高 雄 榮 民 總 醫 院
急性淋巴性白血病診療原則

2022年02月25日 第一版

兒童癌症醫療團隊擬訂

注意事項：這個診療原則主要作為醫師和其他保健專家診療癌症病人參考之用。假如你是一個癌症病人，直接引用這個診療原則並不恰當，只有你的醫師才能決定給你最恰當的治療。

修訂指引

- 本診療原則依下列參考資料制定版本
  – 台灣兒童癌症研究群(TPOG)
  TPOG-ALL-2021 精簡版(2022-02)

會議討論

上次會議：2021/02/19

本共識與上一版的差異

上一版	新版
1. 依據TPOG ALL-2013 21(2021-01-17)版本修訂急性淋巴性白血病診療指引。	1. TPOG ALL-2013 21預計半年試行及增修其他未盡之處後，再定稿為ALL-2021。主要修改處: (1) steroid在induction phase 的劑量調整; (2)危險群分類標準的修改; (3)6MP劑量調整; (4)對T-ALL及B-ALL,MRD1>5%的病患導入Bortezomib治療; (5)B-ALL,MRD1>1%但<5%者加入一次EI療程; (6)B-ALL,MRD2>0.01%者建議使用blinatumomab (Blincyto)(需健保事審)(Ph+ALL 及infant ALL with *KMT2A-R*(兒癌補助); (7)ETP治療加入venetoclax; (8)加入 ruxolitinib 治療建議：CRLF2-R 及 JAK2-R 或 EPOR-R 者，且於 MRD1 ≥5% or MRD2 ≥1%者 (9)只要有 ABL class chimeric fusions者建議加入dasatinib 治療; (10)TIT執行時間點修改 (11)將另外修訂infant ALL的治療指引

兒癌–ALL

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Risk Classification

Patients are classified into one of three categories (**standard**-, **high**-, or **very high-risk**) based on Presenting age, Leukocyte count, Presence or absence of CNS-3 status or testicular leukemia, Immunophenotype, Cytogenetics and molecular genetics, DNA index, and early response to therapy. Hence, definitive risk assignment will be made after completion of remission induction. therapy. The criteria and the estimated proportion of patients in each category are provided below.

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Criteria for Standard-risk(SR) 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(HR) ALL

1. Other B-ALL patients not meeting standard-risk nor very high-risk criteria.
2. Other T-ALL patients not meeting very high-risk criteria

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Criteria for Very High-risk(VHR) ALL

1. Infants with KMT2A rearrangement:
2. All non-hyperdiploid B-ALL with MRD2 ≥1%.
3. Hyperdiploid B-ALL with MRD2 ≥1% and MRD remaining positive (≥0.01%) after consolidation
4. Re-emergence of leukemic lymphoblasts by MRD (at any level) in patients previously MRD negative (<0.01%)
5. Persistently detectable MRD at lower levels
6. All T-ALL with MRD ≥0.1% after early intensification, no matter the MRD results afterward
7. TCF3-HLF/t(17;19) , BCR-ABL-like, PAXalt, ETV6-RUNX1-like, ZENF384 rearrangement and hypodiploidy

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Criteria for 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

[Dr. D-C Liang personal communication with Dr. Campana]

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Treatment Plans

Summary of Induction/Early Intensification/Consolidation

B-ALL

Pro-Risk	Sub-group	MRD1	Up-grade	Ind II	EOI BM Date	MRD2	Final Risk	Early Inten	Consolidation (HD-MTX)	Continuation, week 1
SR		<0.1%		A	D35-42	<0.01%	**SR**	No	2.5 g/m^2	Reinduction
						0.01-0.99%	**HR**	EI	5.0 g/m^2	Blincyto or reintensification#
						≥1%*	**VHR**	EI+		
		0.1-0.99%		A	D35-42	<0.01%	**SR**	EI	5.0 g/m^2	Reinduction
						0.01-0.99%	**HR**	EI	5.0 g/m^2	Blincyto or reintensification#
						≥1%*	**VHR**	EI+		
		1-4.99%	**HR**	B	D42-46	<0.01%	**HR**	EI	5.0 g/m^2	DEX+EPI+VCR+6MP+ASP
						0.01-0.99%	**HR**	EI	5.0 g/m^2	Blincyto or reintensification#
						≥1%*	**VHR**	EI+		
		≥5%	**HR**	C		<0.01%	**HR**	EI+	5.0 g/m^2	DEX+EPI+VCR+6MP+ASP
						0.01-0.99%	**HR**	EI+	5.0 g/m^2	Blincyto or reintensification#
						≥1%*	**VHR**			

Blincyto, blinatumomab; EOI, end of induction; Ind, induction; Inten, intensification; Pro-risk, provisional risk.

*VHR in Hyperdiploid ALL: MRD2 ≥1% and MRD remaining positive (≥0.01%) after consolidation.

#Reintensification will be given: 1). after consolidation for MRD2 ≥1% (VHR) and 2). after reinduction I for HR patients with MRD ≥0.01% on continuation week 7,

Blincyto 使用期間 dasatinib 需繼續使用，Blincyto 最後 1 天予 TIT。不併用 C/T 及 ruxolitinib。

MRD3 at continuation week 7 for patients with MRD2 ≥0.01%; optional MRD4 for patients who completion of Blincyto or reintensification; further MRD for persistent MRD ≥0.01%.

[Blincyto 後將導致 CD19 消失，後續若仍進行 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。]

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Treatment Plans

B-ALL (continued)

Pro-Risk	Sub-group	MRD1	Ind II	EOI BM Date	MRD2	Final Risk	Early Inten	Consolidation (HD-MTX)	Continuation Week 1
HR		<5%	B	D42-46	<0.01%	**HR**	EI	5.0 g/m^2	DEX+EPI+VCR+6MP+ASP
					0.01-0.99%	**HR**	EI	5.0 g/m^2	Blincyto or reintensification#
					≥1%	**VHR**	EI+		
		≥5%	C	D42-46	<0.01%	**HR**	EI+	5.0 g/m^2	DEX+EPI+VCR+6MP+ASP
					0.01-0.99%	**HR**	EI+	5.0 g/m^2	Blincyto or reintensification#
					≥1%	**VHR**			
	t(9;22)‡	<1%	B	D42-46	<0.01%	**HR**	No	5.0 g/m^2	Blincyto*or DEX+EPI+VCR+6MP+ASP
					0.01-0.99%	**HR**	EI	5.0 g/m^2	Blincyto or reintensification#
					≥1%	**VHR**			
		≥1%	B	D42-46	<0.01%	**HR**	EI	5.0 g/m^2	Blincyto*or DEX+EPI+VCR+6MP+ASP
					0.01-0.99%	**HR**	EI	5.0 g/m^2	Blincyto or reintensification#
					≥1%	**VHR**			
VHR		Any	C	D42-46	Any	**VHR**	EI+	5.0 g/m^2	Blincyto or reintensification#

Blincyto, blinatumomab; EOI, end of induction; Ind, induction; Inten, intensification; Pro-risk, provisional risk.

*For patients with MRD2 <0.01%, Blincyto could be sponsored by CCF。

#Reintensification will be given: 1). after consolidation for MRD2 ≥1% (VHR) and 2). after reinduction I for HR patients with MRD ≥0.01% on continuation week 7.

‡Dasatinib 80 mg/m^2/day will start after Dx and continue to the end of therapy.

Blincyto 使用期間 dasatinib 需繼續使用，Blincyto 最後 1 天予 TIT。不併用 C/T 及 ruxolitinib。

MRD3 at continuation week 7 for patients with MRD2 ≥0.01%; optional MRD4 for patients who completion of Blincyto or reintensification; further MRD for persistent MRD ≥0.01%.

