中山醫學大學附設醫院

兒童非何杰金氏淋巴瘤診療指引

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本臨床指引參考TPOG與兒童癌症多專科醫療團隊編修

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一、目的

TPOG 為提昇國內兒童 non-Hodgkin's lymphoma (NHL)之治療成績。參考其他國家的兒童 NHL 治療原則：針對不同之 histology (或 immunophenotype)及 stage，或特定的 subtypes, 給與不同之治療方案，以期達到最好的療效及最少的毒性。因而制定 TPOG NHL 2010 Protocols for Childhood Non-Hodgkin's Lymphomas in Taiwan。(備註: TPOG : Taiwan Pediatric Oncology Group)

二、背景

TPOG-NHL 98 protocols 自 1998 年推出，用於治療國內兒童 NHL，至今已 12 年餘。世界各地兒童 NHL 之治療成績在過去一、二十年的大幅進步，大家有目共睹。TPOG-NHL98 protocols (分 T-LBL for lymphoblastic lymphoma (LBL)及 B-NHL for Burkitt' s lymphoma (BL)，diffuse large B-cell lymphoma (DLBCL), and anaplastic large-cell lymphoma (ALCL))皆 based on NHL BFM 86/90 protocols.後來 BFM group 又推出 NHL-BFM95 protocols，在 2005 年以後已發表大規模治療結果，不僅 BFM group (德、奧、瑞士)，還有其他世界各地兒癌中心用 modified BFM 95 protocols 之成果，也都陸續被發表。

新一代 BFM-04 protocols 目前仍在收案中，但也已有 preliminary report。2009 年 3 月在新加坡舉行的 St. Jude Viva Forum 主題為 childhood NHL，2009 年 6 月在德國 Frankfurt 舉行的第三屆 childhood, adolescent, and young adult (CAYA) NHL 之會議，都發表了有關兒童及青少年 NHL 的最新資訊。

歐美兒童 NHL 治療之 world leaders: 法國 C. Patte, 德國 A. Reiter 及 NY Columbia Prof. Cairo 代表美國 COG 等皆有與會。而大型 international multicenter study results 最具代表性的 FAB/LMB 96, BFM95 等之結果全部出爐，ALCL99 randomized studies for ALCL 也 closed 並發表結果。Rituximab (anti-CD20)在成人 DLBCL 已 routine 與化療合併使用，但在兒童 B- cell NHL 之角色仍在研究中。

1.兒童癌症基金會對於新的淋巴癌治療方案(based on NHL BFM 95)之依據：

(1)治療成果最好的是 mature B-cell lymphoma (BL, DLBCL), 但排除 PMBL (primarymediastinal large B-cell lymphoma). 不論是 FAB/LMB (法、美、英及 BFM 除外之歐洲國家) 或 BFM group, overall survival 皆在九成左右，其中 localized disease 之 survival 在 95%以上，stage III/IV 80-90%, 最差的 CNS disease 也在 75%以上。我們本用 BFM based protocols,既然 FAB/LMB 與 BFM 成績沒有差別，仍用 BFM 就好，只是改用 BFM 95 based. Risk grouping 及一些用藥上 BFM 95 與 BFM 90 有一些改變，risk groups 分 R1-R4, stage 以外, LDH 是很重要之 criteria.

(2) PMBL 是 mature B-cell lymphoma 中比較不同的，用 children's protocols 治療結果較其他 B-NHL 差，可用 CHOP based protocol 加上 Rituximab, 或用 DA-EPOCH-R 6-8cycles 對 PMBL 效果也很好，可減少對 radiation 之需求性；而加用 R(Rituximab) 似有改善治療結果。(備住:According to TPOG 2010-NHL protocol)

(3)治療成果最好的是 mature B-cell lymphoma (BL、DLBCL)，但排除 PMBL (primary mediastinal large B-cell lymphoma)。不論是 FAB/LMB (法、美、英及 BFM 除外之歐洲國家) 或 BFM group, overall survival 皆在九成左右，其中 localized disease 之 survival 在 95%以上，stage III/IV 80-90%, 最差的 CNS disease 也在 75%以上。

(4) Risk grouping 及一些用藥上 BFM 95 與 BFM 90 有一些改變，risk groups 分 R1-R4, stage 以外, LDH 是很重要之 criteriam。

(5)PMBL 是 mature B-cell lymphoma 中比較不同的, 用 children's protocols 治療結果較其他 B-NHL 差, 可用 CHOP based protocol 加上 Rituximab, 或用 DA-EPOCH-R 6-8cycles 對 PMBL 效果也很好，可減少對 radiation 之需求性；而加上 Rituximab 一起使用，似有改善治療結果。

