Taipei Veterans General Hospital Practice Guidelines Oncology

Pediatric Acute Lymphoblastic Leukemia

制定日期: 2014年 6月13日
第一次 修訂日期: 2015年 8月14日
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第五次 修訂日期: 2019年12月31日
第六次 修訂日期: 2020年11月25日
第七次 修訂日期: 2021年10月19日

2021年修正部分

- 修改多專科團隊名單，增加放射線吳佳諳醫師。
- 加入因應D15 MRD及EOI MRD結果，調整induction C/T強度之詳細scheme；並加入blinotumomab/ CAR-T/HSCT使用時機。
- 增加最近期刊論文及成果發表。

Table of Content

Multidisciplinary Team

- Pediatric Oncology
- Pediatric Surgery
- Radiation Oncology
- Pediatric psychology
- Family Medicine (for hospice care)
- Pathology
- Pediatric radiology
- Nuclear medicine
- Specialized Nursing Care & pharmacist
- Social Workers
- Nutritional Support

Panel Members

團隊召集人：顏秀如		
團隊副召集人：洪君儀、蔡昕霖		
（核心成員）		
兒童醫學部	顏秀如	主治醫師
	洪君儀	科主任
	李致穎	主治醫師
兒童外科	劉君恕	科主任
	蔡昕霖	科主任
	葉奕廷	主治醫師
	吳佳諳	主治醫師
核子醫學科	丁建鑫	主治醫師
病理檢驗部	楊靜芬	主治醫師
腫瘤醫學部放射腫瘤科	陳一瑋	主治醫師
	康鈺玫	住院醫師
個案管理師	謝艷秋	護理師
（非核心成員）		
精神部	黃凱琳	主治醫師
藥學部	王笙帆	藥師
護理部	黃鈴雅	護理長
	田怡清	專科護理師
社工室	葉雅芳	社工師
營養部	徐嘉徽	營養師
	謝伊晴	營養師
家醫部(安寧共照)	劉瑞瑤	主治醫師
	黃茱楹	護理師
更新日期：2021/03/01		

Pretreatment workup

- **Complete medical history and physical exam**
- **Blood tests**
  - CBC, DC, WBC morphology
  - BUN/ creatinine
  - ALT/ AST
  - LDH/UA, Na/K, Ca/IP
  - CRP, blood culture (optional)
- **Radiological imaging**
  - CXR
  - Abdominal sonography (optional)
- **Bone marrow survey**
  - BM exam
  - Cytochemical stain (optional)
  - Immunophenotype
  - Cytogenetics
  - RT-PCR for common translocation of leukemia
  - MRD (baseline)
  - Bone marrow biopsy (optional)

Surveillance of ALL

- **Blood tests** (qm)
  - CBC, DC
  - BUN/ creatinine
  - ALT/ AST
  - LDH/ UA

- **Bone marrow survey**
  - BM exam

  If previous positive findings of
  - Cytogenetics
  - RT-PCR for common translocation of leukemia

  - MRD (only day15, day35 & specific time point for T-ALL)

CNS staging

- **CNS status**
  - CNS-1: normal CSF
  - CNS-2: <5 WBC with blasts
  - CNS-3: >=5 WBC with blasts or CNS palsy
  - Traumatic tapping: >10/uL RBC with blasts

Risk Stratifications

Criteria for Standard Risk ALL

1. B-lymphoblastic ALL with DNA index ≥ 1.16 [or hyperdiploidy (51-68)], *TEL-AML*1 fusion, or age 1 to 9.9 years and presenting WBC < 50,000/mm^3. AND

2. **Must not have**:

-CNS 3 status (≥ 5 WBC/μL of cerebrospinal fluid with morphologically identifiable blasts or cranial nerve palsy).

-Overt testicular leukemia (evidenced by ultrasonogram).

-Adverse genetic features: t(9;22) or *BCR-ABL1* fusion; t(1;19) with *E2A-PBX1* fusion; rearranged *MLL* (as measured by FISH and/or PCR); or hypodiploidy (< 44 chromosomes).

-Poor early response (≥ 1% lymphoblasts on day 15 of remission induction, ≥ 0.01% lymphoblasts by immunologic or molecular methods on remission date).

Criteria for High-Risk ALL

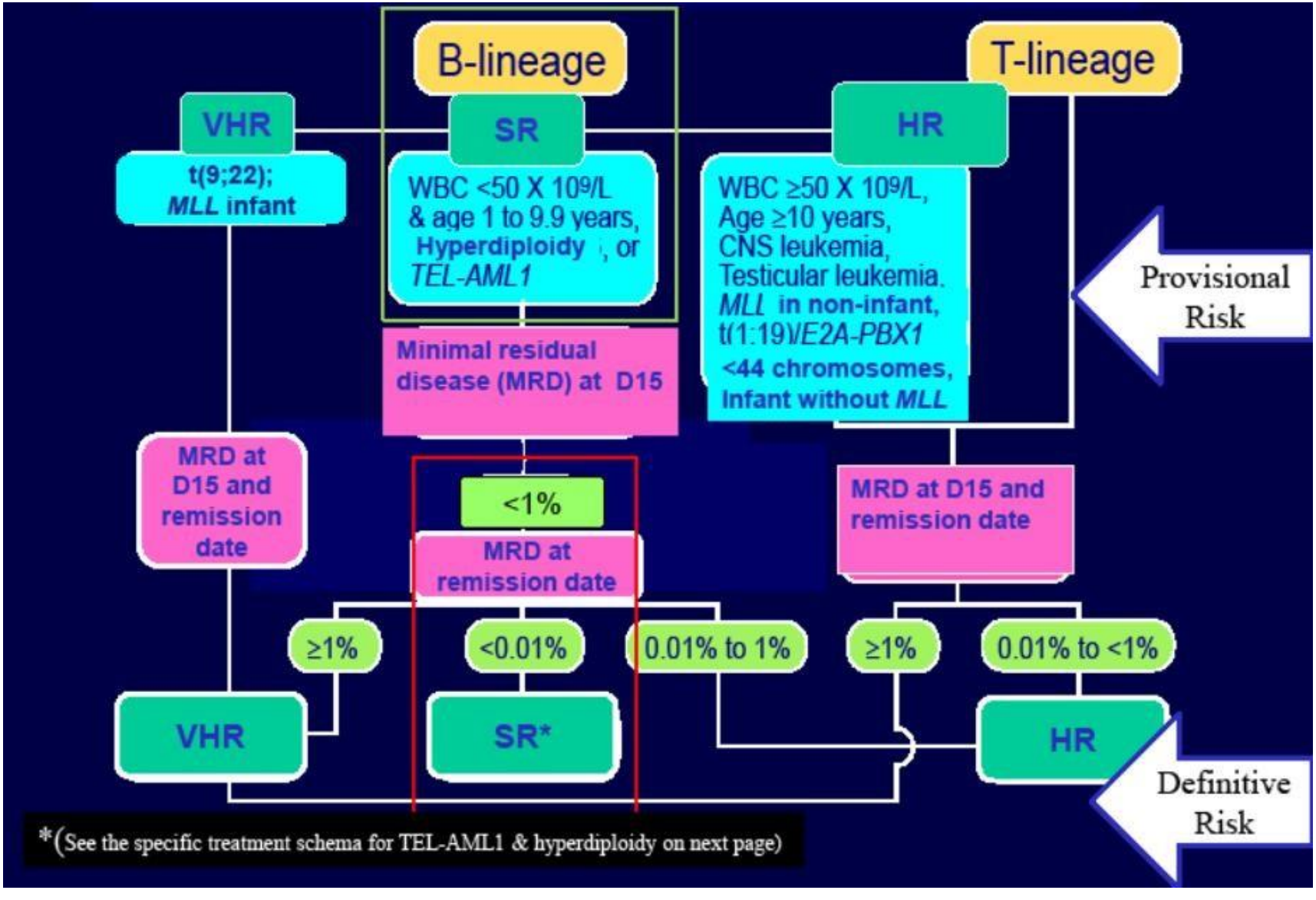
1. All cases of T-cell ALL and those of B- lymphoblastic ALL that do not meet the criteria for standard-risk or very high-risk ALL.

Risk Stratifications

Criteria for Very High-Risk ALL

1. t(9;22) or *BCR-ABL1* fusion (with MRD ≥0.01% after remission induction including dasatinib (60 mg/m^2 per day).
2. Infants with t(4;11) or *MLL* fusion.
3. Induction failure or ≥1% leukemic lymphoblasts in the bone marrow on remission date (with the exception of hyperdiploid (51-68) and *TEL-AML1* cases who should have positive MRD after consolidation therapy).
4. ≥1% leukemic lymphoblasts in the bone marrow in week 7 of continuation treatment (i.e. before reinduction I, ~14 weeks post remission induction).
5. Re-emergence of leukemic lymphoblasts by MRD (at any level) in patients previously MRD negative.
6. Persistently detectable MRD at lower levels.
7. Early T-cell precursor (ETP) ALL, defined by lack of expression of CD1a and CD8 and low or absent expression of CD5 together with aberrant expression of myeloid and hematopoietic stem cell markers (such as CD13, CD33, CD34 and CD117).

Treatment Guideline



Induction chemotherapy for B-ALL

TPOG-ALL-2013-21 Induction (For BCP-ALL)

Day		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Pred	(40)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Vincristine	(1.5)	☐	-	-	-	-	-	-	☐	-	-	-	-	-	-	☐	-	-	-	-	-	-
Epirubicin	(20)	☐	-	-	-	-	-	-	☐	-	-	-	-	-	-	-	-	-	-	-	-	-
L-asp	(6000)	-	-	☐	-	☐	-	☐	-	-	☐	-	☐	-	☐	-	-	☐	-	☐	-	☐
TIT		☐	-	-	☐	-	-	-	☐	-	-	☐	-	-	-	☐	-	-	-	-	-	-
(年:) 月/日		MRD	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	MRD1 D15	☐	☐	☐	☐	☐	☐

For Ph(+), Dasatinib 80mg/m2/day PO QD since D15

Induction-II-A	Day		22	23	24	25	26	27	28	29	30	31	32	33	34	35
t(12,21)/HD, MRD1 <1%	Pred	(40)	☐	☐	☐	☐	☐	☐	☐				tapper			
SR, MRD1 <1%	Vincristine	(1.5)	☐	-	-	-	-	-	-	-	-	-	-	-	-	-
	TIT		☐	-	-	-	-	-	-	-	-	-	-	-	-	-
	(年:)	月/日	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	MRD2 D35-42

Induction-II-B	Day		22	23	24	25	26	27	28	29	30	31	32	33	34	35
t(12;21)/HD, MRD1 ≥1%	Pred	(40)	☐	☐	☐	☐	☐	☐	☐				tapper			
SR, MRD1 1-5%	Vincristine	(1.5)	☐	-	-	-	-	-	-	-	-	-	-	-	-	-
HR, MRD1 <5%	TIT		☐	-	-	-	-	-	-	-	-	-	-	-	-	-
Ph(+), MRD1 any	L-asp	(6000)	-	-	☐	-	☐	-	☐	-	-	-	-	-	-	-
└ if MRD1 ≥1%, 直接接 EI	Cytarabine*	(75) 30min	-	☐	☐	☐	☐	-	-	-	☐	☐	☐	☐	-	-
	6MP*	(60)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	Cyclophosphamide*	(1000) 6hr	☐	-	-	-	-	-	-	-	-	-	-	-	-	-
Induction-II-C (直接接 EI)	Bortezomib	(1.3)	Bortezomib not for Ph(+), 自費 4 劑共 7 萬, 可申請兒癌補助								☐	-	-	☐	-	-
SR, MRD1 ≥5%	(年:)	月/日	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	MRD2 D35-46
HR, MRD1 ≥5%																
Infant with KMT2A-R																

*Cytarabine, 6MP, cyclophosphamide may be delayed for 3 to 7 days if WBC<1000, APC<300, Plt<50k.