[Blincyto 後將導致 CD19 消失，後續若仍進行 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。]

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Treatment Plans

T-ALL

Pro-Risk	MRD1	Ind II	EOI BM Date	MRD2	Risk	Early Inten	MRD3 (D65-70)	Final Risk	Tx options
Non-ETP	Any	C	D42-46	<0.01%	HR	EI+	No	**HR**	
				≥0.01%	HR	EI+	<0.01%	**HR**	
							0.01-0.99%	**HR**	Dasatinib plus C/T or Nelarabine-based or HD-Ara-C-based
							≥0.1%	**VHR**	
ETP	Any	C	D42-46	<0.01%	HR	EI+	<0.01%	**HR**	
							0.01-0.99%	**HR**	V-EI
							≥0.1%	**VHR**	
				≥0.01%	HR	V-EI	<0.01%	**HR**	
							0.01-0.99%	**HR**	V-EI
							≥0.1%	**VHR**	

EOI, end of induction; ETP, early T precursor; Ind, induction; Inten, intensification; Pro-risk, provisional risk。

MRD3 after EI/EI+ for patients with MRD2 ≥0.01% and all ETP; further MRD for persistent MRD ≥0.01%。

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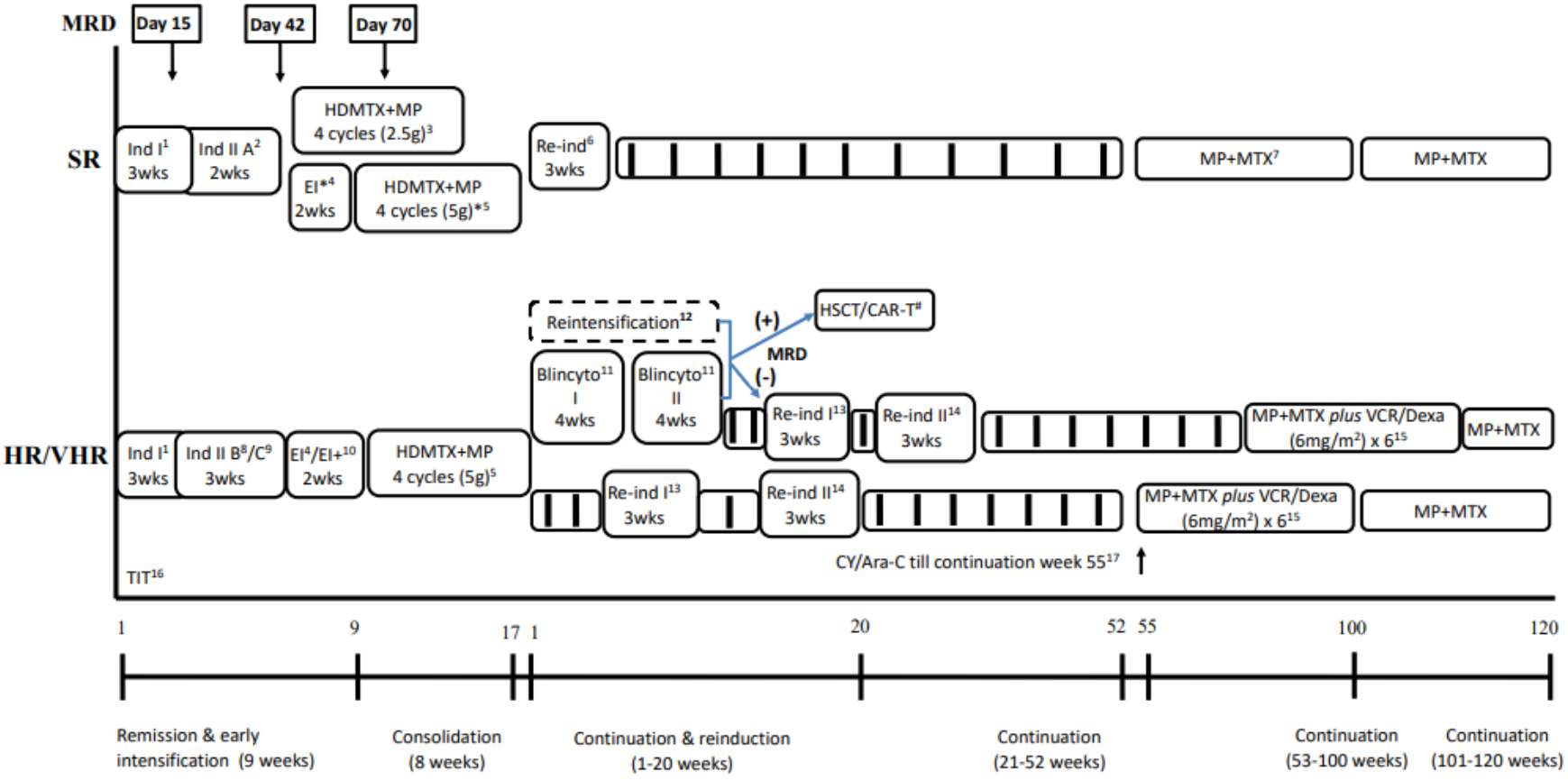
Treatment Plans

Schema of TPOG-ALL-2021, B-ALL



5. SR revisions

A. Final SR with MRD1 0.1-1% & MRD2 <0.01%

(1). Addition of 1 cycle of EI (CY/Ara-C/Asp)

(2). 5 g/m^2 MTX, not 2.5 g/m^2 in consolidation

B. Final SR

(1). Move reinduction treatment immediate to the end of consolidation to reduce the risk of allergic reaction to asparaginase

(2). Omission of pulse-therapy of VCR/Dexa after 1-year of continuation therapy

6. HR revisions

A. MRD1 <5%

(1). Addition of 1 cycle of Induction II-B (CY/Ara-C/6MP/Asp)

(2). Addition of 1 cycle of EI (CY/Ara-C/Asp)

B. MRD1 ≥5%

(1). Addition of 1 cycle of Induction II-C (CY/Ara-C/6MP/Asp plus Bortezomib)

(2). Addition of 1 cycle of EI+ (CY/Ara-C/Asp plus Bortezomib)

C. Final HR

(1). Omission of the courses of CY/Ara-C after week 55 in HR/VHR (as St. Jude Total 17)

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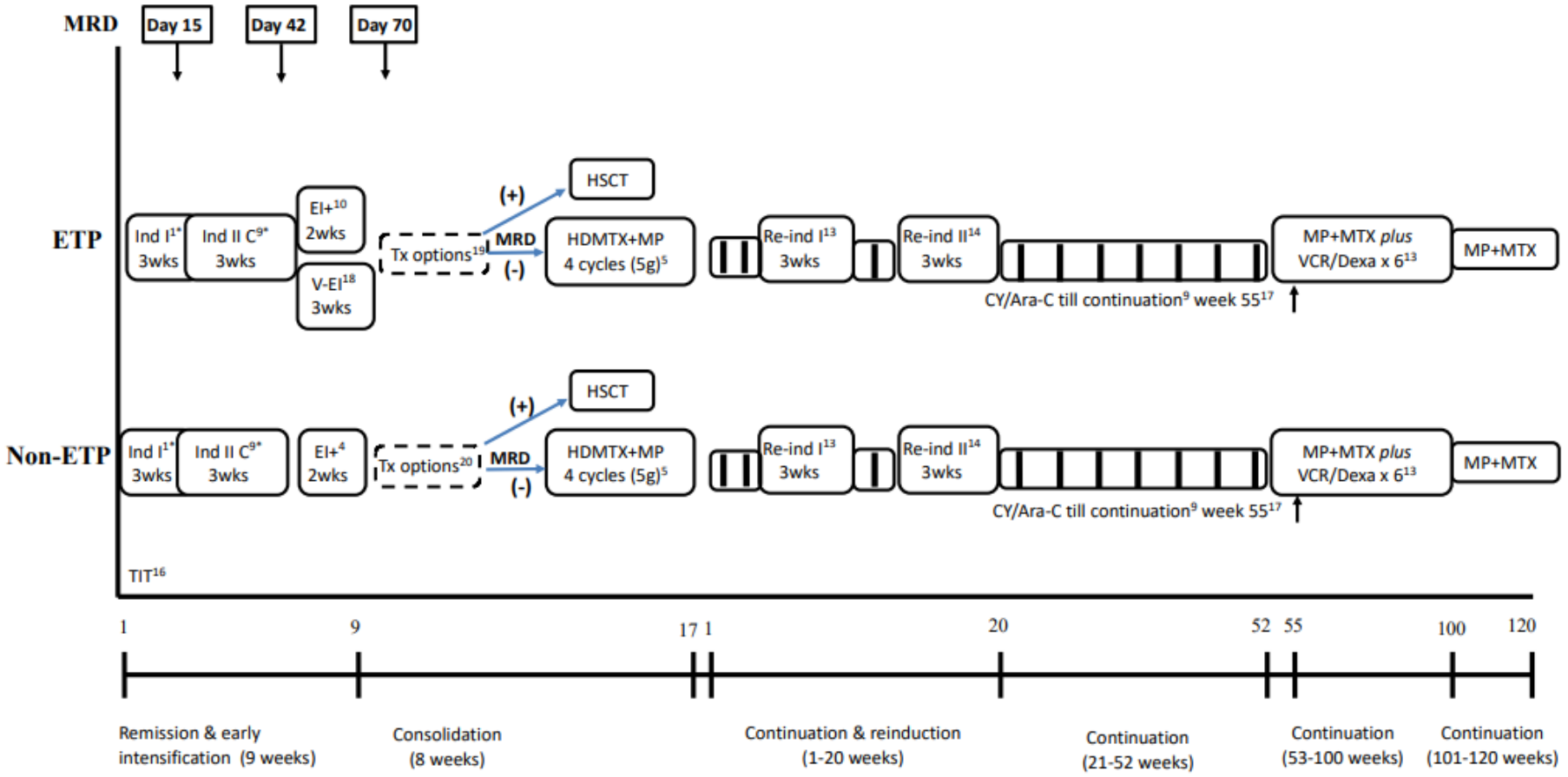
Schema of TPOG-ALL-2021, T-ALL