(6)TPOG-NHL 98 用 B-NHL K1-K3 治療 ALCL, 而 based on BFM 90 之 "K" protocol for ALCL 之 ALCL 99protocol 近年來 enrolled 大量歐洲及日本兒童及青少年 ALCL 病患，已有相當有結論性的 randomized results:比較兩種 MTX 用法及劑量, MTX 3g/m2 over 3 hours and no IT，沒有增加 CNS disease, 3h-infusion toxicities 也比 1g/m2 24hr-infusion 較低:有加用 maintenance weekly vinblastine for 1 year 比沒有使用者，可延後復發,但兩年之存活率並沒有增加；不過可用於治療復發病例。

(7) ALCL 以外之 peripheral NK/T cell lymphomas (PTCL)，subtypes 很多，成人與兒童不同，東西方差異也大，在兒童 PTCL 各 subtype 個案數都算少，大規模之治療結果分析根本沒有，CHOP based or T-NHL protocols 都有人用，也有報告須用 HSCT。

(8)PTLD (post-transplant lymphoproliferative disease)，多為 EBV(+)、CD20(+) mature B-cell lymphoma，尤其多為 DLBCL 輕者，停用免疫抑制劑即可，有用 Rituximabmonotherapy 就可緩解的，或用 B-NHL protocols with or without Rituximab。

(9)Rasburicase (recombinant urate oxidase) 0.1-0.2mg/kg/d day 0 – max. 5 doses, nonalkaline hydration.對預防或治療 acute tumor lysis syndrome 非常有效，在 high risk patients (advanced stage Burkitt's lymphoma with high tumor burden and pre-existing hyperuricemia or renal dysfunction)是首選，大大減少了以往此類

病患血液透析之需求性，而提高治癒率。

(9)復發或頑抗之 B-cell lymphoma 可用 R-ICE (ifosphomaide, carboplatin, etoposide,Rituximab), followed by autologous transplant. 一般而言 BL or LBL 復發後預後差，存活率只 10-30% DLBCL or ALCL 則可達 50%，PMLBL or other rare subtypes 約 25-40%. 無論哪一種 lymphoma,在復發後若要以 SCT 為 consolidation 最重要的是要先想法達到 stable 2nd CR。以 HSCT 為 salvage therapy, auto 和 allo 差不多， 但 LBL 除外，在 LBL allo 比 auto 好得多。

(10) St. Jude or Murphy staging system for childhood NHL 自 1980 起對兒童血液科醫師一直是非常有用之依據，但二、三十年來生物資訊之更新如此之大，此 staging system 想必有需要 revision 之處。經過數度專家集會研商的結果，發現此分期系統仍可沿用，唯須稍微做些修改。

三、治療前評估項目

1.初步評估

(1)History and physical examination
(2)Complete blood counts
(3)Liver and renal serum chemistries include serum LDH and uric acid
(4)Bone marrow examination (aspiration / biopsy)
(5)Cerebrospinal fluid examination
(6)Chest x-ray
(7)Abdominal Sono (include liver/spleen, kidneys, abdomen and pelvis)
(8)Bone scan
(9)Gallium scan (optional, preferred in bone disease

2.進階檢查

(1)Cytochemical and immunological evaluation of ascites or pleural fluid
(2)Chest CT scan (if CxR findings are abnormal or suspiciously abnormal)
(3)Abdominal CT scan (can be waived if ultrasound is adequate)
(4)Head and neck CT scan or MRI (for head and neck primaries)
(5)Dental evaluation in patients with Burkitt' s lymphoma
(6)PET scan (more useful for response and residual disease evaluation)

四、預後因素

1.Stage III
2.Stage IV
3.Stage IV with CNS involvement: worst prognosis
4.LDH＞1000 U/L
5.Uric Acid＞7.1μg/dl
(備註: According to Manual of Pediatric Hematology and Oncology)

五、分類

1.Lymphoblastic lymphoma (T-cell or precursor B-cell type)
2.Burkitt's or Burkitt's-like lymphoma
3.Diffuse large B-cell lymphoma
4.Anaplastic large cell lymphoma (irrelevant of immunophenotype)with CD30-positive
5.Primary mediastinal large B-cell lymphoma (PMBL)
6.Immunodeficiency related/ Post-transplantation lymphoma (PTLD)
7.Post-Transplantation Lymphoproliferative Disease (PTLD) withCD20-positive

六、分期

Stage I

A single tumor (extranodal) or involvement of a single anatomical area (nodal) with the exclusion of the mediastinum and abdomen.