If need EI: take rest for 7d (D36-42) then EI

TPOG-ALL-2013-21 (flow chart VGHTPE version)

Early intensification chemotherapy

TPOG-ALL-2013-21 Early Intensification

BCP-ALL:
-other SR, MRD1≥5%
-other SR, MRD1<5%, but MRD2≥1%
-HR, MRD1≥5%
-HR, MRD1<5%, but MRD2≥1%
-Infant with KMT2A-R
-Ph(+) ALL with MRD1≥1%
-Ph(+) ALL with MRD1<1%, but MRD2≥0.01%

T-ALL:
-non-ETP, MRD1≥1% (已併於 T-ALL 療程表內)
-non-ETP, MRD1<1%, but MRD2≥1%
-ETP (已併於 T-ALL 療程表內)

Chemotherapy day 1: _____/_____/_____

■ Induction II 後，直接 RI，再八周 HDMTX
□ 行四周 HDMTX 後，接 RI，再四周 HDMTX

Day		43	44	45	46	47	48	49	50	51	52	53	54	55	56
Cytarabine*	(75) 30mins	-					-	-	-					-	-
6MP*	(60)														
Cyclophosphamide*	(1000) 6hr		-	-	-	-	-	-	-	-	-	-	-	-	-
Bortezomib	(1.3)	-		-	-		Bortezomib not for Ph(+), 自費 4 劑共 7 萬, 可申請兒癌補助								-
TIT			-	-	-	-	-	-	-	-	-	-	-	-	-
(年:)	月/日														MRD3

D60-75 or D84-96

*Cytarabine, 6MP, cyclophosphamide may be delayed for 3 to 7 days if WBC<1000, APC<300, Plt<50k

Induction chemotherapy for T-ALL (including ETP)

TPOG-ALL-2013-21 Induction (for T-ALL, including ETP)

Day		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Pred	(40)	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
Vincristine	(1.5)	■	-	-	-	-	-	-	■	-	-	-	-	-	-	■	-	-	-	-	-	-
Epirubicin	(20)	■	-	-	-	-	-	-	■	-	-	-	-	-	-	-	-	-	-	-	-	-
L-asp	(6000)	-	-	■	-	■	-	■	-	-	■	-	■	-	■	-	-	■	-	■	-	■
TIT		■	-	-	■	-	-	-	■	-	-	■	-	-	-	■	-	-	-	-	-	-
(年:)	月/日	MRD	■	■	■	■	■	■	■	■	■	■	■	■	■	MRD1 D15	■	■	■	■	■	■

Induction-II-C	Day		22	23	24	25	26	27	28	29	30	31	32	33	34	35
Non-ETP, any MRD	Pred	(40)	■	■	■	■	■	■	■				tapper			
ETP, any MRD	Vincristine	(1.5)	■	-	-	-	-	-	-	-	-	-	-	-	-	-
	TIT		■	-	-	-	-	-	-	-	-	-	-	-	-	-
	L-asp	(6000)	-	-	■	-	■	-	■	-	-	-	-	-	-	-
	Cytarabine*	(75) 30mins	-	■	■	■	■	-	-	-	■	■	■	■	-	-
	6MP*	(60)	■	■	■	■	■	■	■	■	■	■	■	■	■	■
	Cyclophosphamide*	(1000) 6hr	■	-	-	-	-	-	-	-	-	-	-	-	-	-
	Bortezomib	(1.3)	Bortezomib not for Ph(+), 自費 4 劑共 7 萬, 可申請兒癌補助								■	-	-	■	-	-
	(年:)	月/日	■	■	■	■	■	■	■	■	■	■	■	■	■	MRD2 D35-46

*Cytarabine, 6MP, cyclophosphamide may be delayed for 3 to 7 days if WBC<1000, APC<300, Plt<50k

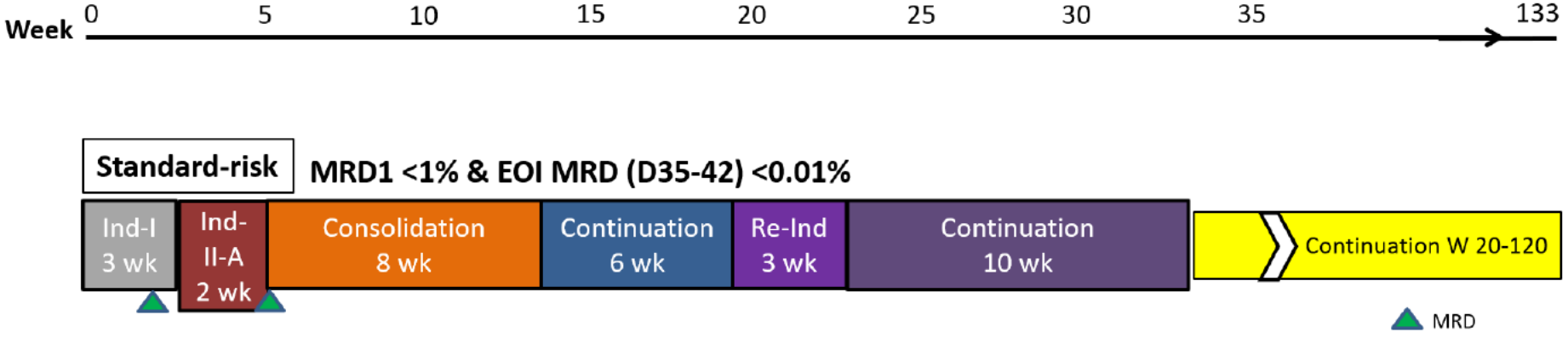
Early Intensification	Day		43	44	45	46	47	48	49	50	51	52	53	54	55	56
Non-ETP, MRD1 ≥1%	Cytarabine*	(75) 30mins	-	■	■	■	■	-	-	-	■	■	■	■	-	-
ETP	6MP*	(60)	■	■	■	■	■	■	■	■	■	■	■	■	■	■
	Cyclophosphamide*	(1000) 6hr	■	-	-	-	-	-	-	-	-	-	-	-	-	-
	Bortezomib	(1.3)	-	■	-	-	■	-	-	-	-	-	-	-	-	-
	TIT		■	-	-	-	-	-	-	-	-	-	-	-	-	-
	(年:)	月/日	■	■	■	■	■	■	■	■	■	■	■	■	■	MRD3 D60-75

*Cytarabine, 6MP, cyclophosphamide may be delayed for 3 to 7 days if WBC<1000, APC<300, Plt<50k

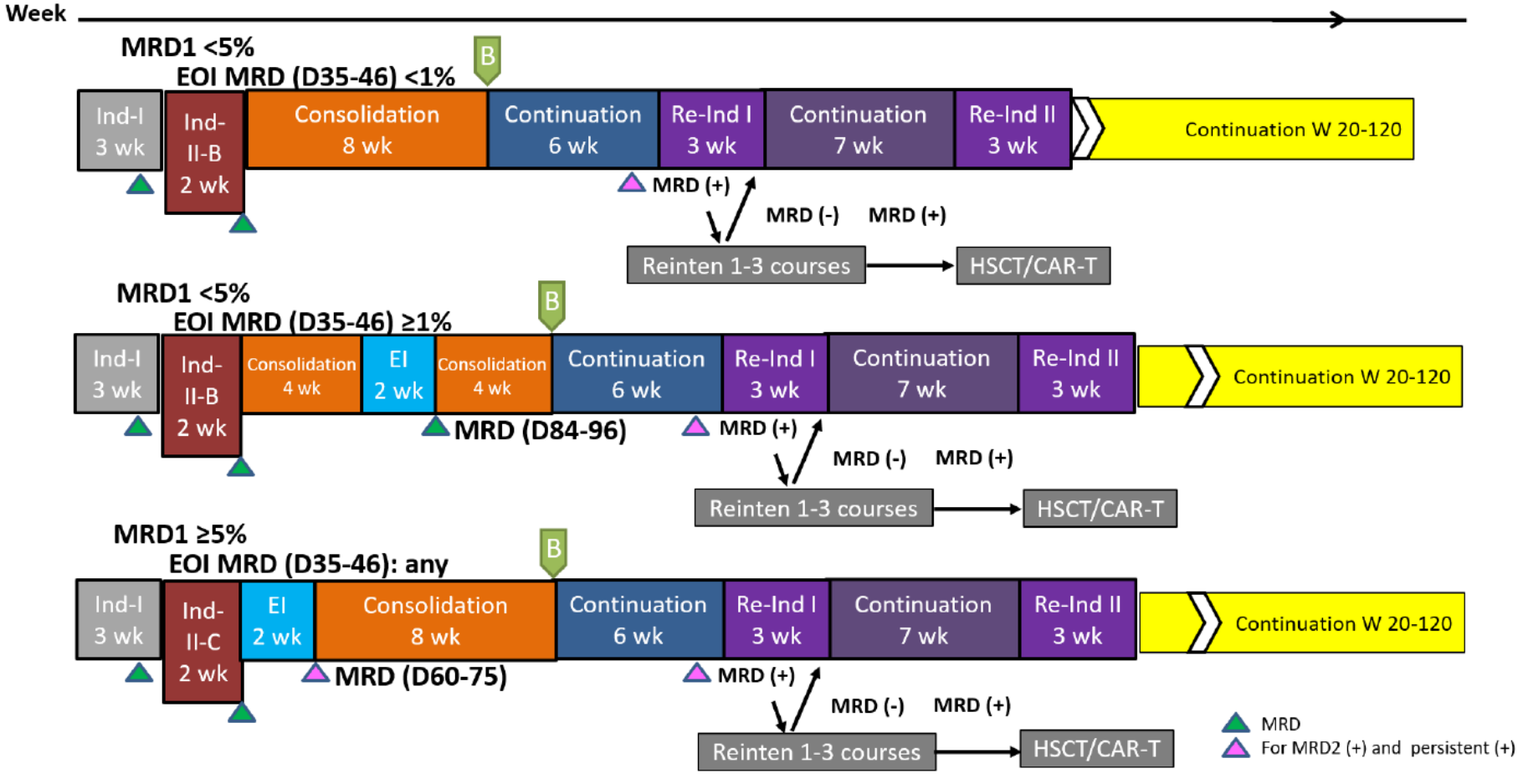
TPOG-ALL-2013-21 (flow chart VGHTPE version)