8. T-ALL revisions

A. Any MRD1

(1). Addition of 1 cycle of Induction II-C (CY/Ara-C/6MP/Asp plus Bortezomib)

B. MRD2

(1). ETP with MRD2 ≥0.01%: Addition of 1 cycle of V-EI (Venetoclax/VCR/Dexa/Asp)

(2). All other T-ALL: Addition of 1 cycle of EI+ (CY/Ara-C/Asp plus Bortezomib)

C. HSCT should be considered for all T-ALL with MRD3 (after EI/EI+) ≥0.1%

8. T-ALL revisions

A. Any MRD1

(1). Addition of 1 cycle of Induction II-C (CY/Ara-C/6MP/Asp plus Bortezomib)

B. MRD2

(1). ETP with MRD2 ≥0.01%: Addition of 1 cycle of V-EI (Venetoclax/VCR/Dexa/Asp)

(2). All other T-ALL: Addition of 1 cycle of EI+ (CY/Ara-C/Asp plus Bortezomib)

C. HSCT should be considered for all T-ALL with MRD3 (after EI/EI+) ≥0.1%

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7. Ph+ALL revisions

A. Ph+ALL is not designated as provisional VHR

B. Dasatinib will be given ASAP after Dx of Ph+ALL and continue to the end of therapy

C. In consolidation, dasatinib should be held 24 hours before start of infusion and until clearance of MTX

D. MRD1 <1%

(1). Addition of 1 cycle of Induction II-B (CY/Ara-C/6MP/Asp)

E. MRD1 ≥1%

(1). Addition of 1 cycle of Induction II-B (CY/Ara-C/6MP/Asp)

(2). Addition of 1 cycle of EI (CY/Ara-C/Asp)

7. Ph+ALL revisions

A. Ph+ALL is not designated as provisional VHR

B. Dasatinib will be given ASAP after Dx of Ph+ALL and continue to the end of therapy

C. In consolidation, dasatinib should be held 24 hours before start of infusion and until clearance of MTX

D. MRD1 <1%

(1). Addition of 1 cycle of Induction II-B (CY/Ara-C/6MP/Asp)

E. MRD1 ≥1%

(1). Addition of 1 cycle of Induction II-B (CY/Ara-C/6MP/Asp)

(2). Addition of 1 cycle of EI (CY/Ara-C/Asp)

9. Ph-like ALL (Mar. 2021 修改)：

A. 加入 ruxolitinib 治療建議：*CRLF2-R* 及 *JAK2-R* 或 *EPOR-R* 者，且於 MRD1 ≥5% or MRD2 ≥1%者，可申請 compassionate use。The dose is 50 mg/m^2/dose PO BID (max 200 mg/day), 2 weeks on and 2 weeks off, starting on the day of Early Intensification。

B. 加入 dasatinib 治療建議：patients with ABL class chimeric fusions (e.g., *ABL1, ABL2, CSF1R, PDGFRA or PDGFRB*) are known to be responsive to dasatinib. The dose is 80 mg/m^2/day, starting on the day when the aberration is identified regardless of MRD level. 實務上，可依 MRD 結果申請健保事前審查。

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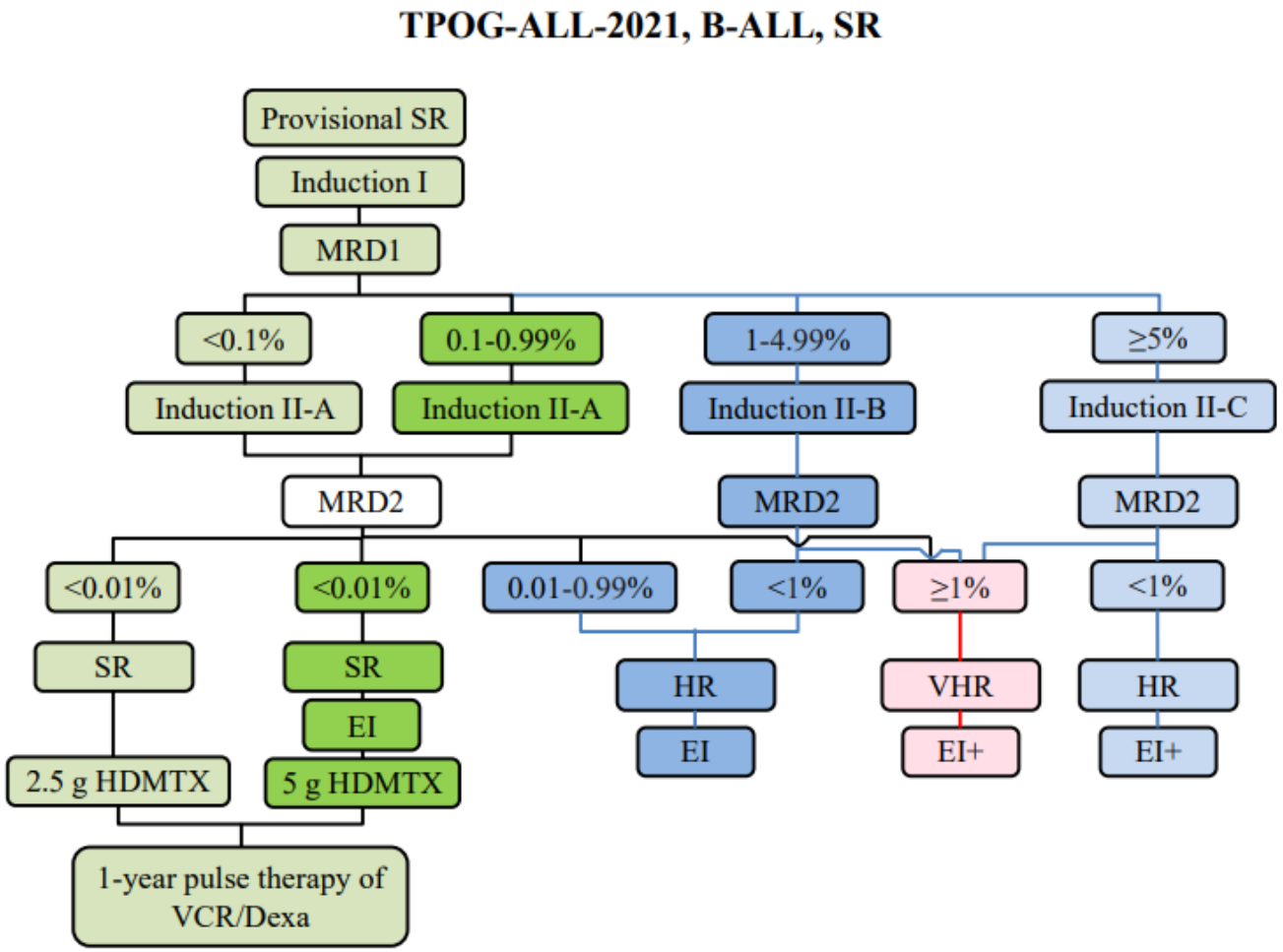
Treatment Plans