Stage II

1.A single tumor (extranodal) with regional node involvement.
2.Two or more nodal areas on the same side of the diaphragm.
3.Two single (extranodal) tumors, with or without regional node involvement on the same side of the diaphragm.
4.A primary gastrointestinal tract tumor (usually in the ileocecal area) with or without involvement of associated mesenteric nodes that is completely resectable.

Stage III

1.Two single tumors (extranodal) on opposite sides of the diaphragm.
2.Two or more nodal areas above and below the diaphragm.
3.Any primary intrathoracic tumor (mediastinal, pleural, or thymic).
4.Extensive primary intraabdominal disease.
5.Any paraspinal or epidural tumor whether or not other sites are involved.

Stage IV

Any of the above with initial involvement of the central nervous system bone marrow or both

七、Stratification of Treatment by NHL Subtypes

1.TPOG 10 T-LBL (based on NHL-BFM 95 protocols)

2.TPOG 10 B-NHL (based on NHL-BFM 95 protocol)

3.TPOG 10 ALCL (based on EICNHL-ALCL99 protocol)

4.TPOG 10 PMBLa & TPOG 10 PMBLb (choose one)

5.TPOG 10 PTLD

八、治療原則

Classifications	Treatment protocols
Lymphoblastic Lymphoma (T-cell or precursor B-cell type)	**TPOG 10 T-LBL** **TPOG 10 T-LBL a for Stage I / Stage II cases** **TPOG 10 T-LBL b for Stage III / Stage IV cases**
Burkitt's lymphoma Diffuse large B-cell lymphoma	TPOG 10 B-NHL
Anaplastic large cell lymphoma (irrelevant of immunophenotype) with CD30+	TPOG 10 ALCL
Primary mediastinal large B-cell lymphoma	TPOG 10 PMBL a & TPOG 10 PMBL b (choose one)
Post-Transplantation Lymphoproliferative Disease (PTLD) with CD20+	TPOG 10 PTLD

(備註:According to TPOG-NHL 2010)

TPOG 10 T-LBL(based on NHL-BFM 95 protocols)

Patient Eligibility:

1.Lymphoblastic Lymphoma (T-cell or precursor B-cell type)

Treatment Plan:

1.Arm a (TPOG 10 T-LBLa) for Stage I / Stage II cases

2.Arm b (TPOG 10 T-LBLb) for Stage III / Stage IV cases

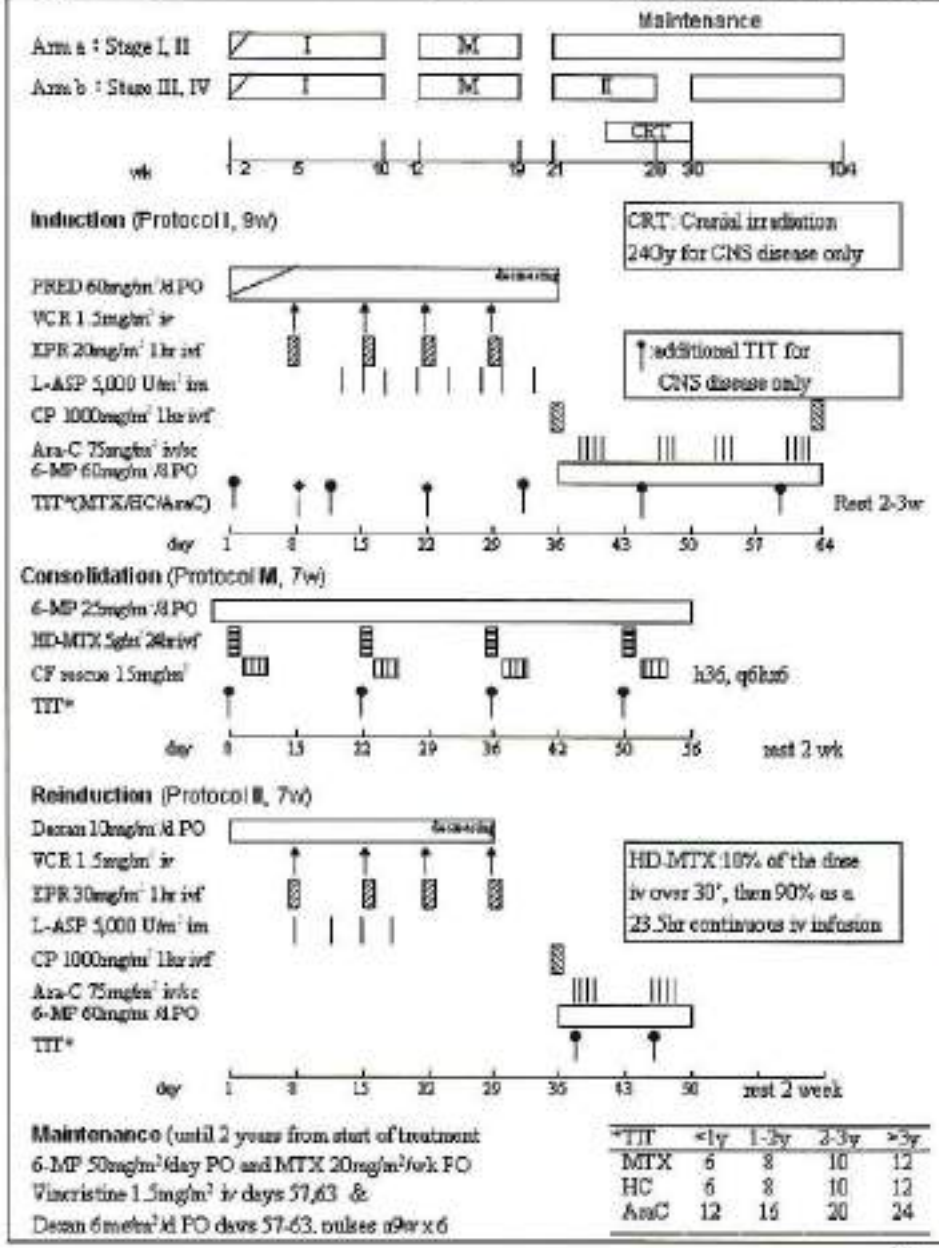
3.If CD20 (+) add Rituximab (Rituximab 375mg/ m2 IVF weekly monotherapy, assess treatment response after 3 weeks，patients showing >25% reduction in tumor volume receive 3 further Rrituximab infusion on a protracted schedule (3-4wk interval).(referred from PTLD with CD20+ protocol)