Schema of TPOG-ALL-2013-2021 Protocol

BCP-ALL, Standard Risk

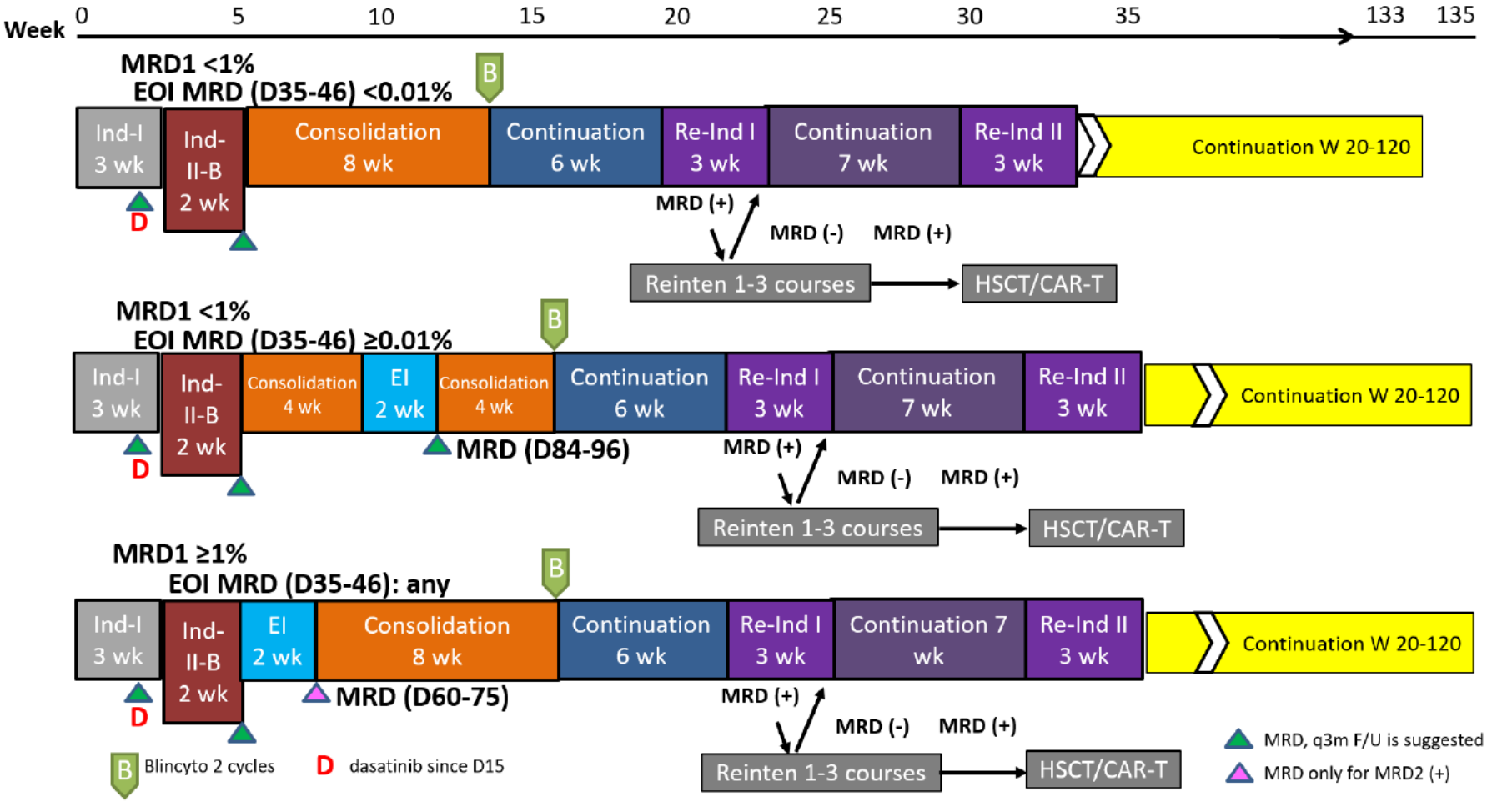


BCP-ALL, High Risk/Very High Risk



B Blincyto 2 cycles only for MRD2 (+)
[≥0.01% or ≤4 log reduction]

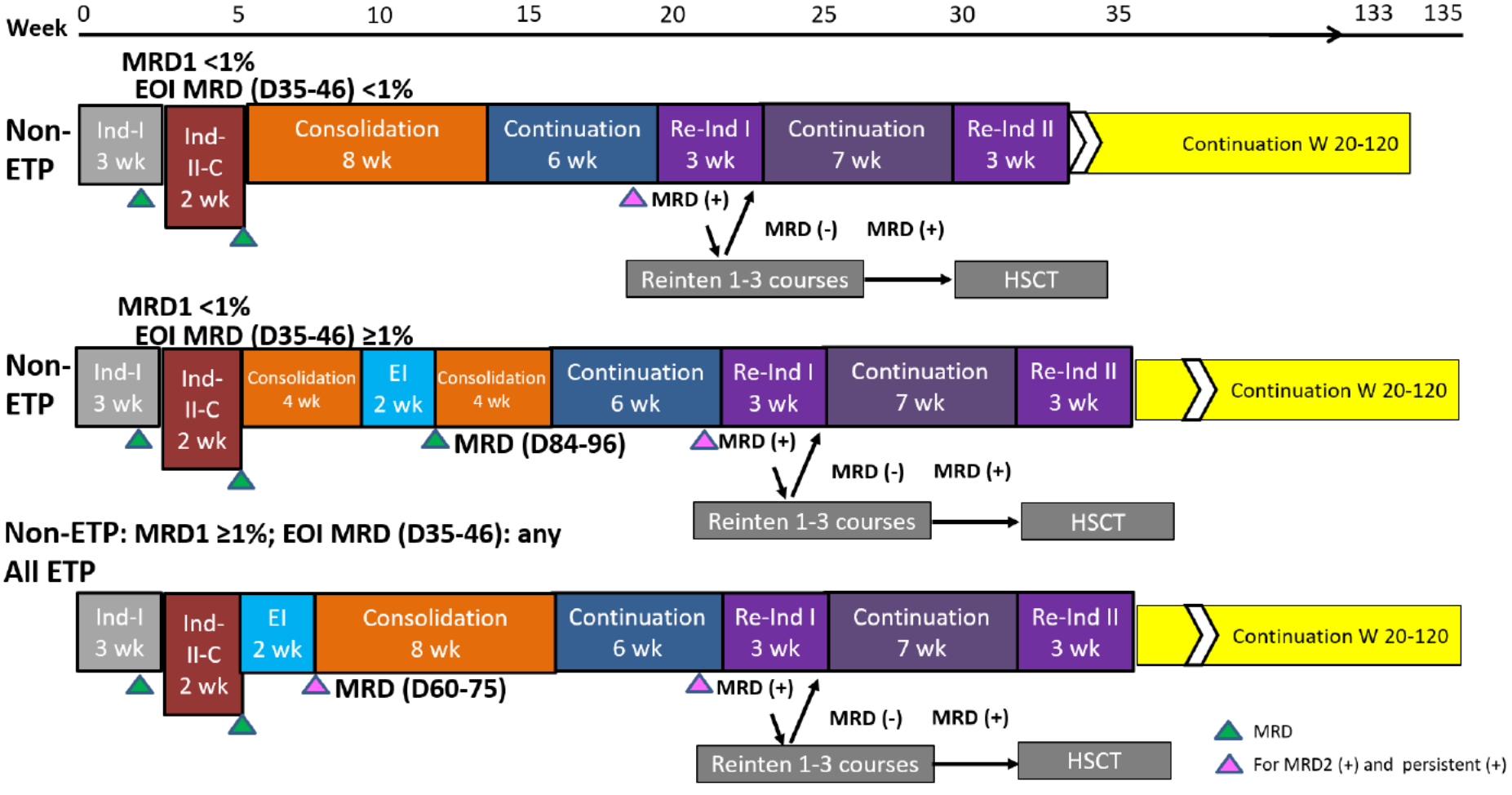
Ph+ALL



Blincyto 後將導致 CD19 消失，後續進行 flow MRD F/U 時，務必告知檢查單位使用 Blincyto 的病史，以另行尋找 markers 或其他 MRD 檢測方法

Pediatric Acute Lymphoblastic Leukemia

T-ALL



Consolidation chemotherapy

TPOG-ALL-2013- Consolidation

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
6MP (40)																												
MTX (2.5 / 5) 24hr		-	-	-	-	-	-	-	-	-	-	-	-	-		-	-	-	-	-	-	-	-	-	-	-	-	-
TIT		-	-	-	-	-	-	-	-	-	-	-	-	-		-	-	-	-	-	-	-	-	-	-	-	-	-
(年:　)　月/日	MRD																											

Day	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56
6MP (40)																												
MTX (2.5 / 5) 24hr		-	-	-	-	-	-	-	-	-	-	-	-	-		-	-	-	-	-	-	-	-	-	-	-	-	-
TIT		-	-	-	-	-	-	-	-	-	-	-	-	-		-	-	-	-	-	-	-	-	-	-	-	-	-
(年:　)　月/日																												

Reintensification (VHR)

Agent	Dosage and Route	Doses	Schedule
Dexamethasone	20 mg/m^2/day PO or IV (divided t.i.d)	18	Days 1-6
Cytarabine	2 grams/m^2, 3-hour IV infusion every 12 hours	4	Days 1-2
Etoposide	100 mg/m^2, 1-hour IV infusion every 12 hours	5	Days 3-5
TIT		1	Day 5
L-asparaginase	25,000iu/m^2 IM	1	Day 6

Treatment Scheme

Continuation (1-20 wks)

Continuation week 1-20

SR		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Dexamethasone	(8)*5	V			V										V			V			V
Vincrisitne	(2)	V			V										V			V			V
6MP	(50)	V	V	V	V	V	V				V	V	V	V	V	V	V	V	V	V	V
MTX	(40)		V	V		V	V				V	V	V	V		V	V		V	V	
~~Epirubicin~~	~~(30)~~																				
~~L-asparaginase~~	~~(10000)~~																				
TIT				V				V					V					V			

HR		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Dexamethasone	(12)*5	V			V										V						
Vincrisitne	(2)	V			V							V			V						
6MP	(40)	V	V	V	V	V	V				V	V	V	V	V	V	V				V
MTX	(40)																				V
Epirubicin	(30)	V			V							V			V						
L-asparaginase	(10000)	→V	V	V	V	V	V				V	V	V	V	V	V	V				
TIT				(V)				V					V					V			

VHR		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Dexamethasone	(12)*5	V			V										V						
Vincrisitne	(2)	V			V							V			V						
6MP	(40)	V	V	V	V	V	V				V	V	V	V	V	V	V				V
MTX	(40)																				V
Epirubicin	(30)	V			V							V			V						
L-asparaginase	(10000)	→V	V	V	V	V	V				V	V	V	V	V	V	V				
TIT				(V)				V					V					V			

Treatment Scheme

Reinduction for SR ALL (3 weeks)

