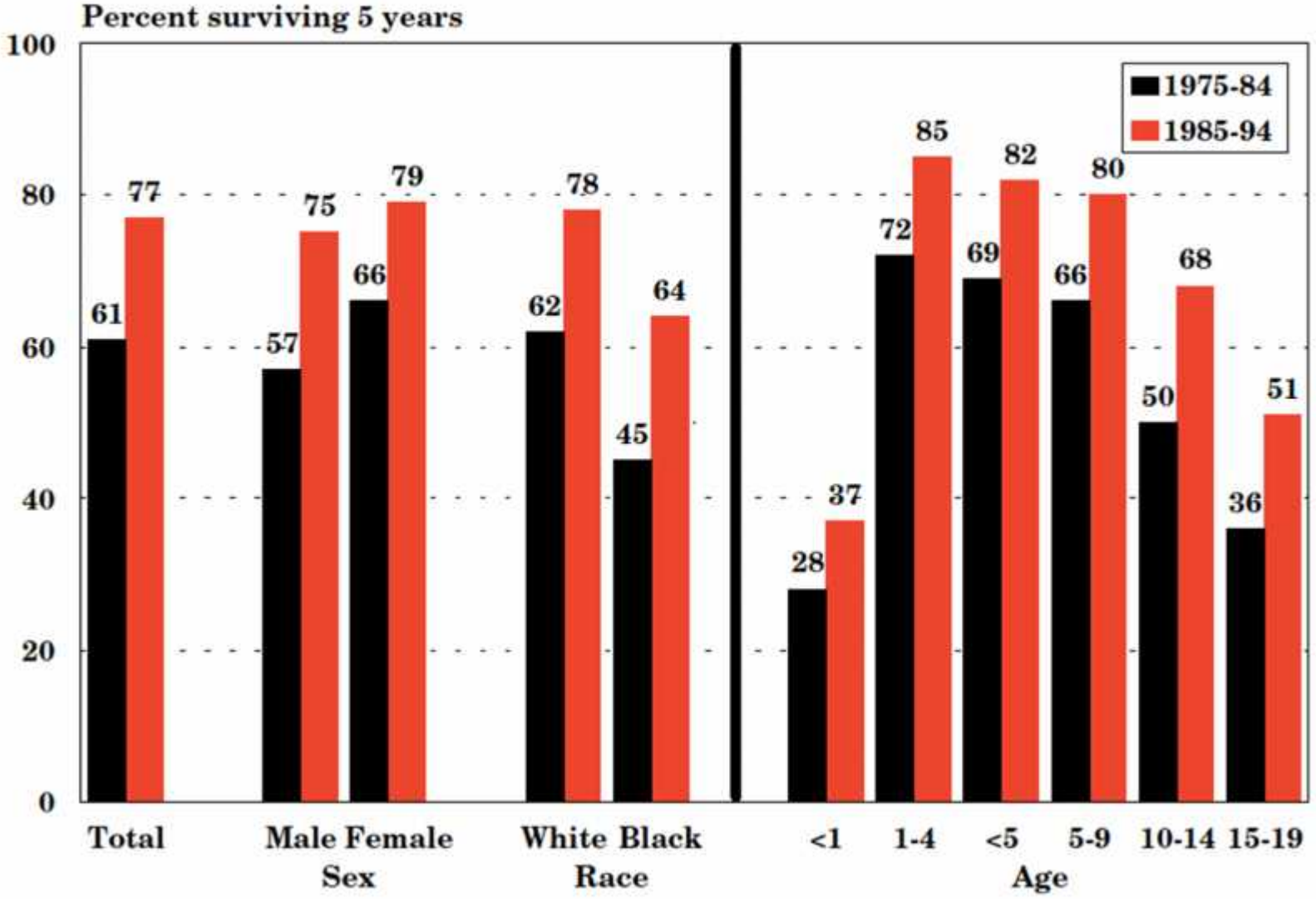
- In 2013 census, approximately 2.38 million children were aged less than 15
- 35.5% of the whole Lao population

Index Omundi, 2013

- Incidence in Lao PDR when compare to incidence in Thailand
  - Leukemia 90 per 2.38 million
  - Acute lymphoblastic leukemia 66.6 per 2.38million

Wiangnon,2011

Figure I.8: ALL 5-year relative survival rates by sex, race, age and time period, SEER (9 areas), 1975-84 and 1985-94



SEER Pediatric Monograph

Survival rate in Thailand

Surapon Wiangnon et al

Table 2. Survival by Group and Type of Childhood Cancer

Diagnosis	No. of patients	Deaths/100 PM (95%CI)	% Survival Probability (95%CI) at 1 year	at 3 years	at 5 years
Leukemia	1,421	1.12 (1.02-1.2)	76.9 (74.6-79.0)	62.0 (59.4-64.5)	57.4 (54.6-60.1)
ALL	1,029	0.82 (0.74-0.91)	83.9 (81.5-86.0)	70.1 (67.2-72.8)	64.9 (61.7-67.9)
ANLL	328	2.45 (2.14-2.81)	54.7 (49.2-59.9)	32.9 (32.9-43.4)	35.5 (30.2-40.8)
Chronic	51	1.23 (0.83-1.82)	79.6 (66.2-88.2)	62.9 (48.7-74.3)	50.6 (35.7-63.8)
Other	13	1.59 (0.66-3.83)	64.8 (30.9-85.2)	55.6 (23.7-78.7)	55.6 (23.7-78.7)