◎Schema of TPOG-ALL-2021精簡版



Treatment Plans

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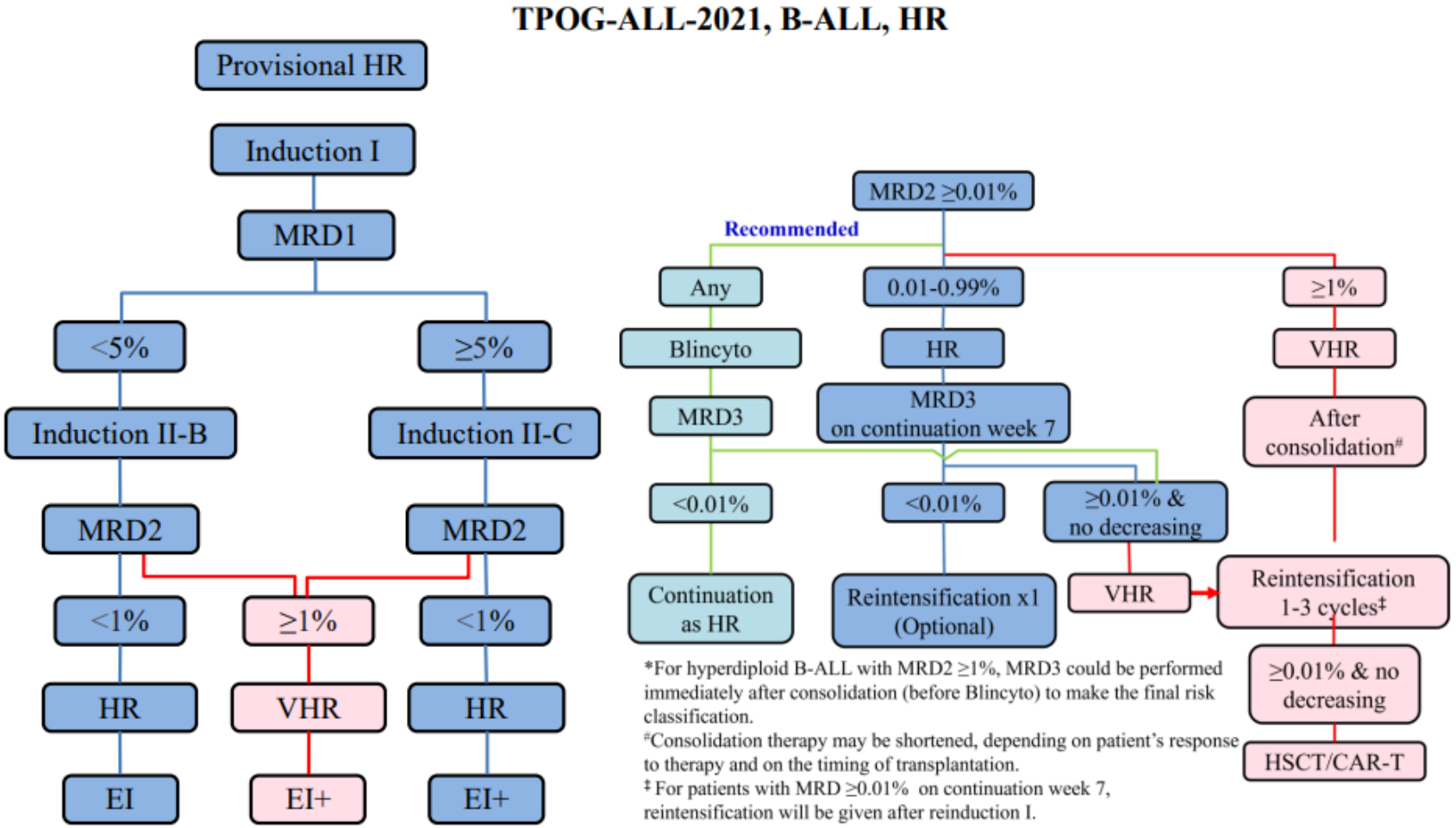
◎Schema of TPOG-ALL-2021精簡版



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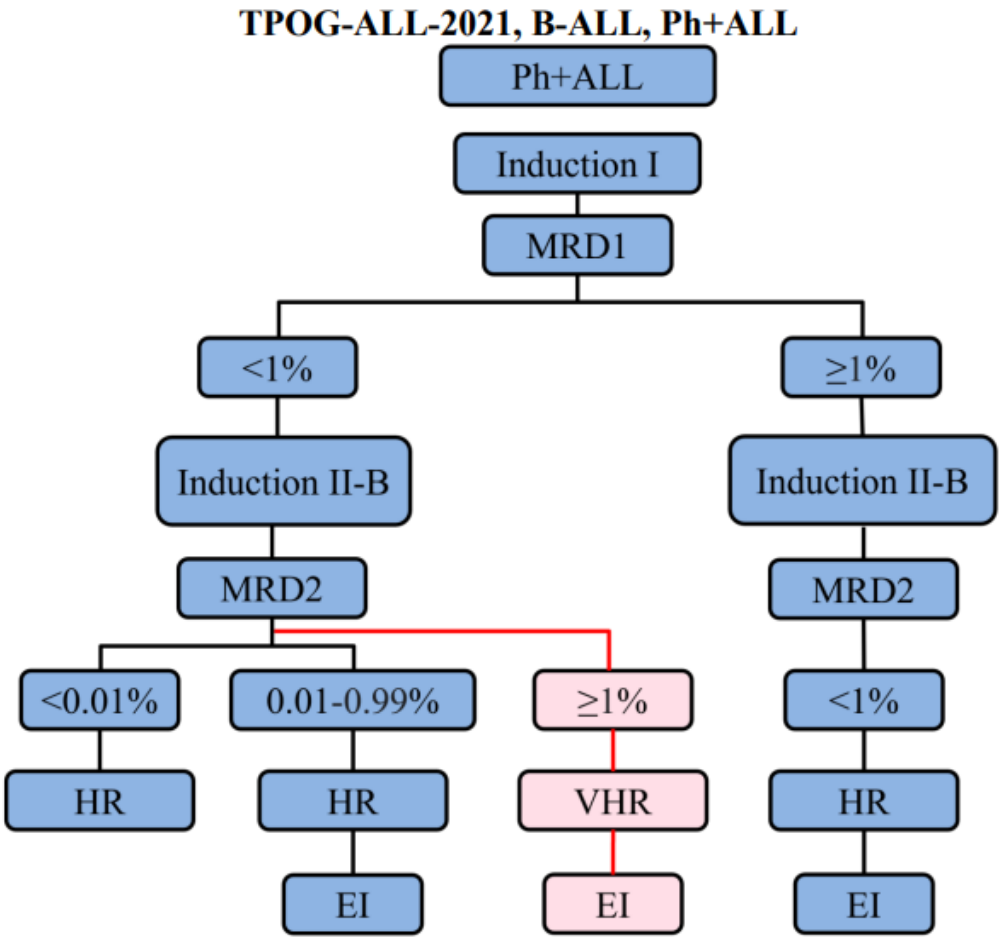
◎Schema of TPOG-ALL-2021精簡版



Dasatinib 80 mg/m²/day will start after Dx and continue to the end of therapy.

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Treatment Plans

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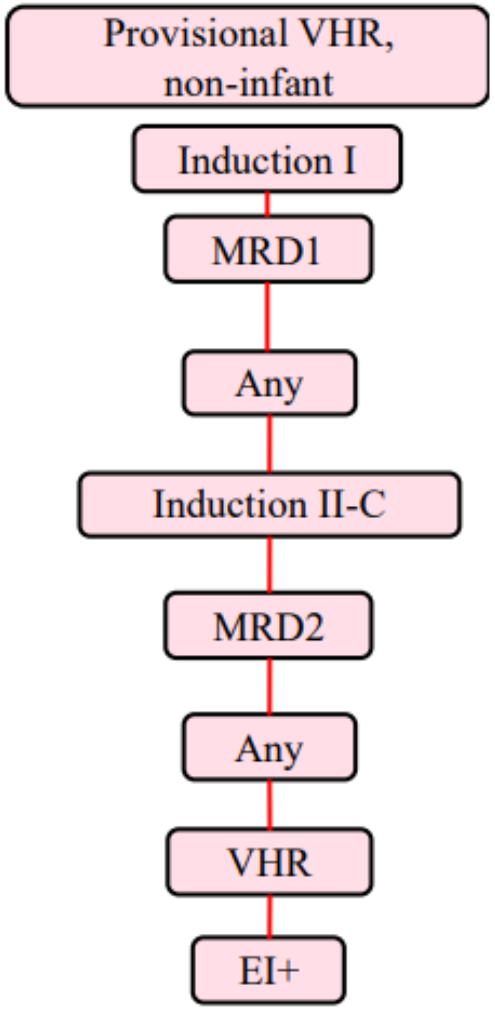
◎Schema of TPOG-ALL-2021精簡版