Agents	Dosages and routes	Doses	Schedules
Dexamethasone	10 mg/m^2/day PO (t.i.d.)	45	Days 1-8, 15-21
Vincristine	1.5 mg/m^2/week IV (max 2 mg)	3	Days 1, 8, 15
L-asparaginase	6,000 U/m^2 thrice weekly IM	9	Days 3, 5, 7, 10, 12, 14,17,19,21
Epirubicin	30 mg/m^2/week IV	1	Day 1
Methotrexate + hydrocortisone + ara-C	Age-dependent, IT	1	Day 1

Treatment Scheme

Reinduction I for VHR/HR ALL excluding infant with *MLL*+(3 weeks)

Agents	Dosages and routes	# Doses	Schedules
Dexamethasone	12 mg/m^2/day PO (t.i.d.)	45	Days 1-8, 15-21
Vincristine	1.5 mg/m^2/week IV (max 2 mg)	3	Days 1, 8, 15
Epirubicin	30 mg/m^2	2	Days 1,8
L-asparaginase	6,000 U/m^2/thrice weekly IM	9	Days 3, 5, 7, 10, 12, 14,17,19,21
Methotrexate + hydrocortisone + ara-C	Age-dependent, IT	1	Day 1

Reinduction II for VHR/HR ALL including infant with *MLL*+ (3 weeks)

Agents	Dosages and routes	# Doses	Schedules
Dexamethasone	12 mg/m^2/day PO (t.i.d.)	45	Days 1-8, 15-21
Vincristine	1.5 mg/m^2/week IV (max 2 mg)	3	Days 1, 8, 15
L-asparaginase	6,000 U/m^2/thrice weekly IM	9	Days 3, 5, 7, 10, 12, 14,17,19,21
Methotrexate + hydrocortisone + ara-C	Age-dependent, IT	1	Day 1

Treatment Scheme

Continuation week 21-120 (SR page 1)

SR		21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
Dexamethasone	(8)*5				V				V				V				V
Vincrisitne	(2)				V				V				V				V
6MP	(50)	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
MTX	(40)	V	V	V		V	V	V		V	V	V		V	V	V	
TIT					V				(V)				V				(V)

SR		37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52
Dexamethasone	(8)*5				V				V				V				V
Vincrisitne	(2)				V				V				V				V
6MP	(50)	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
MTX	(40)	V	V	V		V	V	V		V	V	V		V	V	V	
TIT					V				(V)				V				

SR		53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68
Dexamethasone	(8)*5				V				V				V				V(6)
Vincrisitne	(2)				V				V				V				V
6MP	(50)	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
MTX	(40)	V	V	V		V	V	V		V	V	V		V	V	V	
TIT																	

(V) IT for standard-risk cases, *TEL-AML*1 fusion and hyperdiploidy (51-68) with WBC > 100,000/mm^3 , CNS-2 or traumatic CSF with blasts.

Treatment Scheme

Continuation week 21-120 (SR page 2)

SR		69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84
Dexamethasone	(6)*5				V				V				V				V
Vincrisitne	(2)				V				V				V				V
6MP	(50)	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
MTX	(40)	V	V	V		V	V	V		V	V	V		V	V	V	
TIT																	

SR		85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
Dexamethasone	(6)*5				V				V				V				V
Vincrisitne	(2)				V				V				V				V
6MP	(50)	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
MTX	(40)	V	V	V		V	V	V		V	V	V		V	V	V	
TIT																	

SR		101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120
Dexamethasone	(6)*5																				
Vincrisitne	(2)																				
6MP	(50)	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
MTX	(40)	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
TIT																					

Treatment Scheme

Continuation week 21-120 (HR page 1)

HR		21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
Dexamethasone	(12)*5				V				V				V				V
Vincrisitne	(2)				V				V				V				V
6MP	(40)	V	V			V	V			V	V			V	V		
MTX	(40)	V	V			V	V			V	V			V	V		
Cyclophosphamide	(300)			V				V				V				V	
Ara-C	(300)			V				V				V				V	
TIT					V				V				V				V

HR		37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52
Dexamethasone	(12)*5				V				V				V				V
Vincrisitne	(2)				V				V				V				V
6MP	(40)	V	V			V	V			V	V			V	V		
MTX	(40)	V	V			V	V			V	V			V	V		
Cyclophosphamide	(300)			V				V				V				V	
Ara-C	(300)			V				V				V				V	
TIT					V				V				V				

HR		53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68
Dexamethasone	(12)*5				V				V				V				V(6)
Vincrisitne	(2)				V				V				V				V
6MP	(40)	V	V			V	V			V	V			V	V		V
MTX	(40)	V	V			V	V			V	V			V	V		
Cyclophosphamide	(300)			V				V				V				V	
Ara-C	(300)			V				V				V				V	
TIT					(V)								(V)				

Treatment Scheme

Continuation week 21-120 (HR page 2)

HR		69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84
Dexamethasone	(6)*5				V				V				V				V
Vincrisitne	(2)				V				V				V				V
6MP	(50)	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
MTX	(40)	V	V	V		V	V	V		V	V	V		V	V	V	
TIT					(V)								(V)				

HR		85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
Dexamethasone	(6)*5				V				V				V				V
Vincrisitne	(2)				V				V				V				V
6MP	(50)	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
MTX	(40)	V	V	V		V	V	V		V	V	V		V	V	V	
TIT					(V)								(V)				

HR		101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120
Dexamethasone	(6)*5																				
Vincrisitne	(2)																				
6MP	(50)	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
MTX	(40)	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
TIT																					

(V) TIT will be given to other standard/high-risk cases with WBC ≥100,000/mm^3, T-cell ALL, t (1;19)/*E2A-PBX1*, hypodiploidy <44, or CNS-3 status, with CNS-2 or traumatic lumbar puncture with blasts at diagnosis

Treatment Scheme

Continuation week 21-120 (VHR page 1)

VHR		21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
Dexamethasone	(12)*5				V				V				V				V
Vincrisitne	(2)				V				V				V				V
6MP	(40)	V	V			V	V			V	V			V	V		
MTX	(40)	V	V			V	V			V	V			V	V		
Cyclophosphamide	(300)			V				V				V				V	
Ara-C	(300)			V				V				V				V	
TIT					V				V				V				V

VHR		37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52
Dexamethasone	(12)*5				V				V				V				V
Vincrisitne	(2)				V				V				V				V
6MP	(40)	V	V			V	V			V	V			V	V		
MTX	(40)	V	V			V	V			V	V			V	V		
Cyclophosphamide	(300)			V				V				V				V	
Ara-C	(300)			V				V				V				V	
TIT					V				V				V				V

VHR		53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68
Dexamethasone	(12)*5				V				V				V				V(6)
Vincrisitne	(2)				V				V				V				V
6MP	(40)	V	V			V	V			V	V			V	V		V
MTX	(40)	V	V			V	V			V	V			V	V		
Cyclophosphamide	(300)			V				V				V				V	
Ara-C	(300)			V				V				V				V	
TIT					(V)								(V)				

Treatment Scheme

Continuation week 21-120 (VHR page 2)

VHR		69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84
Dexamethasone	(6)*5				V				V				V				V
Vincrisitne	(2)				V				V				V				V
6MP	(50)	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
MTX	(40)	V	V	V		V	V	V		V	V	V		V	V	V	
TIT					(V)								(V)				

VHR		85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
Dexamethasone	(6)*5				V				V				V				V
Vincrisitne	(2)				V				V				V				V
6MP	(50)	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
MTX	(40)	V	V	V		V	V	V		V	V	V		V	V	V	
TIT					(V)								(V)				

VHR		101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120
Dexamethasone	(6)*5																				
Vincrisitne	(2)																				
6MP	(50)	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
MTX	(40)	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
TIT																					

(V) TIT will be given to other standard/high-risk cases with WBC ≥100,000/mm^3, T-cell ALL, t (1;19)/*E2A-PBX1*, hypodiploidy <44, or CNS-3 status, with CNS-2 or traumatic lumbar puncture with blasts at diagnosis

Summary

- In this protocol, risk classification will only the determined by the level of **minimal residual disease (MRD) at the end of induction therapy**.
- MRD level will be assayed for follow-up. We then have to rely on **accurate MRD assay**.

註記

1. **Clofarabine dosage**：考量toxicity，經Dr Pui同意，由40 mg/m2/day 降為25 mg/m2/day(包括reintensification therapy, 以及infant ALL的induction and reinduction therapy)

2. **The diagnostic criteria of early T-precursor ALL (ETP):**

Classification of ETP-ALL requires the following criteria:

Criteria 1. Unequivocal diagnosis of T-ALL as defined by:

CD3-positive (surface, or cytoplasmic only)

CD7-positive

Myeloperoxidase (MPO)-negative

Criteria 2.

CD1a-negative AND CD8-negative

Criteria 3.

Dim CD5.

Definition of "dim": mean fluorescence intensity (MFI) at least 10-fold lower than that of normal T lymphocytes (use residual normal T cells in the sample to calculate) AND/OR <75% CD5-positive blasts

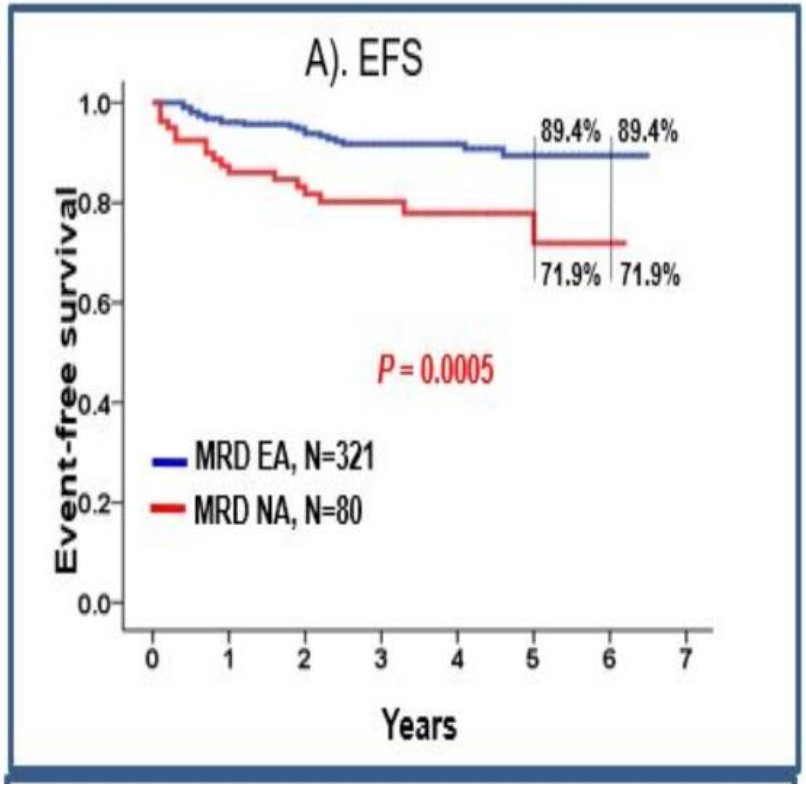
Criteria 4.