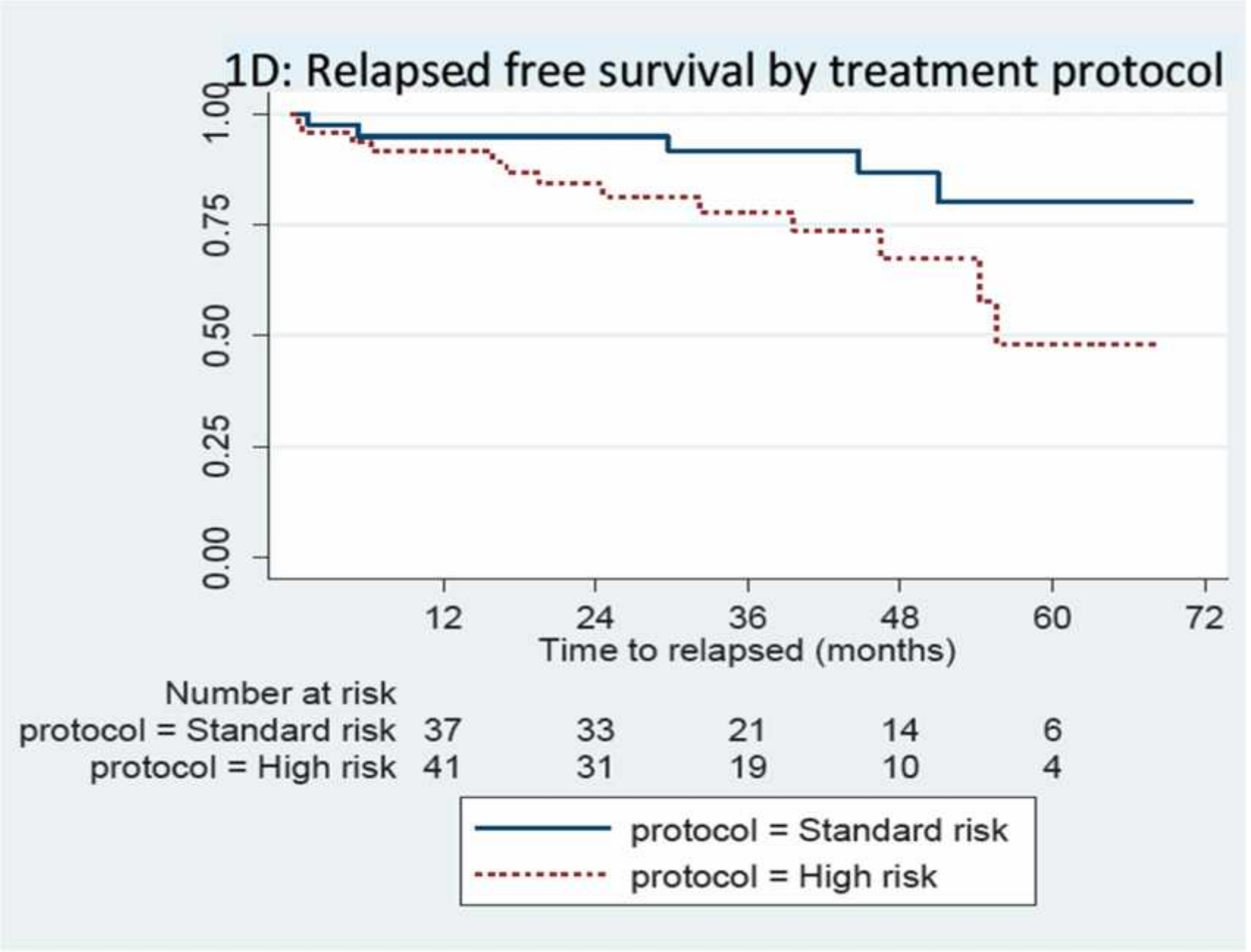
Wiangnon, 2011

Median time relapse and probability of relapse-free at 1,3 and 5years in khonkaen

Variable	Median time to relapse Months (95%CI)	Proportion of relapsed -free (%) (years) 1	3	5
Sex				
Male	**	90	86.1	70.6
Female	**	94.6	83.6	58.3
Age (year)				
1-10	**	96.7	90.6	73.3
<1	39.6 (4.8, 39.6)	60	60	***
>10	54.3 (24.6,*)	90	70.1	46.7
Treatment protocol				
Standard risk protocol	**	94.9	91.7	80.2
High risk protocol	55.5 (39.6,*)	91.5	77.9	48.2
ALL subtype				
ALL, precursor T-cell	54.3 (54.3,*)	84.6	84.6	***
ALL, precursor B-cell	**	94.5	84.7	67.2
initial WBC (mm^3)				
<50,000	**	94.2	86.9	65
>50,000	**	88.2	73.5	63
CNS involvement				
No	**	94.7	86.8	75.8
Yes	54.3 (29.7, 55.3)	80	68.6	18.3

* 95%CI not available due to sample size limitation. ** Median time to relapsed not available due to number of relapse < 50%. *** Relapse-free rate not available due to sample size limitation

Tharnprisan, 2013



Tharnprisan, 2013

Survival rate in Asia

	Year of study	Patients (n)	Age range (years)	Median WBC ($x10^9$/L)	Proportion (%) with T-cell ALL	Proportion (%) with *BCR-ABL1*-positive ALL	Event-free survival (%)	Overall survival (%)
China								
BCH-2003/CCLG-2008 (Gao et al)[6]	2003–10	1004	0–16	N/A	10·2	6·5	82·6 (SD 1·5) at 5 years for BCH-2003 82·9 (SD 2·4) at 3 years for CCLG-2008	..
TPOG-2002 (Liang et al)[7]	2002–07	788	1–18	N/A	9·7	4·4	77·4 (SD 1·7) at 5 years	83·5 (SD 1·6) at 5 years
HK 93/97 (Li et al)[8]	1997–2002	171	1–17	12·6	14	3·5	79·0 at 4 years	86·5 at 4 years
India								
Modified BFM 76/79 (Bajel et al)[9]	1985–2003	307	1–14	10	22	5·7	56 (SD 3·2) at 5 years*	59·8 (SD 2·3) at 5 years
MCP-841 (Arya et al)[10]	1992–2002	254	1–15	N/A	31	..	51·6 (SD 3·8)	69·1 (SD 4·1)
Japan								
TCCSG L95-14 (Tsuchida et al)[11]	1995–99	597	1–15	About 10	9·7	4·0	76·8 (SD 1·8) at 5 years	84·9 (SD 1·5) at 5 years
JCCLSG ALL 2000 (Yamaji et al)[12]	2000–04	305	1–15	N/A	9·8	0	79·7 (SD 2·4) at 5 years†	89·2 (SD 1·8) at 5 years†
KYCCSG ALL-96 (Nagatoshi et al)[13]	1996–2002	201	1–15	7·3	10·4	4·9	72·1 at 7 years‡	84·8 at 7 years‡
Singapore								
Ma-Spore ALL 2003 (Yeoh et al)[14]	2002–11	556	0–18	N/A	8·8	4·0	80·6 (SD 3·5) at 6 years	88·4 (SD 3·1) at 6 years
Korea								
B-ALL (Koh et al)[15]	2004–08	98	N/A	N/A	0	N/A	..	88·8 (SD 5·3) at 3 years

ALL=acute lymphoblastic leukaemia. N/A=not available. WBC=white-blood-cell count. *30 patients were censored because they stopped treatment or were lost to follow-up. †Excluded patients with t(9;22). ‡Excluded patients with t(9;22) or t(4;11).