TPOG-ALL-2022, B-ALL, VHR



Treatment Plans

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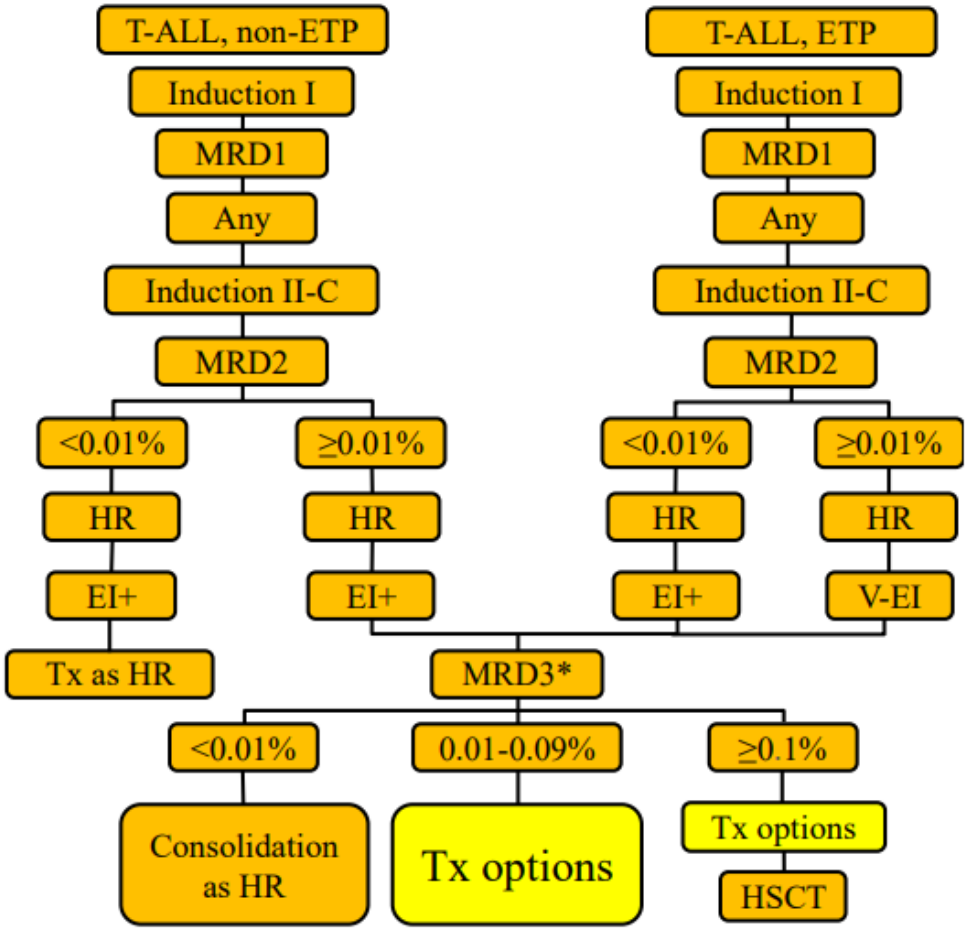
◎Schema of TPOG-ALL-2021精簡版



Tx options

ETP: V-EI

Non-ETP:

1. Dasatinib if drug sensitivity could be confirmed.
2. Nelarabine-based therapy
3. High-dose Ara-C-based

MRD3* for all ETP & non-ETP with MRD2 ≥0.01%

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Treatment Plans

◎Induction I (1-3 weeks)

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Induction I (first 3 weeks) for B-ALL

Wk 1	Day1 PRED VCR EPI TIT*	Day2 PRED	Day3 PRED L-ASP (1)	Day4 PRED	Day5 PRED L-ASP (2)	Day6 PRED	Day7 PRED L-ASP (3)
Wk 2	Day8 PRED VCR EPI#	Day9 PRED	Day10 PRED L-ASP (4)	Day11 PRED	Day12 PRED L-ASP (5)	Day13 PRED	Day14 PRED L-ASP (6)
Wk 3	Day15 PRED VCR TIT **BMA,** **MRD1**	Day16 PRED	Day17 PRED L-ASP (7)	Day18 PRED	Day19 PRED L-ASP (8)	Day20 PRED	Day21 PRED L-ASP (9)

*Delayed TIT until the disappearance of blast from PB, but no later than D10.
#The second dose of epirubicin on day 8 may be delayed in SR patients who has cleared circulating blasts and has severe neutropenia, or in any risk group patient who is sick with infection. The second dose of epirubicin could be omitted in SR with MRD1 <0.1%; but it is suggested to be given on weeks 3/4 in SR with MRD1 ≥0.1%.

Agent	Dosage and Route	# Doses	Schedule
Prednisone (PRED)	40/60 mg/m^2/day, PO (tid)	84	Days 1-28
Vincristine (VCR)	1.5 mg/m^2 (max 2), IV	3	Days 1, 8, 15
Epirubicin (EPI)	20 mg/m^2, IV	2	Days 1, 8#
L-asparaginase (ASP)	6,000 U/m^2, IM	9	Days 3, 5, 7, 10, 12, 14, 17, 19, 21
Dasatinib‡	80 mg/m^2/day	Daily	Starting after Dx
Triple intrathecal therapy (TIT)			Days 1*, 15

PRED: 40 mg/m^2/day for SR and 60 mg/m^2/day for HR.
‡For Ph+ALL.

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Treatment Plans

Induction II-A

BCP-ALL
-SR, MRD1 <1%

Induction II-A for B-ALL

	Day22	Day23	Day24	Day25	Day26	Day27	Day28
Wk 4	PRED VCR	PRED	PRED	PRED	PRED	PRED	PRED
Wk 5	Day29 PRED Taper	Day30 PRED Taper	Day31 PRED Taper	Day32 PRED Taper	Day33 PRED Taper	Day34 PRED Taper	Day35 PRED Taper

Agent	Dosage and Route	# Doses	Schedule
Prednisone (PRED)*	40/60 mg/m^2/day, PO (tid)	84	Days 1-28
Vincristine (VCR)	1.5 mg/m^2 (max 2), IV	1	Day 22

*40 mg/m^2/day for SR and 60 mg/m^2/day for HR.

兒癌–ALL

Treatment Plans

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Induction II-B

BCP-ALL
- **t(12;21)/HD ≥1%**
- **Other SR, MRD1 1-5%**
- **HR, MRD1 <5%**
- ***Dasatinib for Ph+ALL**

Induction II-B for B-ALL

Wk 4	Day22	Day23	Day24	Day25	Day26	Day27	Day28
	PRED VCR	PRED	PRED L-ASP (10)	PRED	PRED L-ASP (11)	PRED	PRED L-ASP (12)
Wk 5	Day29	Day30	Day31	Day32	Day33	Day34	Day35
	PRED Taper CY MP	PRED Taper Ara-C MP	PRED Taper Ara-C MP	PRED Taper Ara-C MP	PRED Taper Ara-C MP	PRED Taper MP	PRED Taper MP
Wk 6	Day36	Day37	Day38	Day39	Day40	Day41	Day42
	MP	Ara-C MP	Ara-C MP	Ara-C MP	Ara-C MP	MP	MP

Agent	Dosage and Route	# Doses	Schedule
Prednisone (PRED)*	40/60 mg/m^2/day, PO (tid)	84	Days 1-28
Vincristine (VCR)	1.5 mg/m^2 (max 2), IV	1	Day 22
L-asparaginase (ASP)	6,000 U/m^2 IM	3	Days 24, 26, 28
Cyclophosphmide (CY)	1,000 mg/m^2 IV 1 hr	1	Day 29‡
Cytarabine (Ara-C)	75 mg/m^2/dose IV 30 mins, QD	8	Days 30-33, 37-40
6-mercaptopurine (MP)	30 mg/m^2/dose	14	Days 29-42
Dasatinib#	80 mg/m^2/day	Daily	Starting after Dx

*40 mg/m^2/day for SR and 60 mg/m^2/day for HR.
#For Ph+ALL.
‡Suggested criteria to start D29 C/T:

- WBC ≥1000/mm^3 with ANC ≥300/mm^3. G-CSF is suggested if the treatment is delayed.
- Following Day 29 treatment, cytarabine and mercaptopurine may be delayed or omitted (after Day 35) if patient develops febrile neutropenia or Grade 3 or 4 mucositis.
- Doses may be completely omitted if the patient is beyond Day 35 of remission induction (i.e., 50% or more doses of mercaptopurine and cytarabine have been given), to allow early bone marrow recovery, on-time (Days 42-46) bone marrow examination, MRD detection and early initiation of continuation therapy or early intensification therapy.

兒癌–ALL

Treatment Plans

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Induction II-C (=Induction B *plus* Bort) for B-ALL

Wk 4	Day22	Day23	Day24	Day25	Day26	Day27	Day28
	PRED VCR	PRED	PRED L-ASP (10)	PRED	PRED L-ASP (11)	PRED	PRED L-ASP (12)
Wk 5	Day29	Day30	Day31	Day32	Day33	Day34	Day35
	PRED Taper CY MP	PRED Taper Ara-C MP Bort (1)	PRED Taper Ara-C MP	PRED Taper Ara-C MP	PRED Taper Ara-C MP Bort (2)	PRED Taper MP	PRED Taper MP
Wk 6	Day36	Day37	Day38	Day39	Day40	Day41	Day42

Agent	Dosage and Route	# Doses	Schedule
Prednisone (PRED)*	40/60 mg/m^2/day, PO (tid)	84	Days 1-28
Vincristine (VCR)	1.5 mg/m^2 (max 2), IV	1	Day 22
L-asparaginase (ASP)	6,000 U/m^2 IM	3	Days 24, 26, 28
Cyclophosphmide (CY)	1,000 mg/m^2 IV 1 hr	1	Day 29#
Cytarabine (Ara-C)	75 mg/m^2/dose IV 30 mins, QD	4	Days 30-33
6-mercaptopurine (MP)	30 mg/m^2/dose	7	Days 29-35
Bortezomib (Bort)	1.3 mg/m^2 IV	2	Days 30, 33

*40 mg/m^2/day for SR and 60 mg/m^2/day for HR.
#Suggested criteria to start D29 C/T:

- WBC ≥1000/mm^3 with ANC ≥300/mm^3. G-CSF is suggested if the treatment is delayed.