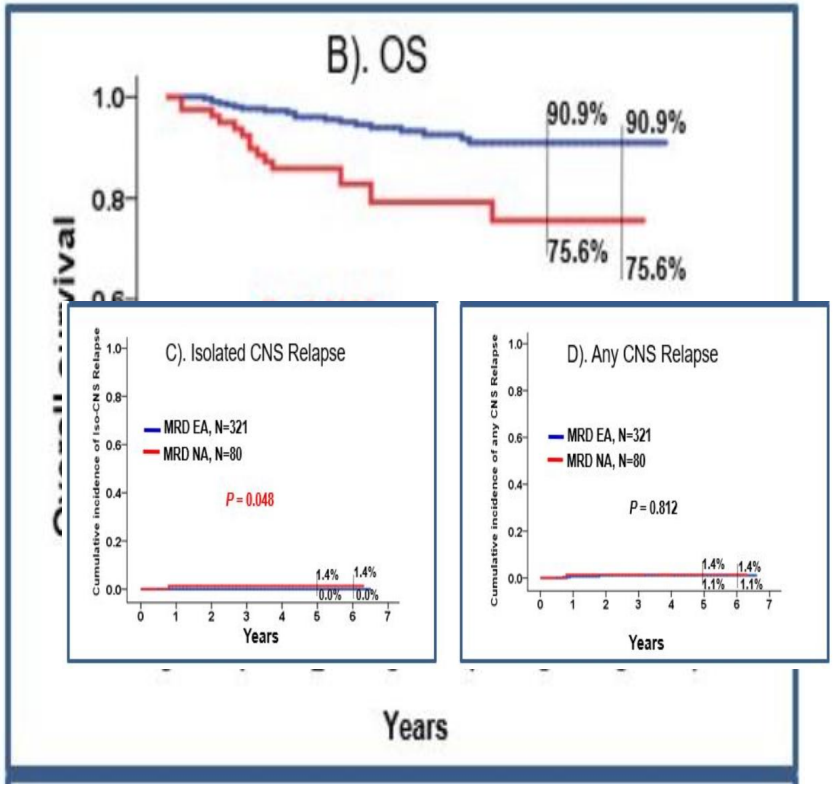
Expression of stem-cell associated antigens (CD34, CD133, CD117 and/or HLA-Dr) AND/OR expression of myeloid-associated antigens (CD13, CD33, CD15 and/or CD11b). Positivity with any one of these markers is sufficient.

ALL 4 CRITERIA MUST BE MET TO DEFINE ETP-ALL

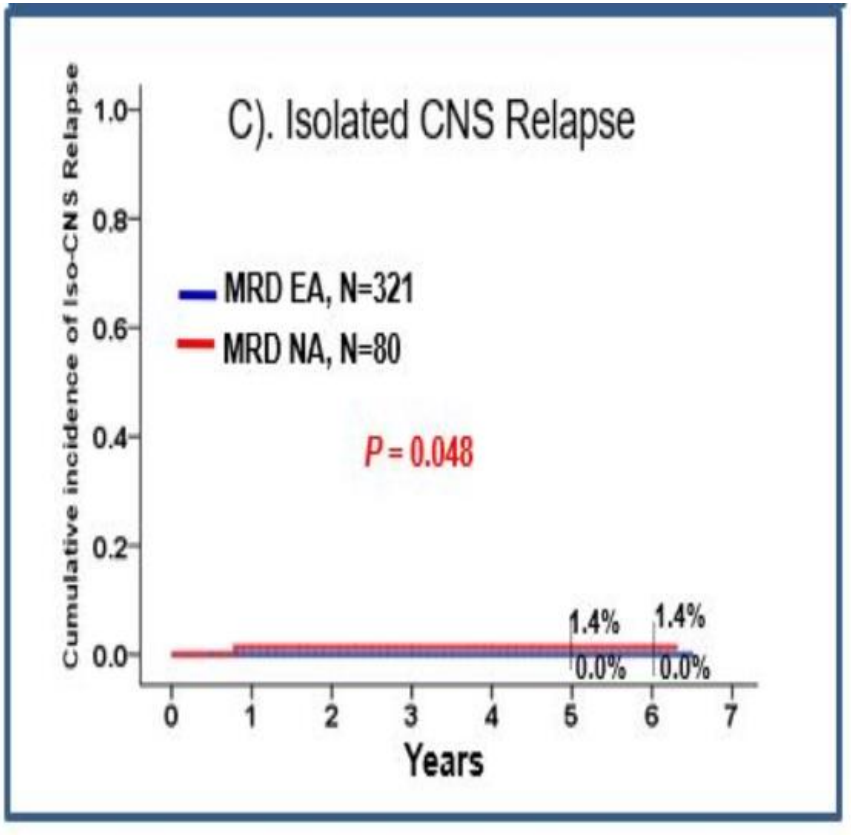
The Adherence of MRD timepoints: prognostic predictors

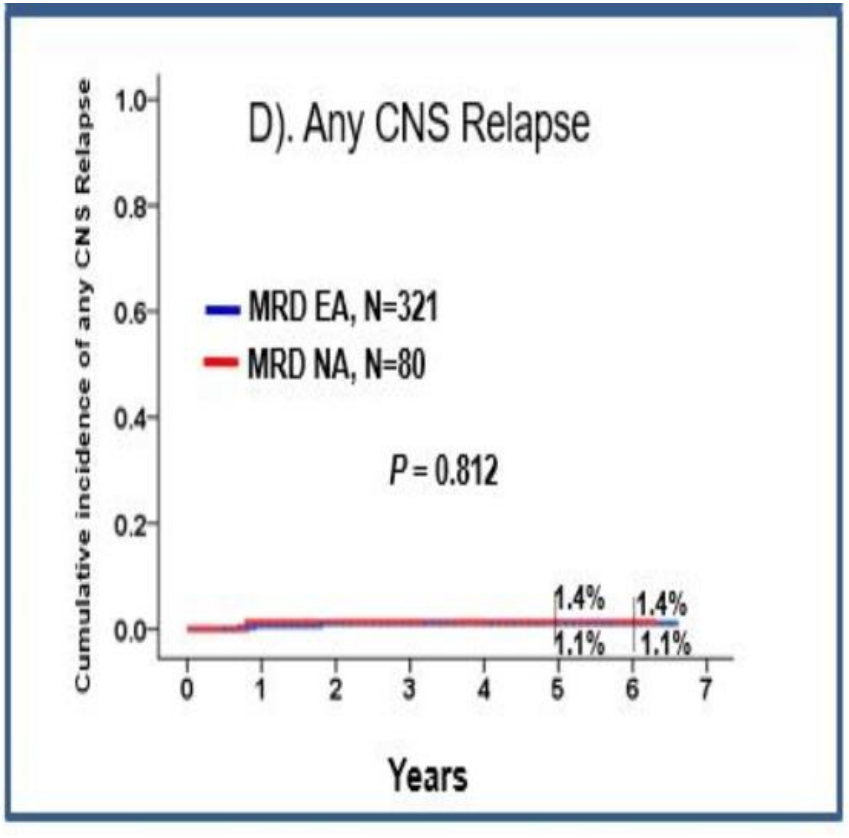
Figure 1. Comparative Outcome Analysis between MRD EA & MRD NA Groups





The Adherence of MRD timepoints: prognostic predictors





About TCF3-PBX1 (+) ALL

Background:

•t(1;19)(q23;p13.3) with *TCF3-PBX1* fusion is one of the most frequent translocations in childhood ALL.

•Historically, it has been associated with poor prognosis. Intensive treatment has improved its outcome.

Procedure:

•Based on presenting features, immunophenotype and genotype, patients were assigned to SR, HR, VHR.

•Patients with t(1;19)/*TCF3-PBX1* were treated in the HR

•The outcomes of patients with *t(1;19)/TCF3-PBX1* were compared to that of patients with other subtypes of B-precursor ALL (B-ALL).

About TCF3-PBX1 (+) ALL

TABLE 1 Comparison of clinical characteristics of B-precursor ALL patients between t(1;19) positive and t(1;19) negative patients

Clinical features	N (%)	t(1;19) positive		t(1;19) negative		*P* value
		N (%)	Median (range)	N (%)	Median (range)	
Total	1,129 (100)	64 (100)		1,065 (100)		
Age at diagnosis						0.002
Infant	50 (4)	1 (2)	0.9	49 (5)	0.4 (0.0–0.95)	
1–10 years old	835 (74)	38 (59)	3.5 (1.3–9.4)	797 (75)	3.9 (1.0–9.8)	
Older than 10 years old	244 (22)	25 (39)	12.2 (10.5–16.4)	219 (21)	13.7 (10–18)	
As continuous variable	1,129 (100)	64 (100)	6.9 (1.0–16.4)	1,065(100)	4.6 (0.0–18.0)	0.026
WBC at diagnosis						0.0004
WBC <10,000	470 (42)	11 (17)	5.7 (0.7–8.8)	459 (43)	4.1 (0.3–9.9)	
WBC 10,000–50,000	383 (34)	33 (52)	18.6 (10.4–47.6)	350 (33)	21.9 (10.0–49.8)	
WBC 50,000–100,000	127 (11)	11 (17)	65.6 (50.5–92.1)	116 (11)	65.4 (50.0–99.7)	
WBC >100,000	149 (13)	9 (14)	182.6 (126.5–996)	140 (13)	189.9 (100.1–1696.8)	
As continuous variable	1,129 (100)	64 (100)	21.7 (0.7–996)	1,065(100)	13.5 (0.3–1696.8)	0.004
Hb <10 g/dl at diagnosis	949 (84)	38 (59)	6.6 (3.2–9.9)	911 (86)	6.6 (1.4–9.9)	<0.0001
As continuous variable	1,129 (100)	64 (100)	8.9 (3.2–16.0)	1,065 (100)	7.0 (1.4–17.7)	<0.0001
Sex						0.436
Male	640 (57)	33 (52)		607 (57)		
Female	489 (43)	31 (48)		458 (43)		
CNS status at diagnosis						0.369
CNS1	1,020 (90)	59 (92)		961 (90)		
CNS2	47 (4)	2 (3)		45 (4)		
CNS3	26 (2)	3 (5)		23 (2)		
TLP with blasts	22 (2)	0		22 (2)		
Hepatomegaly	625 (55)	37 (58)		588 (55)		0.700
Splenomegaly	479 (42)	27 (42)		452 (42)		1.000

Hb, hemoglobin; TLP, traumatic lumbar puncture; WBC, white blood cell.