Table 1: **Patients' characteristics and treatment results from selected clinical trials enrolling children with ALL in Asia**

Lancet Oncol 2013

Survival rate in India

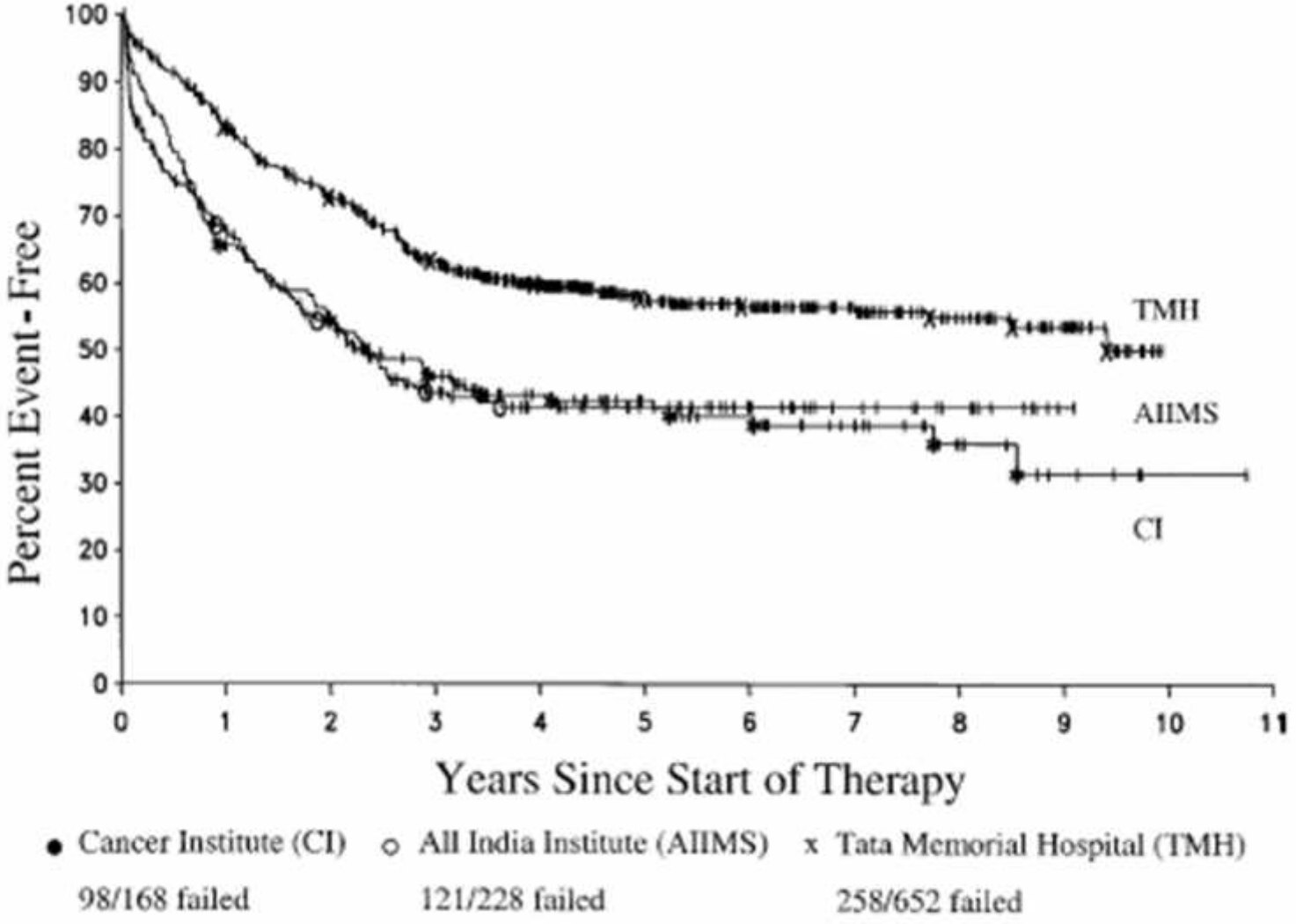
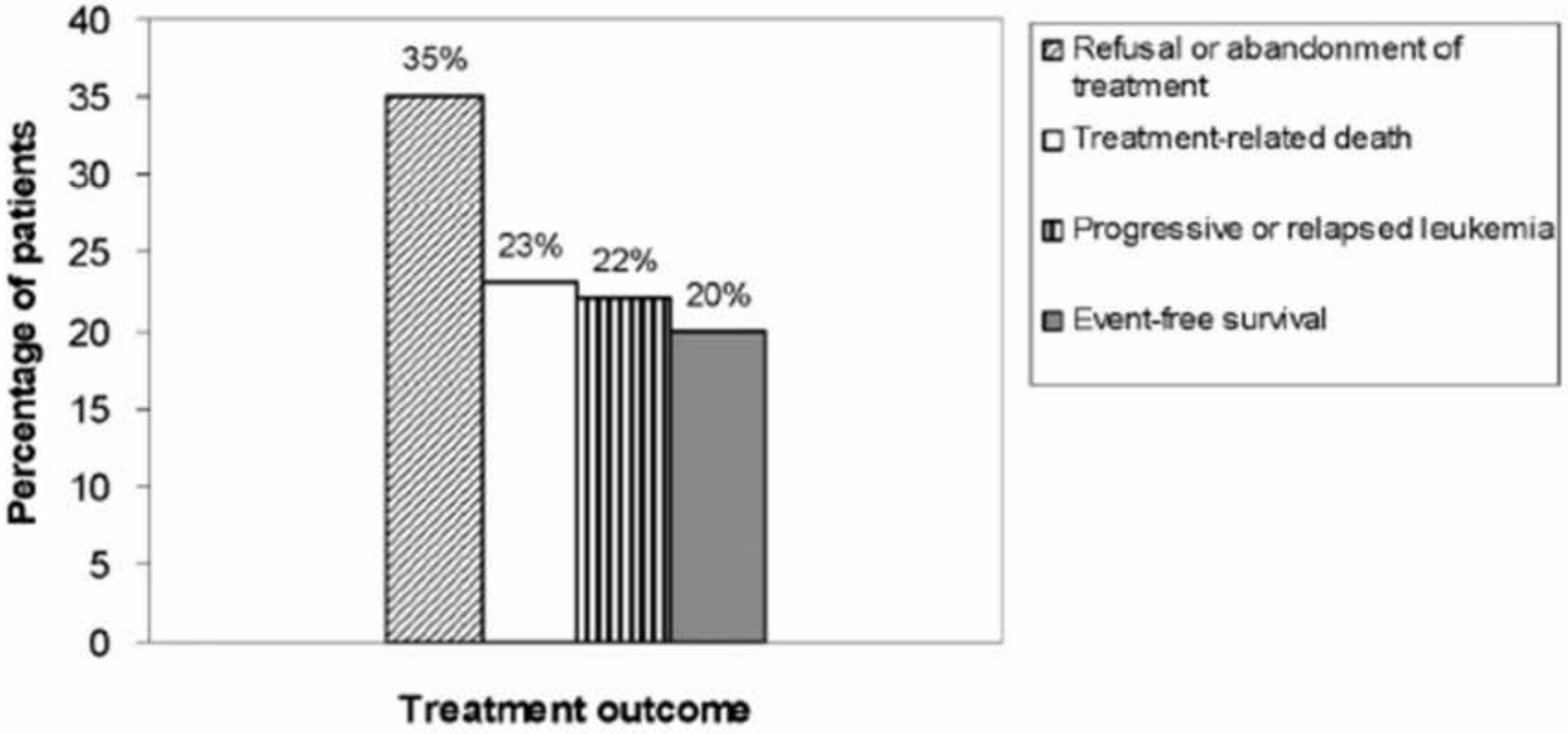


Fig. 2. Event-free survival (EFS) at the three centres.