兒癌-ALL

Treatment Plans

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Induction II-C (=Induction B *plus* Bort) for B-ALL

Wk 4	Day22	Day23	Day24	Day25	Day26	Day27	Day28
	PRED VCR	PRED	PRED L-ASP (10)	PRED	PRED L-ASP (11)	PRED	PRED L-ASP (12)
Wk 5	Day29	Day30	Day31	Day32	Day33	Day34	Day35
	PRED Taper CY MP	PRED Taper Ara-C MP Bort (1)	PRED Taper Ara-C MP	PRED Taper Ara-C MP	PRED Taper Ara-C MP Bort (2)	PRED Taper MP	PRED Taper MP
Wk 6	Day36	Day37	Day38	Day39	Day40	Day41	Day42

Agent	Dosage and Route	# Doses	Schedule
Prednisone (PRED)*	40/60 mg/m^2/day, PO (tid)	84	Days 1-28
Vincristine (VCR)	1.5 mg/m^2 (max 2), IV	1	Day 22
L-asparaginase (ASP)	6,000 U/m^2 IM	3	Days 24, 26, 28
Cyclophosphmide (CY)	1,000 mg/m^2 IV 1 hr	1	Day 29#
Cytarabine (Ara-C)	75 mg/m^2/dose IV 30 mins, QD	4	Days 30-33
6-mercaptopurine (MP)	30 mg/m^2/dose	7	Days 29-35
Bortezomib (Bort)	1.3 mg/m^2 IV	2	Days 30, 33

*40 mg/m^2/day for SR and 60 mg/m^2/day for HR.

#Suggested criteria to start D29 C/T:

- WBC ≥1000/mm^3 with ANC ≥300/mm^3. G-CSF is suggested if the treatment is delayed.

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Induction I (first 3 weeks) for T-ALL

Wk 1	Day1	Day2	Day3	Day4	Day5	Day6	Day7
	DEXA VCR EPI TIT*	DEXA	DEXA L-ASP (1)	DEXA	DEXA L-ASP (2)	DEXA	DEXA L-ASP (3)
Wk 2	Day8	Day9	Day10	Day11	Day12	Day13	Day14
	DEXA VCR EPI	DEXA	DEXA L-ASP (4)	DEXA	DEXA L-ASP (5)	DEXA	DEXA L-ASP (6)
Wk 3	Day15	Day16	Day17	Day18	Day19	Day20	Day21
	DEXA VCR TIT BMA, MRD1	DEXA	DEXA L-ASP (7)	DEXA	DEXA L-ASP (8)	DEXA	DEXA L-ASP (9)

Agent	Dosage and Route	# Doses	Schedule
Dexamethasone Dexa)#	10/8 mg/m^2/day, PO (tid)	63	Days 1-21
Vincristine (VCR)	1.5 mg/m^2 (max 2), IV	3	Days 1, 8, 15
Epirubicin (EPI)	20 mg/m^2, IV	2	Days 1, 8
L-asparaginase (ASP)	6,000 U/m^2, IM	9	Days 3, 5, 7, 10, 12, 14, 17, 19, 21
TIT			Days 1*, 15

*Delayed TIT until the disappearance of blast from PB, but no later than D10.
#Dexa: 10 mg/m^2/day for age<10; 8 mg/m^2/day for age ≥10

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Treatment Plans

Induction II-C for T-ALL

Wk 4	Day22	Day23	Day24	Day25	Day26	Day27	Day28
	DEXA Taper VCR TIT	DEXA Taper	DEXA Taper L-ASP (10)	DEXA Taper	DEXA Taper L-ASP (11)	DEXA Taper	DEXA Taper L-ASP (12)
Wk 5	Day29	Day30	Day31	Day32	Day33	Day34	Day35
	CY MP TIT	Ara-C MP Bort (1)	Ara-C MP	Ara-C MP	Ara-C MP Bort (2)	MP	MP
Wk 6	Day36	Day37	Day38	Day39	Day40	Day41	Day42

Agent	Dosage and Route	# Doses	Schedule
Dexamethasone (Dexa)*	10/8 mg/m^2/day, PO (tid)	63	Days 1-21
Vincristine (VCR)	1.5 mg/ m^2 (max 2), IV	1	Day 22
L-asparaginase (ASP)	6,000 U/m^2 IM	3	Days 24, 26, 28
Cyclophosphmide (CY)	1,000 mg/m^2 IV 1 hr	1	Day 29#
Cytarabine (Ara-C)	75 mg/m^2/dose IV 30 mins, QD	4	Days 30-33
6-mercaptopurine (MP)	30 mg/m^2/dose	7	Days 29-35
Bortezomib (Bort)	1.3 mg/m^2 IV	2	Days 30, 33
TIT	Age-dependent	2	Days 22, 29

*Dexa: 10 mg/m^2/day for age<10; 8 mg/m^2/day for age ≥10

#Suggested criteria to start D29 C/T:

- WBC ≥1000/mm^3 with ANC ≥300/mm^3. G-CSF is suggested if the treatment is delayed.

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Treatment Plans

Induction II-C for T-ALL

Wk 4	Day22 DEXA Taper VCR TIT	Day23 DEXA Taper	Day24 DEXA Taper L-ASP (10)	Day25 DEXA Taper	Day26 DEXA Taper L-ASP (11)	Day27 DEXA Taper	Day28 DEXA Taper L-ASP (12)
Wk 5	Day29 CY MP TIT	Day30 Ara-C MP Bort (1)	Day31 Ara-C MP	Day32 Ara-C MP	Day33 Ara-C MP Bort (2)	Day34 MP	Day35 MP
Wk 6	Day36	Day37	Day38	Day39	Day40	Day41	Day42

Agent	Dosage and Route	# Doses	Schedule
Dexamethasone (Dexa)*	10/8 mg/m^2/day, PO (tid)	63	Days 1-21
Vincristine (VCR)	1.5 mg/ m^2 (max 2), IV	1	Day 22
L-asparaginase (ASP)	6,000 U/m^2 IM	3	Days 24, 26, 28
Cyclophosphmide (CY)	1,000 mg/m^2 IV 1 hr	1	Day 29#
Cytarabine (Ara-C)	75 mg/m^2/dose IV 30 mins, QD	4	Days 30-33
6-mercaptopurine (MP)	30 mg/m^2/dose	7	Days 29-35
Bortezomib (Bort)	1.3 mg/m^2 IV	2	Days 30, 33
TIT	Age-dependent	2	Days 22, 29

*Dexa: 10 mg/m^2/day for age<10; 8 mg/m^2/day for age ≥10

#Suggested criteria to start D29 C/T:

- WBC ≥1000/mm^3 with ANC ≥300/mm^3. G-CSF is suggested if the treatment is delayed.

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Treatment Plans

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Early Intensification *plus* (EI+)

Wk 8	Day50	Day51	Day52	Day53	Day54	Day55	Day56
	CY TIT	Ara-C Bort (1)	Ara-C L-ASP (1)	Ara-C	Ara-C L-ASP (2) Bort (2)		L-ASP (3)
Wk 9	Day57	Day58	Day59	Day60	Day61	Day62	Day63
		Ara-C	Ara-C	Ara-C	Ara-C		

Agent	Dosage and Route	# Doses	Schedule
Cyclophosphmide (CY)	1,000 mg/m^2 IV 1 hr	1	Day 50
Cytarabine (Ara-C)	75 mg/m^2/dose IV 30 mins, QD	8	Days 51-54, 58-61
L-asparaginase (ASP)	6,000 U/m^2 IM	3	Days 52, 54, 56
TIT		1	Day 50
Bortezomib (Bort)	1.3 mg/m^2 IV	2	Days 51, 54

Suggested criteria to start EI+:
Day 50 chemotherapy can be given earlier if the patient has early count recovery (WBC ≥1,500/mm^3 with ANC ≥300/mm^3 or APC ≥500/mm^3, and platelet count ≥75 x 10^9/L). G-CSF is suggested if the treatment is delayed.