About TCF3-PBX1 (+) ALL

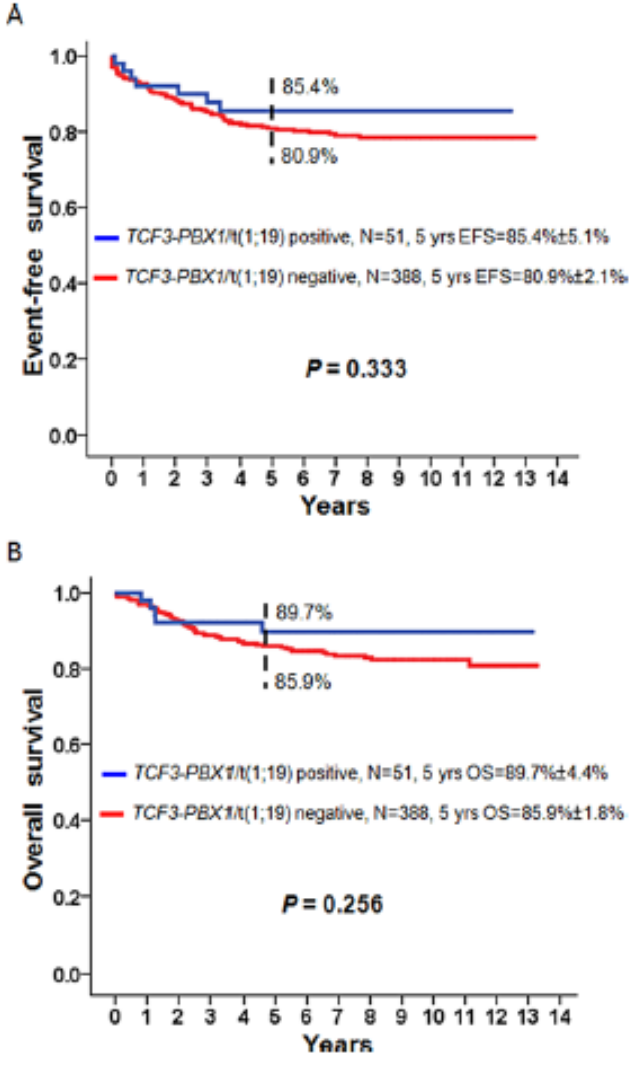


FIGURE 1 Outcome of patients in HR group of childhood B-precursor ALL according to t(1;19) status. (A) 5-year EFS. (B) 5-year OS

About TCF3-PBX1 (+) ALL

TABLE 2 Comparison of treatment outcome and cumulative incidence of relapse rate at 5 years between patients with t(1;19)/*TCF3-PBX1* and those with other B-precursor ALL treated with HR regimen

Status	t(1;19) positive	t(1;19) negative	Odds risk (95% CI)	*P* value
EFS	85.4 ± 5.1% (N = 51)	80.9 ± 2.1% (N = 388)	1.49 (0.66–3.36)	0.333
OS	89.7 ± 4.4% (N = 51)	85.9 ± 1.8% (N = 388)	1.11 (0.53–2.32)	0.256
Cumulative risk				
All relapse	14.6 ± 5.2% (N = 7)	17.3 ± 2.0% (N = 68)	22.9 (10.2–51.6)	0.464
CNS relapse				
Isolated	6.6 ± 3.7% (N = 3)	2.8 ± 0.9% (N = 9)	2.63 (0.69–10.06)	0.160
Any	6.6 ± 3.7% (N = 3)	3.6 ± 1.0% (N = 12)	1.92 (0.52–7.03)	0.324
BM relapse				
Isolated	6.0 ± 3.4% (N = 3)	12.7 ± 1.8% (N = 51)	0.41 (0.124–1.38)	0.146
Any	6.0 ± 3.4% (N = 3)	14.7 ± 1.9% (N = 58)	0.36 (0.11–1.18)	0.089
Isolated testes	2.6 ± 2.6% (N = 1)	0% (N = 0)	NA	0.058
Other combination	0% (N = 0)	0.9 ± 0.5% (N = 3)	NA	0.529
Nonrelapse	83.9 ± 5.2% (N = 44)	82.1 ± 2.2% (N = 314)	0.054 (0.024–0.121)	0.257
Induction failure	0% (N = 0)	1.6 ± 0.6% (N = 6)	NA	0.793

CI, confidence interval; NA, not applicable.

About TCF3-PBX1 (+) ALL

TABLE 3 Comparisons of treatment outcome of children with t(1;19)/*TCF3-PBX1* and other B-precursor ALL subtypes

Genetic alterations	Frequency	5-year EFS	*P* value	5-year OS	*P* value	CI of CNS relapse at 5 years	*P* value	CI of BM relapse at 5 years	*P* value	CI of other types of relapse at 5 years	*P* value
TCF3-PBX1 (64 cases)	5.7%	83.3 ± 4.8%		88.5 ± 4.1%		8.7 ± 3.8%		9.8 ± 3.9%		2.2 ± 2.1%	
MLL-R	3.5%	23.4 ± 6.8%		28.6 ± 7.4%		15.7 ± 9.2%		63.8 ± 9.6%		0.0%	
BCR-ABL1	2.8%	31.8 ± 9.0%		44.7 ± 9.0%		7.8 ± 5.5%		52.9 ± 12.0%		0.0%	
TEL-AML1	17.6%	85.2 ± 3.4%	< 0.0001	92.5 ± 2.6%	< 0.0001	5.8 ± 2.3%	0.021	7.0 ± 2.6%	<0.0001	0.0%	0.505
Hyperdiploid >50	13.8%	84.0 ± 3.1%		93.1 ± 2.1%		4.1 ± 1.8%		9.2 ± 2.6%		3.0 ± 1.5%	
Down Syndrome	0.8%	88.9 ± 10.5%		88.9 ± 10.5%		0%		0%		0%	
Other B-ALL	55.8%	77.3 ± 1.6%		83.5 ± 1.4%		4.7 ± 8.4%		18.8 ± 1.5%		1.0 ± 0.4%	

CI, cumulative incidence.

About TCF3-PBX1 (+) ALL

Results:

- Similar 5-year event-free survival
  - t(1;19)/*TCF3-PBX1* (83.3 ± 4.8%)
  - *TEL-AML1 (85.2 ± 3.4%, P = 0.984)*
  - *hyperdiploidy >50* (84.0 ± 3.1%, *P = 0.748).*
- Cumulative risk of any CNS relapse
  - t(1;19)/*TCF3-PBX1 (8.7 ± 3.8%)*
  - *TEL-AML1 (5.8±2.3%, P=0.749)*
  - *hyperdiploidy (4.1±1.8%, P=0.135), albeit* no significance.

Conclusions:

- With contemporary intensive chemotherapy, children with t(1;19)/*TCF3-PBX1 fared* as well as those with favorable genotypes (*TEL-AML1 or hyperdiploidy).*

About L-asparaginase use

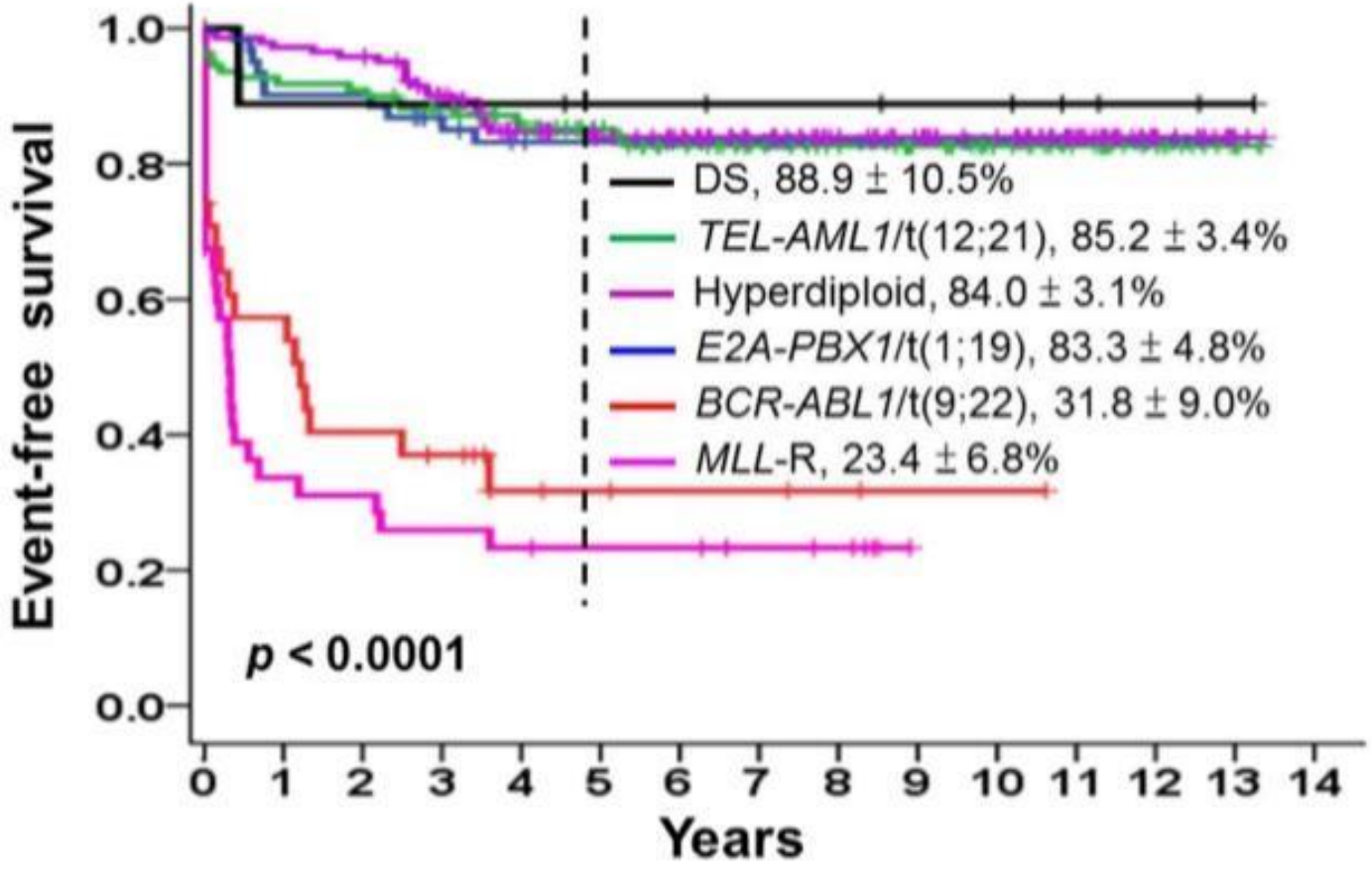
Severe allergy after L-asp

- Severe allergy ➔ shift to Erwinase, or DC
- Incidence: 4.7%
- Survival: no difference in comparison to normal cohort
- Erwinase (>=70%) dose continuation or DC: no difference
- If accumulative dose of L-asp < 50% in DC group: poor

➔ pts who had received >= 50% of scheduled doses of *L*-asparaginase before the development of severe allergic reactions do not need to continue tx with Erwinase.