European Journal of Cancer, 2005

Survival rate in Indonesia



Mostert,2006 Journal of the American Academy of Pediatrics

Cases

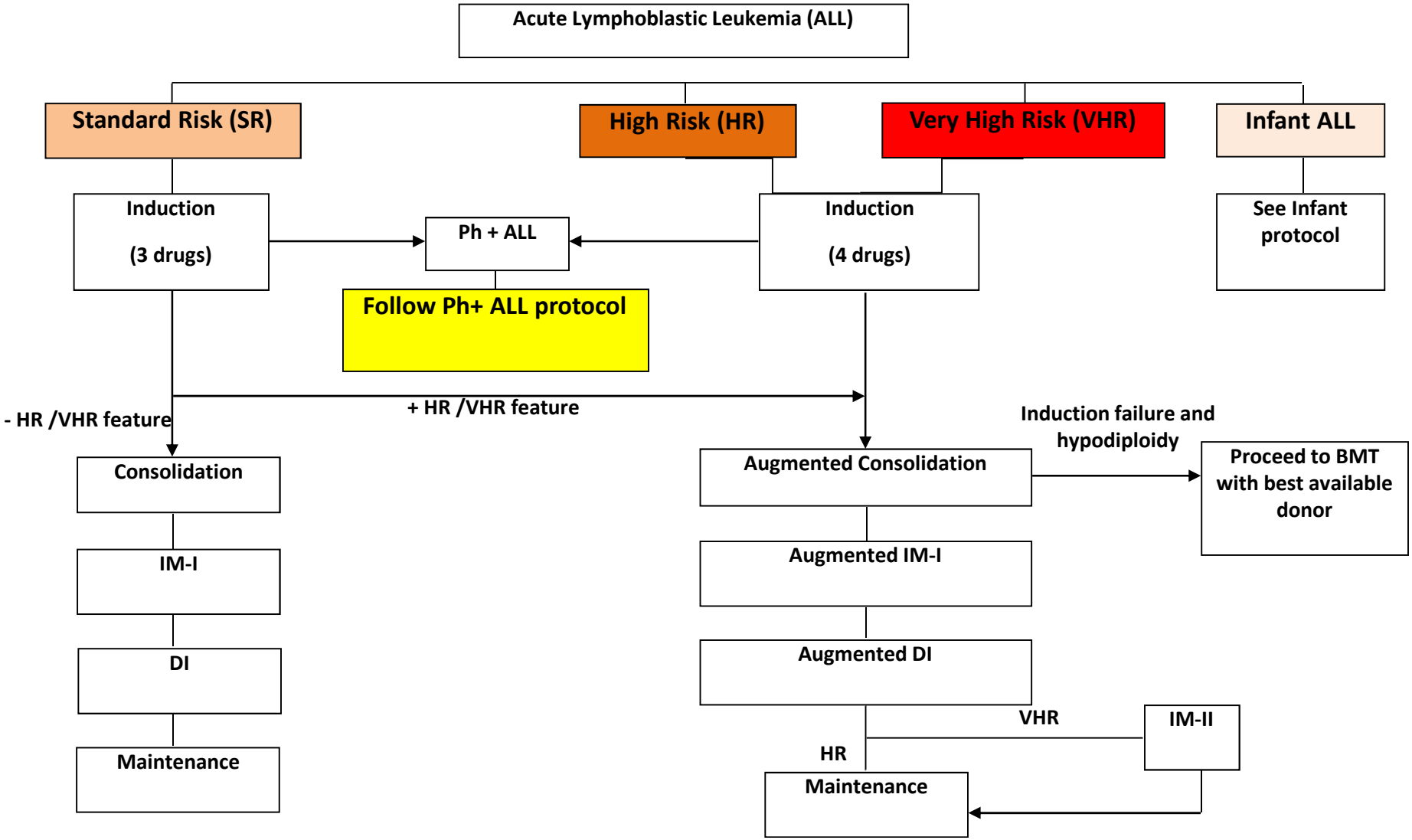
Case 1: Boy, age
Xayabury
Wbc 15.560
Dx: Standard Risk ALL (SR-ALL)

Case 2: Boy, aged 5 yr. Address: VT
Wbc 75.240
Dx: High Risk ALL (HR-ALL)

Management of ALL

- Epidemiology
- Pathogenesis and molecular epidemiology
- Genetics
- Risk group stratification
- Treatment
- Minimal Residual Disease
- Adverse reaction
- Supportive care
- Emergency condition