Venetoclax-Early Intensification (V-EI)

Agent	Dosage and Route	# Doses	Schedule
Vincristine	1.5 mg/m^2 /day (max 2), IV	2	Days 1, 15
Dexamethasone	8 mg/m^2 /day		Days 1-8, 15-21
Venetoclax	240 mg/m^2	21	Days 1-21
L-asparaginase	6,000 U/m^2 IM	6	Days 8, 10, 12, 15, 17, 19

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Treatment Plans

◎選擇induction II的A,B或C及Blincyto的使用建議請參閱下表

BCP-ALL

Pro-Risk	Subgroup	MRD1	Up-grade	Ind II	EOI BM Date	MRD2	Final Risk	Early Inten	Consolidation (HD-MTX x 4)	Continuation Week 1
SR	t(12;21)/HD	<1%		A	D35-42	<0.01%	SR	No	2.5 g/m²	
	t(12;21)/HD	<1%		A	D35-42	≥0.01%	HR	No	5.0 g/m²*	2 cycles of Blincyto
	t(12;21)/HD	≥1%	HR	B	D35-46	<0.01%	HR	No	5.0 g/m²	
	t(12;21)/HD	≥1%	HR	B	D35-46	≥0.01%	HR	No	5.0 g/m²	2 cycles of Blincyto
	Others	<1%		A	D35-42	<0.01%	SR	No	2.5 g/m²	
	Others	<1%		A	D35-42	0.01-0.99%	HR	No	5.0 g/m²	2 cycles of Blincyto
	Others	<1%		A	D35-42	≥1%	VHR	Yes	5.0 g/m²*	2 cycles of Blincyto
	Others	1-5%	HR	B	D35-46	<0.01%	HR	No	5.0 g/m²	
	Others	1-5%	HR	B	D35-46	0.01-0.99%	HR	No	5.0 g/m²	2 cycles of Blincyto
	Others	1-5%	HR	B	D35-46	≥1%	VHR	Yes	5.0 g/m²	2 cycles of Blincyto
	Others	≥5%	HR	C	D35-46	<0.01%	HR	Yes	5.0 g/m²	
	Others	≥5%	HR	C	D35-46	0.01-0.99%	HR	Yes	5.0 g/m²	2 cycles of Blincyto
	Others	≥5%	HR	C	D35-46	≥1%	VHR	Yes	5.0 g/m²	2 cycles of Blincyto
HR		<1%		B	D35-46	<0.01%	HR	No	5.0 g/m²	
		<1%		B	D35-46	0.01-0.99%	HR	No	5.0 g/m²	2 cycles of Blincyto
		<1%		B	D35-46	≥1%	VHR	Yes	5.0 g/m²	2 cycles of Blincyto
		1-5%		B	D35-46	<0.01%	HR	No	5.0 g/m²	
		1-5%		B	D35-46	0.01-0.99%	HR	No	5.0 g/m²	2 cycles of Blincyto
		1-5%		B	D35-46	≥1%	VHR	Yes	5.0 g/m²	2 cycles of Blincyto
		≥5%		C	D35-46	<0.01%	HR	Yes	5.0 g/m²	
		≥5%		C	D35-46	0.01-0.99%	HR	Yes	5.0 g/m²	2 cycles of Blincyto
		≥5%		C	D35-46	≥1%	VHR	Yes	5.0 g/m²	2 cycles of Blincyto
VHR	t(9;22)	<1%		B+Dasa	D35-46	<0.01%	VHR	No	5.0 g/m²	2 cycles of Blincyto#
		<1%		B+Dasa	D35-46	≥0.01%	VHR	No	5.0 g/m²	2 cycles of Blincyto
		≥1%		B+Dasa	D35-46	<0.01%	VHR	Yes	5.0 g/m²	2 cycles of Blincyto#
		≥1%		B+Dasa	D35-46	≥0.01%	VHR	Yes	5.0 g/m²	2 cycles of Blincyto
	Infant with *KMT2A*-R	Any		C	D35-46	Any	VHR	Yes	5.0 g/m²	2 cycles of Blincyto#

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Treatment Plans

◎Induction (5-7weeks)

T-ALL

Pro-Risk	Subgroup	MRD1	Up-grade	Ind II	EOI BM Date	MRD2	Final Risk	Early Inten	Consolidation (HD-MTX x 4)
Non-ETP		<1%		C	D35-46	<0.01%	HR	No	5.0 g/m^2*
		<1%		C	D35-46	0.01-0.99%	HR	No	5.0 g/m^2
		<1%		C	D35-46	≥1%	VHR	No	5.0 g/m^2
		≥1%		C	D35-46	<0.01%	HR	Yes	5.0/m^2
		≥1%		C	D35-46	0.01-0.99%	HR	Yes	5.0 g/m^2
		≥1%		C	D35-46	≥1%	VHR	Yes	5.0 g/m^2
ETP		Any		C	D35-46	Any	VHR	Yes	5.0 g/m^2

Blincyto, blinatumomab; MRD2(+)之 BCP-ALL，且通過健保事前審查者，建議於 continuation 第 1 周即開始使 Blincyto.

Dasa, dasatinib; EOI, end of induction; HD, hyperdiploidy; KMT2A-R, KMT2A-rearrangement; Ind, induction; Inten, intensification, Pro-risk; provisional risk

*If MRD (+), the provisional standard-risk case will then be classified as high-risk or very high-risk accordingly, and will receive subsequent 3 doses of HDMTX at a higher dosage (i.e., 5 gm/m^2). (These cases would have received the first HDMTX of consolidation therapy at 2.5 gm/m^2)

For patients with MRD2 (-), the Blincyto could be sponsored by TPOG.

兒癌-急性淋巴性白血病

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Treatment Plans

◎Induction (5-7weeks)

For infant with *MLL+*

Agent	Dosage and Route	Doses	Schedule
Clofarabine	25 mg/m^2/day, 2-hour IV infusion	5	Days 22-26
Etoposide	100 mg/m^2/day, 2-hour IV infusion	5	Days 22-26
Cyclophosphamide	300 mg/m^2/day, 1-hour IV infusion	5	Days 22-26

Day 22 Vincristine will be omitted for infants with MLL+

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Treatment Plans

Summary of Intrathecal Therapy on TPOG-ALL-2021 (紅字為與 TPOG-ALL-2013 不同之處)

		Induction/Early intensification		Consolidation		Continuation Week 1-20		Continuation Weeks 21-120		All Phases
Risk-group	CNS Status	Days	Total	Days	Total	Weeks	Total	Weeks	Total	**Total**
SR	CNS-1	#, 15	2	1, 15, 29, 43	4	1, 6, 11, 16	4	24, 32, 40, 48	4	**14**
SR with MRD1, 0.1-0.99%	CNS-1	#, 15, 43	3	1, 15, 29, 43	4	1, 6, 11, 16	4	24, 32, 40, 48	4	**15**
SR with ≥100 x 10^9/L	CNS-1	#, 8, 15, 22	4	1, 15, 29, 43	4	1, 6, 11, 16	4	24, 28, 32, 36, 40, 44, 48	7	**19**
SR	CNS-2 or TLP with blasts	#, 8, 15, 22	4	1, 15, 29, 43	4	1, 6, 11, 16	4	24, 28, 32, 36, 40, 44, 48	7	**19**
HR/VHR	CNS-1	#, 15, 29, 50	4	1, 15, 29, 43	4	7, 12, 17	3	24, 28, 32, 36, 40, 44, 48	7	**18**
HR/VHR	CNS-2, CNS-3 or TLP with blasts	#, 8, 11, 15, 22, 29, 50	7*	1, 15, 29, 43	4	3, 7, 12, 17	4	24, 28, 32, 36, 40, 44, 48, 56, 64, 72, 80, ~~88, 96~~	11	**26**
Other HR/VHR with ≥100 x 10^9/L, T-ALL, t(1;19), Ph+, hypodiploidy <44	CNS-1	#, 8, 15, 22, 29, 50	6	1, 15, 29, 43	4	3, 7, 12, 17	4	24, 28, 32, 36, 40, 44, 48, 56, 64, 72, 80, ~~88, 96~~	11	**25**

#The first TIT will be performed after the disappearance of blasts from peripheral blood by 10 days of induction therapy. But, exception remained for patients presenting with cranial nerve palsy or other evidence of CNS disease, lumbar puncture and first TIT will be initiated on the day of Dx.

* TIT twice a week for 2 weeks followed by weekly TIT for 2 weeks (totally 6 TITs during induction therapy):

Abbreviations: SR, standard-risk; HR, high-risk; VHR, very high-risk; TLP, traumatic lumbar puncture

Treatment Plans

◎IT Chemotherapy During Induction Treatment

Leucovorin rescue (5 mg/m2/dose, max 5 mg) PO will be given at 24 and 30 hours after each triple intrathecal treatment during induction.
Follow plasma methotrexate levels (starting 24 hours after intrathecal therapy and until level becomes undetectable) in patients with renal dysfunction or extra fluid in third space, and rescue with leucovorin.