Report of TPOG-ALL-2002 outcome

Results



Report of TPOG-ALL-2002 outcome

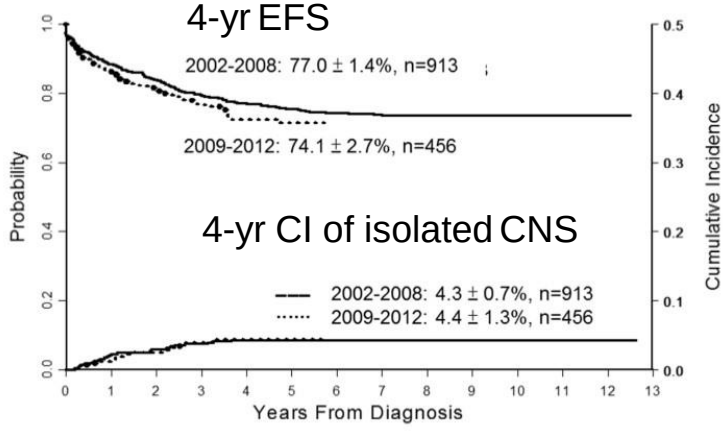
Reinduction x 1 or 2 times in SR group

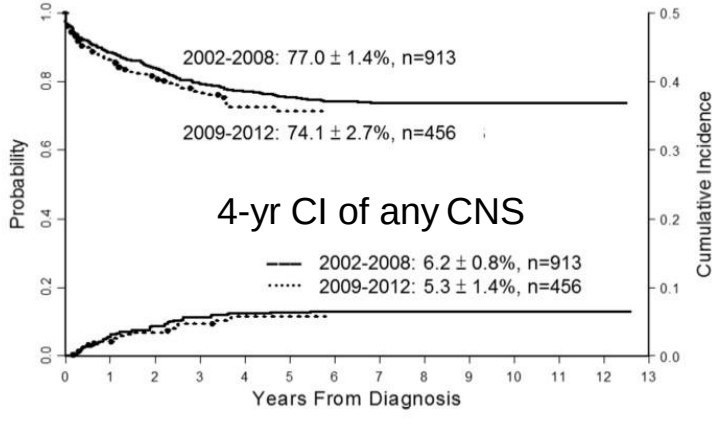
- RI x 1
  - 5-year OS: 91.6 ± 2.1%
  - 5-year EFS: 85.2 ± 2.7%
- RI x 2
  - 5-year OS: 93.7 ± 1.8%
  - 5-year EFS: 89.8 ± 2.3%

Conclusion:

For SR patients, one-course reinduction was adequate. TIT alone successfully prevented CNS relapse.

TIT alone in CNS therapy





Principles of Chemotherapy

Induction

- No dose modifications are planned for prednisolone, asparaginase, or epirubicin therapies during induction. Only acute hemorrhagic pancreatitis or severe coagulopathy resulting in stroke syndrome warrants discontinuation of asparaginase.
- Epirubicin may be delayed in patients with febrile neutropenia, evidence of mucositis or increased hyperbilirubinemia (i.e., total bilirubin $\geq$ 2.0 mg/dl and direct bilirubin > 1.4 mg/dl).

Consolidation Treatment

- When WBC >1500/mm^3, ANC >300/mm^3, platelet count >50,000/mm^3, and renal function is normal, consolidation treatment will be started.
- The subsequent dose of HDMTX, 6-MP and IT will be delayed if WBC < 1,000/mm^3, ANC < 300/mm^3, platelet count < 50,000/mm^3, SGPT > 500U/L, total bilirubin > 2 mg/dl and direct bilirubin > 1.4 mg/dl, mucositis is present, or renal function is abnormal.

Principles of Chemotherapy

Continuation Treatment

- Post-remission continuation treatment begins after the completion of consolidation, provided that the ANC ≥300/mm^3, WBC ≥1500/mm^3 and platelet count ≥50,000/mm^3 as well as no evidence of mucositis.

Reinduction Treatment

- This phase of treatment will be started at weeks 7 and/or 17 if patients have ANC ≥500/mm^3, WBC ≥1500/mm^3, and platelet count ≥50,000/mm^3.

•Note that WBC and ANC counts should be double a week following dexamethasone pulse therapy. If WBC or ANC counts fail to double (indicating low bone marrow reserve), 6-MP and MTX dosages should be reduced to half.

•If WBC or ANC remains the same or is lower, 6-MP and MTX should be held because the patient is at high risk of infection, and blood counts should be repeated in 3 to 4 days to decide if 6-MP can be resumed.

Principles of Intrathecal Chemotherapy

(during induction)

1. All patients will receive triple intrathecal treatment at the disappearance of blast from PB, no later than D10. It is suggested to perform the 2nd TIT with bone marrow evaluation on D15.

2. Patients with any of the following features will receive totally 4 weekly TIT during induction therapy:
   - Philadelphia chromosome
   - *MLL* rearrangement
   - Hypodiploidy (< 44)
   - WBC >100,000/mm3 at presentation
   - T-cell ALL
   - t (1;19)/*E2A-PBX1*

3. Patients with any of the following features will receive TIT twice a week for 2 weeks followed by weekly TIT for 2 weeks (totally 6 TIT during induction therapy):
   - CNS-2 status (<5 WBC/μL of CSF with blasts)
   - CNS-3 status (≥ 5 WBC/ μ L of CSF with blasts or cranial nerve palsy)
   - Traumatic lumbar puncture with blasts

Principles of Intrathecal Chemotherapy

(during induction)

- All diagnostic lumbar punctures will be performed by experienced personnel, preferably under general anesthesia or deep sedation.
- Triple intrathecal chemotherapy (TIT) will be administered immediately after CSF is collected at the disappearance of blast from PB, no later than D10.
- The dosage is age-dependent as following:

Age (months)	Methotrexate (mg)	Hydrocortisone (mg)	Ara-C (mg)	Volume (ml)
<12	6	12	18	6
12-23	8	16	24	8
24-35	10	20	30	10
≥ 36	12	24	36	12

- Leucovorin rescue (5 mg/m^2/dose, max 5 mg) PO will be given at 24 and 30 hours after each triple intrathecal treatment during induction.

Principles of Intrathecal Chemotherapy

(during continuation)

- **SR cases with CNS-1 status**
  - TIT will be given on wks 3, 7, 12, 17, 24, 32, 40, and 48.
  - Total 14 times
- **SR cases with CNS-2 or traumatic CSF with blasts status**
  - TIT will be given on wks 3, 7, 12, 17, 24, 28, 32, 36, 40, 44 and 48.
  - Total 19 times
- **HR cases with CNS-1 status**
  - TIT will be given on wks 7, 12, 17, 24, 28, 32, 36, 40, 44 and 48.
  - Total 16 times

- **Other high/very high-risk cases with WBC ≥ 100,000/mm^3 at presentation, , T-cell ALL, t (1;19)/*E2A-PBX1,*presence of Philadelphia chromosome, *MLL* rearrangement, hypodiploidy <44, CNS-2 or CNS-3 status, or traumatic lumbar puncture with blasts –**
  - TIT will be given on wks 3, 7, 12, 17, 24, 28, 32, 36, 40, 44, 48, 56, 64, 72, 80, 88 and 96.
  - Total 25 times

Principles of Intrathecal Chemotherapy

(during continuation)

- **SR cases with CNS-1 status**
  - TIT will be given on wks 3, 7, 12, 17, 24, 32, 40, and 48.
  - Total 14 times
- **SR cases with CNS-2 or traumatic CSF with blasts status**
  - TIT will be given on wks 3, 7, 12, 17, 24, 28, 32, 36, 40, 44 and 48.
  - Total 19 times
- **HR cases with CNS-1 status**
  - TIT will be given on wks 7, 12, 17, 24, 28, 32, 36, 40, 44 and 48.
  - Total 16 times

- **Other high/very high-risk cases with WBC ≥ 100,000/mm^3 at presentation, , T-cell ALL, t (1;19)/*E2A-PBX1,*presence of Philadelphia chromosome, *MLL* rearrangement, hypodiploidy <44, CNS-2 or CNS-3 status, or traumatic lumbar puncture with blasts –**
  - TIT will be given on wks 3, 7, 12, 17, 24, 28, 32, 36, 40, 44, 48, 56, 64, 72, 80, 88 and 96.
  - Total 25 times

New therapeutic agents for relapsed ALL

Blinatumomab (blincyto)

- 適用於治療先前接受至少兩種化療療程(如TPOG之療程表)**治療無效或已復發第二次**或以上**費城染色體陰性**復發型或頑固型B細胞前驅因子之急性淋巴芽細胞白血病之(Ph(-) Relapse/Refractory B-cell precursor Acute Lymphoblastic Leukemia；Ph(-) B-cell precursor R/R ALL)成人病患，且計畫進行造血幹細胞移植的病人，每位病人**限給付2療程**。

- 須事前審查核准後使用，申請時須檢附完整之造血幹細胞移植計畫，並詳細記載確認捐贈者名單、確認移植之執行醫院及移植前調適治療等資料。

New therapeutic agents for relapsed ALL

Inotuzumab ozogamicin (besponsa)

- 適用於治療患有復發型或頑固型且**CD22為陽性**之B細胞前驅因子之急性淋巴芽細胞白血病(B-ALL)，且計畫進行造血幹細胞移植之**成人**病患。
- 上述成人病患如具**費城染色體陽性(Ph+)**，應至少使用過**兩種**酪胺酸激酶抑制劑**(TKI)藥物治療無效**。
- 每位病人**限給付2療程**，需事前審查核准後使用。申請時需檢附完整之造血幹細胞移植計畫，並詳細記載確認移植之執行醫院及移植前調適治療等資料。
- 不得與blinatumomab（如Blincyto）或酪胺酸激酶抑制劑(TKI)（如imatinib、dasatinib、ponatinib）等併用。

New therapeutic agents for relapsed ALL

Clofarabine（Evoltra）

- 使用於先前接受至少兩種化療療程(如TPOG之療程表)**治療無效或已復發第二次**或以上之急性淋巴母細胞白血病(acute lymphoblastic leukemia)病，且計畫進行造血幹細胞移植的病人**(限21歲以下)**，每位病人限**給付一療程**。

- 須事前審查核准後使用，申請時須檢附完整之造血幹細胞移植計畫，並詳細記載確認捐贈者名單、確認移植之執行醫院及移植前調適治療等資料。

Comparisons

	Clofarabine	Blinatumomab	Inotuzumab ozogamycin
Age	<21 y/o		Adult
Indication	R/R ALL (T/B) (無效或復發第二次ALL)	R/R ALL, CD19+ Ph(-) (無效或復發第二次ALL)	R/R ALL, CD22+ Ph(-)　(復發或頑固) Or Ph(+) fail to TKIs x2
給付次數	1	2	2
附移植資料	YES	YES	YES
備註	cytopenia	Low tumor burden CRS	Hepatotoxicity, VOD CRS
	傳統化療 T/B復發都可 一療程5天	Ph(-) B-ALL, CD19+ MRD低效果較好 連續滴注28天/休14天	B-ALL, CD22+ 限成人　肝毒性 每周一針連三針
	蔡泯/張仁威/張胤麒 林孝宸/尤姵淳/林恩睿	尤姵淳/林恩睿 ~~林孝宸~~	林恩睿？ 林孝宸？

Follow-up

- Postprandial blood sugar, cholesterol, triglyceride, albumin, amylase, and lipase twice every week during L-asparaginase therapy
- Sodium every week in induction therapy (watching for SIADH)
- Chemical profile, if needed, esp. within 48 hours after chemotherapy is started.
- BUN, creatinine, ALT, AST before and after HDMTX
- CBC, DC
- Plasma MTX level and ALT level after HDMTX therapy