General ALL protocol outline

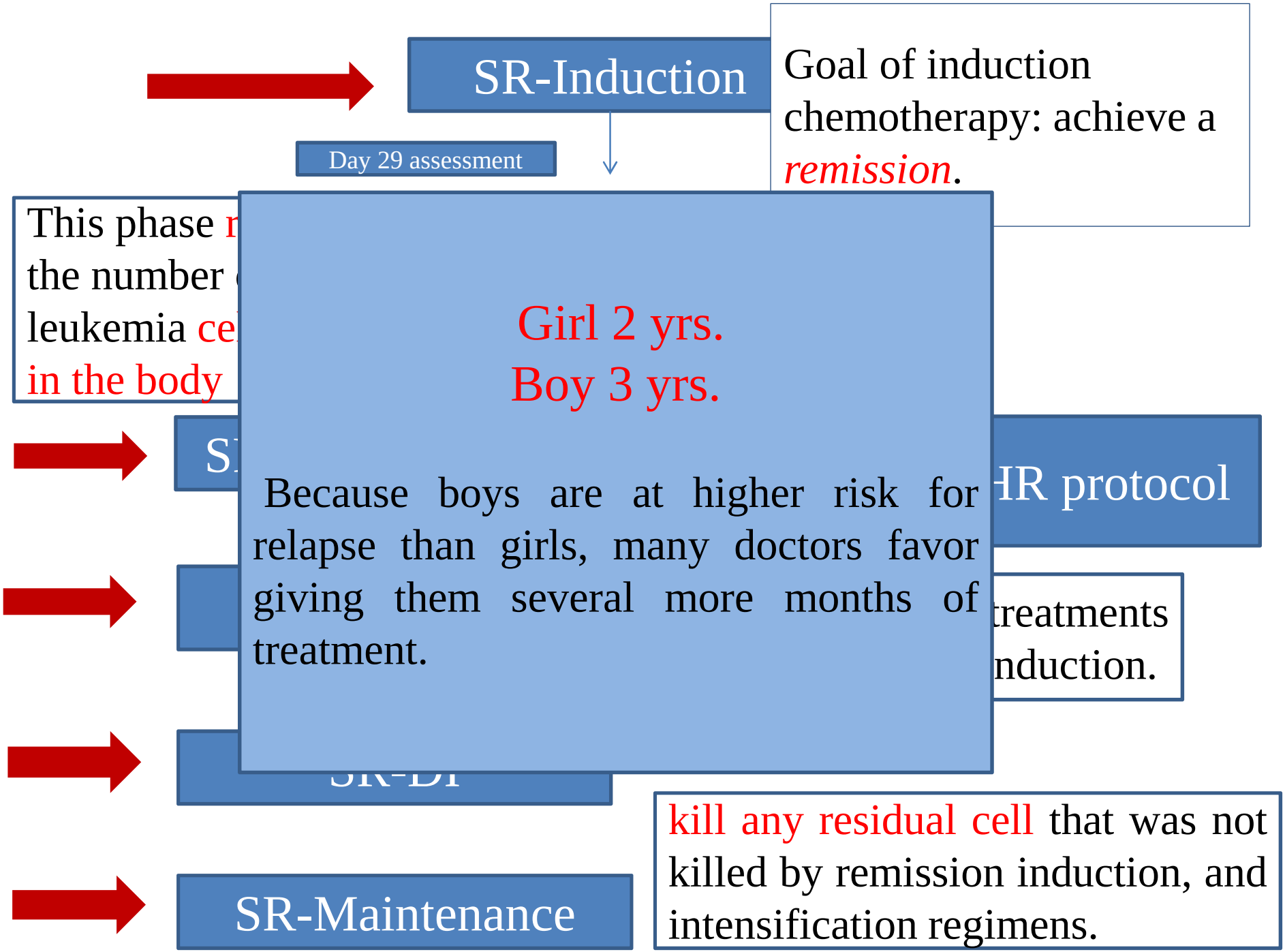


National protocol for the treatment of childhood cancer 2014, Thailand

Risk stratification

Standard Risk (SR)	High Risk (HR)	Very High Risk (VHR)

National protocol for the treatment of childhood cancer 2014, Thailand


SR-Induction
Goal of induction chemotherapy: achieve a *remission*.
Day 29 assessment
This phase r
the number
leukemia ce
in the body
Girl 2 yrs.
Boy 3 yrs.
Because boys are at higher risk for relapse than girls, many doctors favor giving them several more months of treatment.
HR protocol
treatments
nduction.
kill any residual cell that was not killed by remission induction, and intensification regimens.
SR-Maintenance

ALL treatment: effective drugs are

1. vincristin*e*-----> arrest cell mitosis

2. predinsone ----> Lympholysis

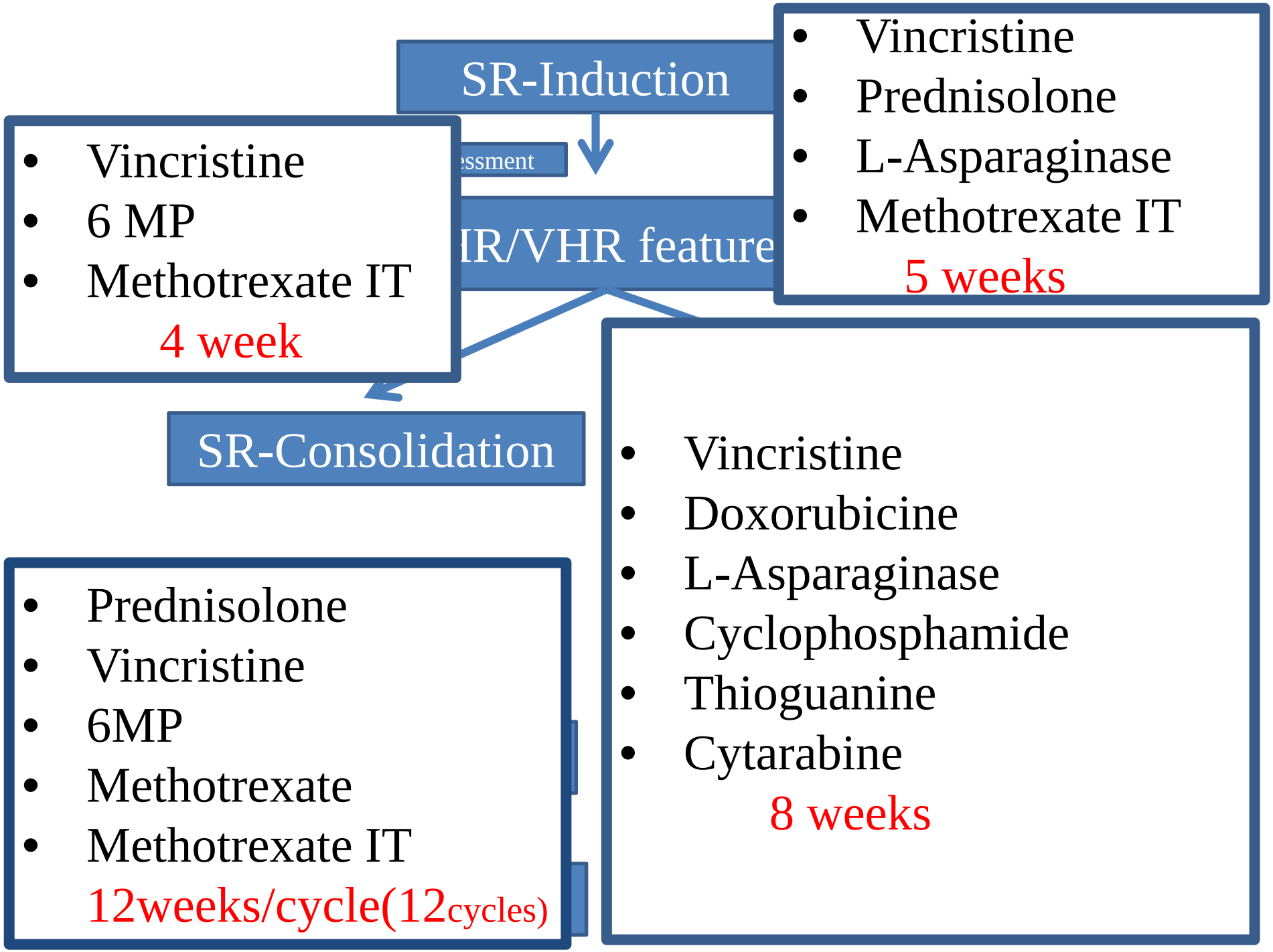
3. 6MP ----> inhibit DNA synthesis.