It is also important to correct hypertension and to prevent constipation during remission induction because patients with these features are at high risk of seizure (posterior reversible encephalopathy syndrome). Avoid syndrome of inappropriate antidiuretic hormone secretion from vincristine treatment.

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Treatment Plans

Consolidation (TPOG ALL-2021 SR, HR, VHR)

Wk 1	Day1	Day2	Day3	Day4	Day5	Day6	Day7
	MTX 6-MP TIT	6-MP	6-MP	6-MP	6-MP	6-MP	6-MP
Wk 2	Day8	Day9	Day10	Day11	Day12	Day13	Day14
	6-MP	6-MP	6-MP	6-MP	6-MP	6-MP	6-MP
Wk 3	Day15	Day16	Day17	Day18	Day19	Day20	Day21
	MTX 6-MP TIT	6-MP	6-MP	6-MP	6-MP	6-MP	6-MP
Wk 4	Day22	Day23	Day24	Day25	Day26	Day27	Day28
	6-MP	6-MP	6-MP	6-MP	6-MP	6-MP	6-MP
Wk 5	Day29	Day30	Day31	Day32	Day33	Day34	Day35
	MTX 6-MP TIT	6-MP	6-MP	6-MP	6-MP	6-MP	6-MP
Wk 6	Day36	Day37	Day38	Day39	Day40	Day41	Day42
	6-MP	6-MP	6-MP	6-MP	6-MP	6-MP	6-MP
Wk 7	Day43	Day44	Day45	Day46	Day47	Day48	Day49
	MTX 6-MP TIT	6-MP	6-MP	6-MP	6-MP	6-MP	6-MP
Wk 8	Day50	Day51	Day52	Day53	Day54	Day55	Day56
	6-MP	6-MP	6-MP	6-MP	6-MP	6-MP	6-MP

SR	HR/VHR
MTX 2.5 g/m^2 IV drip Days 1, 15, 29, 43	MTX 5 g/m^2 IV drip Days 1, 15, 29, 43
6-MP 40 mg/m^2/day Days 1-56	6-MP 40 mg/m^2/day Days 1-56
TIT Days 1, 15, 29, 43 (8-12 hrs before HDMTX)	TIT Days 1, 15, 29, 43 (8-12 hrs before HDMTX)

Suggested criteria to start consolidation:

- WBC ≥1,500/mm^3 with ANC ≥300/mm^3 or APC ≥500/mm^3, and platelet count ≥75 x 10^9/L).

Dasatinib should be held 24 hours before start of infusion and until clearance of MTX. (~5 days)

Treatment Plans

◎ Consolidation Treatment(8 weeks)

Leucovorin rescue

Leucovorin, 15 mg/m2 (IV or PO) for high-/very high-risk or 10 mg/m2 (PO or IV) for standard-risk cases, will be started at 42 hours after the start of methotrexate and repeated every 6 hours for a total of three doses. The dosage of leucovorin will be increased in patients with high plasma methotrexate concentrations (>1.0μM at 42 hours) and continued until the methotrexate concentration is less than 0.10μM. Additional measures, such as hydration, hemoperfusion, or carboxypeptidase will be considered in patients with 42-hour methotrexate levels > 10μM. Patients with a history of delayed Grade 3 or 4 gastrointestinal toxicity with prior methotrexate or a history of typhlitis with any chemotherapy should have leucovorin continue for 5, rather than 3 doses; those with early toxicity should have leucovorin begin at 36 hours with subsequent methotrexate; if toxicity recurs, the baseline leucovorin dosage should also be increased.

Blood counts should be followed after high-dose methotrexate twice weekly; 6-MP dose should be reduced to half dose (20 mg/m2/day) if WBC is between 1000 to 1500/mm3, and should be held if WBC is less than 1000/mm3.

Avoid the use of concomitant Bactrim or penicillin during high-dose methotrexate treatment because they will delay methotrexate clearance.

*Alternatively, monitoring of MTX levels (starting at 30 hrs) and leucovorin rescue regimen can follow the guidelines of TPOG-ALL-2002 Protocol. Please give adequate prehydration and bolus NaHCO3 before the infusion of high-dose MTX.

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Treatment Plans

Continuation Therapy of SR

Weeks 1-3: Reinduction for SR

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
Epirubicin	30 mg/m^2	1	Day 1
L-asparaginase	6,000 U/m^2/thrice weekly IM	9	Days 3, 5, 7, 10, 12, 14, 17, 19, 21
TIT	Age-dependent	1	Day 1

Week 4 to end of therapy

Agent	Dosage and Route
6-mercaptopurine (6MP)	50 mg/m^2 PO daily x 7 days, Days 1-7
Methotrexate (MTX)	40 mg/m^2 IV or IM, Day 1
Vincristine (VCR)*	2.0 mg/m^2 IV push (max. 2 mg), Day 1
Dexamethasone (Dexa)*	8 mg/m^2 PO daily (tid) x 5 days, Days 1-5
TIT	Age-dependent

*Omission of VCR/Dexa pulse after 1-year of continuation

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Treatment Plans

Reintensification: Regimen-A

Agent	Dosage and Route	Doses	Schedule
Dexamethasone	20 mg/m^2/day PO or IV (t.i.d)	18	Days 1-6
Cytarabine	2 grams/m^2, 3-hour IV q12 hrs	4	Days 1-2
Etoposide	100 mg/m^2, 1-hour IV q12 hrs	5	Days 3-5
L-asparaginase	25,000iu/m^2 IM	1	Day 6
TIT	Age-dependent	1	Day 5

Reintensification: Regimen-B

Agent	Dosage and Route	Doses	Schedule
Clofarabine	25 mg/m^2/day, 2-hr IV infusion	5	Days 1-5
Etoposide	100 mg/m^2/day, 2-hr IV infusion	5	Days 1-5
Cyclophosphamide	300 mg/m^2/day, 30-60 minute IV	5	Days 1-5
Dexamethasone	8 mg/m^2/day PO daily (tid)	15	Days 1-5

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Treatment Plans

Continuation therapy of HR/VHR

Weeks 1 to 6 and 10 to 16

Agent	Dosage and Route
Dexamethasone (Dexa)	12 mg/m^2 PO daily (tid) x 5 days, Days 1-5
Epirubicin (EPI)	30 mg/m^2 IV, Day 1
Vincristine (VCR)*	2.0 mg/m^2 IV push (max. 2 mg), Day 1
6-mercaptopurine (6MP)	40 mg/m^2 PO daily x 7 days, Days 1-7
L-asparaginase (ASP)	10,000 U/m^2 IM, Day 1
Methotrexate (MTX)	40 mg/m^2 IV or IM, Day 1
Dasatinib#	80 mg/m^2/day

Reinduction I for HR/VHR

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
TIT	Age-dependent	1	Day 1
Dasatinib#	80 mg/m^2/day		

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Treatment Plans

Reinduction II for HR/VHR

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
TIT	Age-dependent	1	Day 1
Dasatinib#	80 mg/m^2/day		

Continuation Therapy: week 21 to end of therapy

Agent	Dosage and Route
6-mercaptopurine (6MP)	50 mg/m^2 PO daily x 7 days, Days 1-7
Methotrexate (MTX)	40 mg/m^2 IV or IM, Day 1
Vincristine (VCR)*	2.0 mg/m^2 IV push (max. 2 mg), Day 1
Dexamethasone (Dexa)*	12 mg/m^2 PO daily (tid) x 5 days, Days 1-5, at the first year; 6 mg/m^2 PO daily (tid) x 5 days, Days 1-5, at the 2nd year
Cyclophosphamide (CY)‡	300 mg/m^2 IV, Day 1
Cytarabine(Ara-C)‡	300 mg/m^2 IV, Day 1
TIT	Age-dependent
Dasatinib#	80 mg/m^2/day till the end of therapy

*VCR/Dexa pulse will be decreased from q4 wks to q8 wks after 1-year of continuation. Dexa will be decreased to 6 mg/m^2 at the 2nd year of continuation

#For Ph+ALL

‡Omission of CY/Ara-C after continuation week 55

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DROP OFF CRITERIA

1.Incorrect diagnosis.
2.Patient and/or parents refuse to allow additional therapy.
3.A patient who, in the judgement of the Principal Investigator, could not or did not follow the assigned treatment, may be removed from study.
4.Patients who fail to meet all eligibility requirements of protocol (i.e., ineligible) will be taken off study, e.g., using other protocols, or not newly diagnosed patients.

癌症藥物停藥準則

骨髓及血液檢查，腫瘤有復發或變大情況，應停止或改變治療方式。