Acronym

- ALL: acute lymphoblastic leukemia
- MRD: minimal residual disease
- TIT: triple intrathecal chemotherapy
- HSCT: hematopoietic stem cell transplant
- CSF: craniospinal fluid

Publications

Article

- Hao-Chuan Liu, **Giun-Yi Hung**, **Hsiu-Ju Yen**, Ming-Yun Hsieh, Tzeon-Jye Chiou. Acute Siatica: An Unusual Presentation of Extramedullary Relapse of Acute lymphoblastic Leukemia. *International Journal of Hematology 2007;86:163-165* (SCI)

- **Hsiu-Ju Yen**, Tzeon-Jye Chiou, **Giun-Yi Hung**, Chia-Yau Chang, Ming-Yun Hsieh, Cheng-Hwai Tzeng, Po-Min Chen, Ren-Bin Tang. Long-term mixed full-donor chimerism with dominance reversion after a double-unit cord blood transplant. *European Journal of Haematology 2008;80(4):366-7* (SCI)

- Ting-Yao Wang, ***Hsiu-Ju Yen**, Giun-Yi Hung, Ming-Yun Hsieh, Ren-Bin Tang. A Rare Complication in a Child Undergoing Chemotherapy for Acute Lymphoblastic Leukemia: Superior Sagittal Sinus Thrombosis. *Journal of the Chinese Medical Association 2011;74:183-187* (SCI)

Poster

- **Hsiu-Ju Yen**, Tzeon-Jye Chiou, **Giun-Yi Hung**, Chia-Yau Chang, Ming-Yun Hsieh, Cheng-Hwai Tzeng, Po-Min Chen, Ren-Bin Tang. Donor Lymphocyte Infusion for Prophylaxis and Treatment of Relapse in Pediatric Hematological Malignancies after HSCT: A Single Institution Experience. *XXXIII World congress of International Society of Hematology, Jerusalem, Israel, October 10-13, 2010*

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- **Yen HJ**, Chang WH, **Hung GY** et al. Outcomes Following Discontinuation of E. coli l-Asparaginase Upon Severe Allergic Reactions in Children With Acute Lymphoblastic Leukemia. *Pediatr Blood Cancer. 2016;63(4):665-70.*

- Li MJ, Liu HC, **Yen HJ**, **Hung GY**, et al. Treatment for Childhood Acute Lymphoblastic Leukemia in Taiwan: a Taiwan Pediatric Oncology Group 2002 Study Emphasizing the Optimal Reinduction Therapy and CNS Preventive Therapy without Cranial Radiation. *Pediatr Blood Cancer. 2017;64(2):234-241.*

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- Yeh TC, Liang DC, Hou JY, Jaing TH, Lin DT, Yang CP, Peng CT, Hung IJ, Lin KH, Hsiao CC, Jou ST, Chiou SS, Chen JS, Wang SC, Chang TK, Wu KH, Sheen JM, **Yen HJ**, Chen SH, Lu MY, Li MJ, Chang TT, Huang TH, Chang YH, Chen SH, Yang YL, Chang HH, Chen BW, Lin PC, Cheng CN, Chao YH, Yang SH, Chao YY, Liu HC. Treatment of Childhood Acute Lymphoblastic Leukemia with Delayed First Intrathecal Therapy and Omission of Prophylactic Cranial Irradiation: Results of the Taiwan Pediatric Oncology Group (TPOG)-ALL-2002 Study. *Cancer. 2018 Dec 1;124(23):4538-4547*. doi: 10.1002/cncr.31758. Epub 2018 Oct 10

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Conference Abstract

- Hsi-Che Liu, Ting-Chi Yeh, Tang-Her Jaing, Shih-Hsiang Chen, Chih-Cheng Hsiao, Shih-Chung Wang, Kang-Hsi Wu, Fang-Liang Huang, Shyh-Shin Chiou, **Hsiu-Ju Yen**, Yu-Hsiang Chang, Shu-Huey Chen, Yu-Hua Chao, Shin-Nan Cheng, Jinn-Li Wang, Rong-Long Chen, Chao-Ping Yang, Iou-Jih Hung, Jen-Yin Hou, Ting-Huan Huang, Jiunn-Ming Sheen, Yu-Chieh Chen, Ching-Tien Peng, Pei-Chin Lin, Yu-Mei Liao, Te-Kau Chang, Chien-Hui Hung, Lee-Yung Shih. The Adherence to MRD Time Points Is a Significantly Prognostic Predictor in an MRD-Directed Therapy for Childhood Acute Lymphoblastic Leukemia in Taiwan. *61st ASH Annual Meeting, Orlando, USA, Decmber 1-10, 2019*.
- **Hsiu-Ju Yen**, Neel S. Bhatt, Hesham M. Eissa, Sujuan Huang, Matthew J. Ehrhardt, Nickhill Bhakta, Kirsten K. Ness, Kevin R. Krull, Deo Kumar Srivastava, Leslie L. Robison, Melissa M. Hudson, I-Chan Huang. Patient-reported outcomes in adult survivors of childhood hematopoietic cell transplant: A report from the St. Jude lifetime cohort study. *2019 North Aemrican Sympopsium Late Ccomplications after Childhood Cancer Annual Meeting, Atlanta, USA, June 20-22, 2019.*

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- **Hung GY**, Yu TY, **Yen HJ**, Yang CF, Lin LY, Horng JL. Systemic Epstein-Barr Virus-positive T-Cell Lymphoma of Childhood Presentation with Hemophagocytosis. ***J Pediatr Hematol Oncol. 2019****;41(4):319-20.*
- **Yen HJ**, Hesham M. Eissa, Neel S. Bhatt, Sujuan Huang, Matthew J. Ehrhardt,…. Leslie L. Robison, Melissa M. Hudson, I-Chan Huang. Patient-Reported Outcomes in Survivors of Childhood Hematologic Malignancies with Hematopoietic Stem Cell Transplant. ***Blood. 2020****;135(21):1847-58.*

- Ho WL, **Hung GY, Yen HJ**, ...,, Lin DT. Characteristics and outcomes of second cancers in patients with childhood cancer: A report from the Taiwan Pediatric Oncology Group. ***J Formos Med Assoc. 2021****;18:S0929-6646(21)00227-8.*

- Yang YL, Jaing TH, Chen SH, …**Hung GY, Yen HJ**,..., Liang DC, Chang TT. Treatment outcomes of pediatric acute myeloid leukemia: A retrospective analysis from 1996 to 2019 in Taiwan. ***Sci Rep. 2021****;11(1):5893.*

- Ying-Jung Huang, Hsi-Che Liu, Tang-Her Jaing, Kang-Hsi Wu,.... **Yen HJ**,…Tung-Huei Lin, Lee-Yung Shih. RAS pathway mutation is an added-value biomarker in pediatric Philadelphia-negative B-cell acute lymphoblastic leukemia with IKZF1 deletions. ***Pediatr Blood Cancer. 2021****;68(4):e28899.*

Pediatric ALL Survival Curves at Taipei VGH

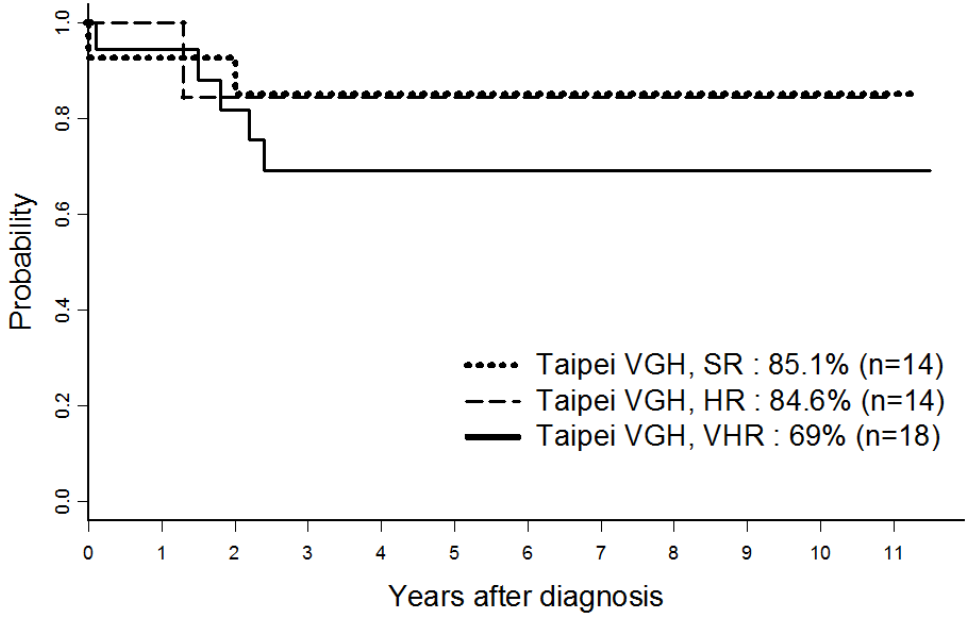

Fig. TPOG-ALL 2002. Overall survivals of patients treated at Taipei VGH by risk groups.

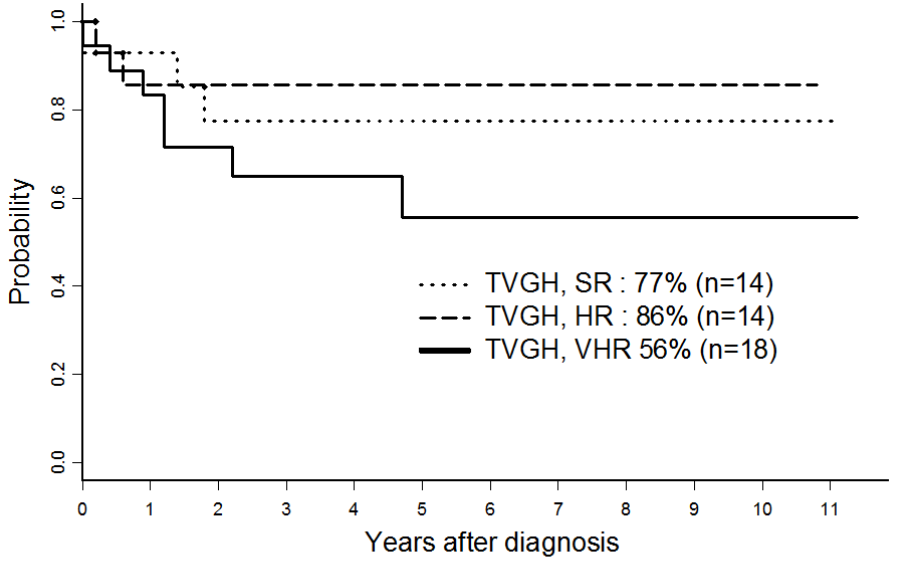

Fig. TPOG-ALL 2002. Event-free survivals of patients treated at Taipei VGH by risk groups.

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- Liang DC, Yang CP, Lin DT, et al. Long-term results of Taiwan Pediatric Oncology Group studies 1997 and 2002 for childhood acute lymphoblastic leukemia. *Leukemia. 2010;24(2):397-405.*