4. Methotrexate ----> inhibit RNA and protein synthesis

5. Doxorubich (adriamycin) ----> inhibit DNA synthesis

6. L- asparaginase ---->Asparagine depletion; ↓ protein synthesis

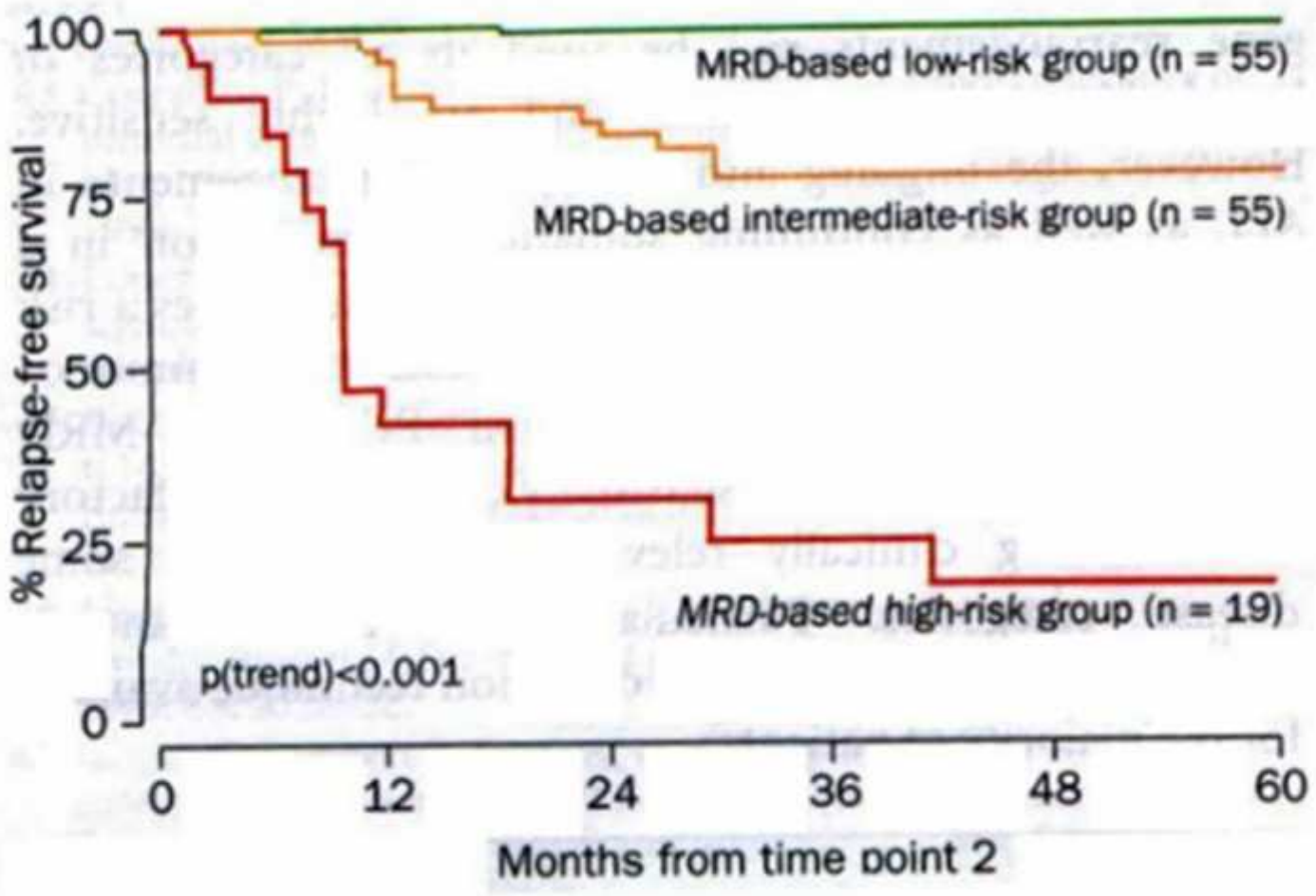
UpToDate 2014


SR-Induction
- Vincristine
- Prednisolone
- L-Asparaginase
- Methotrexate IT
5 weeks
- Vincristine
- 6 MP
- Methotrexate IT
4 week
SR-Consolidation
- Vincristine
- Doxorubicine
- L-Asparaginase
- Cyclophosphamide
- Thioguanine
- Cytarabine
8 weeks
- Prednisolone
- Vincristine
- 6MP
- Methotrexate
- Methotrexate IT
12weeks/cycle(12cycles)

VCR+Steroid	85%
L-Asparaginase +/- Daunorubicin	95%

UpToDate 2014

Minimal Residual Disease



Shripad Banavali Hem-Onc 2000

Chemotherapy

Adverse reaction and management

L-Asparaginase(L-ASP)

Adverse reaction	management
Allergy	
• **Local allergic reactions**	• continue
• **Systemic allergic reactions**	• discontinue
• **Anaphylaxis**	• discontinue future asparaginase therapy.

UpToDate 2014

L-Asparaginase(L-ASP)

- Coagulopathy
- Hyperbillirubinemia
- Hyperglycemia
- Ketoacidosis
- Hyperlipidemia
- Pancreatitis
- Thrombosis
- CNS event (bleed, thrombosis or infarction)

UpToDate 2014

Vincristine(VCR)

- Extravasation
- Constipation
- Hyperbilirubinemia

UpToDate 2014

Cytarabine(Ara-C)

- ARAC Syndrome

UpToDate 2014

Cyclophosphamide(CPM)

- Hematuria
- Renal dysfunction

UpToDate 2014

Doxorubicine(Doxo) (1)

- Cardiac toxicity
- Extravasation
- Myelosupression
- Hyperbilirubinemia

Prednisolone(PRED)

- Hypertension
- Hyperglycemia
- Pancreatitis
- Osteonecrosis

Prednisolone(PRED)

Inability to use oral doses:

- Dexamethasone
- Prednisolone
- Severe infection
- Severe psychosis

Methotrexate(MTX) (IT)

Systemic - Leucovorin

Methotrexate(MTX) HD Infusion

Adverse reaction	Management
Nephrotoxicity:	• Postpone course if serum Creatinine > 1.5 x baseline or GFR < 65 ml/minute/1.73m^2. If renal function does not recovery, omit MTX.
Liver dysfunction: • ALT<20 • ALT>20 • direct hyperbillirubinemia > 2.0 mg/dl	 • Continue • Discontinue • Hold IV MTX

Hydration 125ml/m^2/h
Urine spec <=1.010
pH 7-8

Methotrexate(MTX) HD Infusion

Adverse reaction	Management
Mucositis:	• Hold IV MTX for grade 3-4 mucositis until resolved • Increase leucovorin rescue following the next course to 5 doses on a Q 6 H schedule • If mucositis recurs despite the extended leucovorin, decrease the dose of MTX by 25% and increase hydration to 200 ml/m^2/hr with 5 doses of leucovorin. • Should subsequent courses be well tolerated, use a stepwise approach to resuming full MTX dose.
Myelosupression:	• All chemotherapy should be held for ANC < 750/ul and platelet < 75,000/ul

Mercaptopurine(6 MP) and Methotrexate(MTX)

Adverse reaction	Management
<u>For low blood count:</u> • ANC <500 or PLT < 50,000 • Prolonged cytopenia more than 4 weeks	• Held 6-MP and MTX until recovery • BM evaluation to rule out relapse • TPMT status evaluation
<u>For persistent ANC >= 1500</u> • ANC >= 1500 for 2 consecutive month	• alternate increase dose of MTX or 6-MP by 25%

Supportive Care

Infection prophylaxis and treatment

- **Antibiotic Prophylaxis:**
  ciprofloxacin plus fluconazole = high risk

- **Pnuemocystis prophylaxis:**

  - **First line:** Trimethoprin-sulfamethoxazole
  - **Second line options**: Dapsone

Mucositis

- Moderate (Grade 3)
- severe (Grade 4)

IV fluids, hyper-alimentation and strong consideration of broad-spectrum antibiotics if febrile or appearing ill

Antiemetic protection

Antiemetic should be given as needed. The routine use of steroids should be avoided.

Management of Oncologic Emergencies

Oncology emergency

- Metabolic emergencies
- Hematologic emergencies
- Febrile neutropenia

Metabolic Emergencies

Tumor lysis Syndrome

70% lab criteria, 3% clinical

- Tumor cell death: Spontaneously, Chemotherapy

potassium ↑
phosphate ↑
uric acids ↑
Hypocalcaemia ↓

Metabolic Emergencies

Prevention

- IV hydration
  - Initiation iv 2-3L/m²/d, 200ml/kg/d
  - Maintenance 80-100ml/m²/h, 2ml/kg/h
  - Furosemide

- Urinary alkalinization — sodium bicarbonate, urine pH of 6.5 to 7.0

- Allopurinol

UpToDate

Febrile Neutropenia

- A single oral temp ≥ 38.3 ° C (101 ° F) *or*
- A temperature of ≥ 38 î C (100.4 F) on two occasions separated by 1 hour
- ANC á 500/mm3 or á 1000/mm3 and predicted decline to á 500/mm

hyperleukocytosis

- Defined as a peripheral WBC >100,000 cells/uL
- Symptoms include dyspnea due to pulmonary infiltration and altered mental status due to CNS effects;
- emergency leukapheresis to rapidly reduce the WBC count

Karen Seiter, MD Medscape 2014

Blood bank support

- Transfusion: Hb <7g/dl

- Plt < 10,000/mm^3 = Plt transfusion
- Plt > 50.000/mm^3 = LP
- Plt > any = BMA
- Plt > 20.000/mm^3 =DIC

Costs

Thai POG
BSA 1m²
Normal < 1m²

Phase	Medication (unit/	Cost/cycle	# Cycle	Subtotal
Induction	Vincristine (mg/m2)			
	Prednisone (mg/m2)			
	L-ASP (IU/m2)			
	IT-MTX (mg)			
		12230	1	12230
Consolidatio	Vincristine (mg/m2)			
	6-MP (mg/m2)			
	IT-MTX (mg)			
		2252	1	2252
IM-I	Vincristine (mg/m2)			
	HD-MTX (g/m2)			
	Leucovorin (mg/m2)			
	IT-MTX (mg)			
		26259	1	26259
DI	Dexamethasone (mg			
	Vincristine (mg/m2)			
	Doxorubicin (mg/m2)			
	L-ASP (IU/m2)			
	CPM (mg/m2)			
	6-TG (mg/m2)			
	ARA-C (mg/m2)			
	IT-MTX (mg)			
		16531	1	16531
Maintenance	Prednisone (mg/m2)			
	Vincristine (mg/m2)			
	6-MP (mg/m2)			
	MTX (mg/m2)			
	IT-MTX (mg)			
		4878	12	58538
Total cos				**115811**

THE LANCET Oncology

Volume 14, Issue 12, November 2013, Pages e508–e523

Review

Management of adult and paediatric acute lymphoblastic leukaemia in Asia: resource-stratified guidelines from the Asian Oncology Summit 2013

Allen E J Yeoh, MBBS[a], Daryl Tan, MBBS[b], Prof Chi-Kong Li, MD[c], Prof Hiroki Hori, MD[d], Eric Tse, MBBS[e], Prof Ching-Hon Pui, MD[f]

	Total population (x1000)	Proportion age 0–14 years (%)	Doctors (n/10 000 population)	Nurses and midwives (n/10 000 population)	Tuberculosis prevalence (cases/100 000 population)	Proportion of underweight children among under-5s (%)	Under-5 mortality (deaths/ 1000 births)	Measles immunisation coverage among under-1s (%)	Annual government expenditure per person (US$)	Annual total health-care expenditure per person (US$)
Basic resources										
Burma	48 337	25%	5	8	525	30%	62	88%	4	34
Afghanistan	32 358	46%	2	5	352	33%	101	62%	5	44
Bangladesh	150 494	31%	3	3	411	41%	46	94%	19	57
Pakistan	176 745	35%	8	6	364	31%	72	86%	23	59
Nepal	30 486	35%	2	5	238	39%	48	86%	22	66
Timor-Leste	1154	46%	1	22	643	45%	54	66%	47	84
Laos	6288	34%	3	10	130	36%	42	64%	32	97
Limited resources										
Indonesia	242 326	27%	3	20	289	20%	32	89%	55	112
Cambodia	14 305	31%	2	8	660	29%	43	93%	45	121
India	1 241 492	30%	6	13	256	44%	61	74%	39	132
Philippines	94 852	35%	12	60	502	21%	25	88%	50	142
Sri Lanka	21 045	25%	5	19	101	22%	12	99%	66	148
Vietnam	88 792	23%	12	10	334	20%	22	98%	81	215
Mongolia	2800	28%	28	35	331	5%	31	97%	120	218
Bhutan	738	29%	<1	3	181	13%	54	95%	239	275
Enhanced resources										
Thailand	69 519	20%	3	15	182	7%	12	98%	247	330
China	1 347 565	19%	14	14	108	3%	15	99%	203	379
Maldives	320	26%	16	45	13	18%	11	97%	281	464
Malaysia	28 859	30%	9	27	107	13%	7	96%	356	641
Brunei	406	26%	14	49	91	N/A	7	94%	1230	1449
Maximum resources										
South Korea	48 391	16%	20	53	151	N/A	5	98%	1193	2023
Singapore	5188	17%	18	59	44	3%	3	95%	825	2273
New Zealand	4415	20%	27	109	9	N/A	6	91%	2514	3020

Panel 1: Recommendations for diagnostic work-up, according to resource availability

Basic resources

Children and adults

- Morphology with or without cytochemistry
- Chest radiography to detect mediastinal mass

Limited resources

Children

- Morphology and cytochemistry
- Immunophenotyping (restricted)
- DNA index
- RT-PCR of *BCR-ABL1*, *MLL-AFF1*, and *ETV6-RUNX1*

Adults

- Morphology and cytochemistry
- Immunophenotyping (restricted to exclude acute myeloid leukaemia and mixed-lineage acute leukaemia)
- RT-PCR of *BCR-ABL1*
- Cytogenetics for Philadelphia chromosome or fluorescence in-situ hybridisation of *BCR-ABL1*

Enhanced resources

Children

- Morphology
- Immunophenotyping
- DNA index
- RT-PCR of *BCR-ABL1*, *MLL-AFF1*, *ETV6-RUNX1*, and

Lancet Oncol 2013

Panel 2: Recommendations for risk assignment, according to resource availability

Basic resources

Children and adults

- Age
- Leucocyte count
- Day 8 peripheral-blood response

Limited resources

Children

- Age
- Leucocyte count
- Immunophenotype (T cell *vs* B cell)
- Blast-cell count in peripheral blood after 1 week of prednisone treatment, or percentage of leukaemic blast cells in bone marrow at day 8
- Day 15 and end-of-induction bone-marrow response
- If available, RT-PCR of *BCR-ABL1*, *MLL-AFF1*, and *ETV6-RUNX1*

Lancet Oncol 2013

Panel 3: **Proposed protocol for children and adults with acute lymphoblastic leukaemia in countries with basic resources (not risk-stratified)**

Induction (two-drug), for 1 month

- Vincristine 1·5 mg/m² per dose*, days 1, 8, 15, and 22
- Prednisolone 40–60 mg/m² per day, for 28 days
- Asparaginase (if available) 6000 U/m² per dose, days 4, 6, 8, 11, 13, and 15
- Intrathecal methotrexate, days 8, 15, and 22

Interim maintenance (part 1), for 8 weeks

- Mercaptopurine 37·5–50 mg/m² or tioguanine 30–40 mg/m²† per night (before bedtime)
- Oral methotrexate 15–20 mg/m² per dose, weeks 2, 4, 6, and 8
- Intrathecal methotrexate, weeks 1, 3, 5, and 7

Delayed intensification (part 1), for 4 weeks

- Vincristine 1·5 mg/m² per dose*, days 1, 8, 15, and 22
- Dexamethasone 4–6 mg/m² per day, for 28 days
- Intrathecal methotrexate, days 1 and 15

Interim maintenance (part 2), for 8 weeks

- Same as interim maintenance part 1

Delayed intensification (part 2), for 4 weeks

- Same as delayed intensification part 1

Maintenance, 4-week block, repeated until 2 years

- Mercaptopurine 37·5–50 mg/m² or tioguanine 30–40 mg/m²† per night, for 28 days
- Oral methotrexate 15–20 mg/m² per week, for 4 weeks
- Dexamethasone 4–6 mg/m² per day, for 5 days during week 3
- Vincristine 1·5 mg/m² per dose*, week 3

*Maximum dose of vincristine should be capped at 2 mg. †Prolonged treatment with tioguanine can be associated with veno-occlusive disease of the liver and thrombocytopenia and should only be used when mercaptopurine is not available.

Lancet Oncol 2013

	Children
Basic resources	
Antiemetics	Metoclopramide and diphenhydramine, lorazepam, chlorpromazine, dexamethasone
Analgesics	Paracetamol, codeine, morphine
Antibiotics	Cephalosporins, antipseudomonas semisynthetic penicillins, aminoglycosides, trimethoprim-sulfamethoxazole
Blood products	Whole blood (directed), platelets
Prevention of tumour lysis	Allopurinol
Limited resources	
Antiemetics	Metoclopramide and diphenhydramine, lorazepam, chlorpromazine, dexamethasone, ondansetron
Analgesics	Intravenous midazolam and ketamine for painful procedures, codeine, methadone, morphine (multiple formulations)
Antibiotics	Broad-spectrum antibiotics, amphotericin B
Prophylaxis	Trimethoprim-sulfamethoxazole for *Pneumocystis jirovecii*
Blood products	Packed red-blood cells, platelets
Prevention of tumour lysis	Allopurinol
Enhanced and maximum resources	
Antiemetics	Ondansetron, granisetron, aprepitant
Analgesics	Central venous catheters, sedation or general anaesthesia for painful procedures, fentanyl and other opioids
Antibiotics	Broad-spectrum antibiotics, carbapenems, azoles, echinocandins
Prophylaxis	Trimethoprim-sulfamethoxazole for *Pneumocystis jirovecii*; lamivudine, entecavir, tenofovir for hepatitis B carriers
Blood products	Leucocyte-depleted or irradiated blood components, single-donor platelets
Nutrition	..
Prevention of tumour lysis	Allopurinol with or without rasburicase

***Table 3*: Recommendations for supportive care for children and adults with acute lymphoblastic leukaer**

Lancet Oncol 2013

Psychosocial

- Shock at diagnosis
- Denial - Guilt
- Information overload
- Procedures
- Care of siblings
- Finances, Job loss
- Uncertain future
  - Short versus long term

Summary

1. ALL, SR 2/3
2. Survival by 60% (In Laos save…..
3. Practical and feasible in Laos
4. Cost affordable
5. supportive care possible