Special Notes:

1.Before, during and 24 hours after the infusion of HD-MTX, hydration with alkalinized isotonic fluid should be given and be sure of having adequate renal function. Serum MTX level should be measured at 42 hours (or 48 hours) after starting MTX infusion. If the MTX level is <1μM at hr 42 (or <0.4μM at hr 48), leucovorin will be given as scheduled (15mg/m2 iv，starting at hr 42, q6h for 5 doses; iv or po for the following 4 doses); if the MTX level is >1μM at hr 42 (or ≧0.4μM at hr 48), it should be monitored daily and leucovorin dose should be increased and extended till the MTXlevel falls <0.1μM.

2.Cranial irradiation will be only given to patients with overt CNS disease, the dosage will be 18 Gy in the second year of life and 24 Gy in older children. Children less than 1 year of age do not receive cranial radiotherapy, even with overt CNS disease. In males with testicular involvement, irradiation (24 Gy) of the testes will be performed if persistent biopsy-proved testicular disease after consolidation therapy.

3.Patients with a persistent tumor after induction protocol I may receive either local radiotherapy (30 Gy) or surgical resection.



Maintenance (until 2 years from start of treatment)
6-MP 50mg/m²/day PO and MTX 20mg/m²/wk PO
Vincristine 1.5mg/m² iv days 57,63 &
Dexa 6mg/m²/d PO days 57-63, pulses q9w x 6

*TIT	<1y	1-2y	2-3y	>3y
MTX	6	8	10	12
HC	6	8	10	12
AraC	12	16	20	24

TPOG 10 T-LBL Protocol

Drug	Dose	Days when administration*
Induction protocol I, week 1-9		
Prednisolone (orally)	60 mg/m²	1-28, then taper over 3x3 days
Vincristine (IV bolus)	1.5 mg/m² (max 2mg)	8, 15, 22, 29
Epirubicin (1-hr iv infusion)	30 mg/m²	8, 15, 22, 29
Asparaginase (IM)	5,000 IU/m²	12,15,18,21,24,27,30,33
Cyclophosphamide (1-hr ivf)	1,000 mg/m²	36, 64
Cytarabine (IV/SC)	75 mg/m²	38-41, 45-48, 52-55, 59-62
Mercaptopurine (orally)	60 mg/m²	36-63
TIT (MTX, HC, AraC)	(12, 12, 24 mg)	1, 22, 33, 45, 59[£]
Consolidation protocol M, starting 2 weeks after the end of protocol I		
Mercaptopurine	25 mg/m²	1-56
MTX (24-hour infusion)[#]	5 gm/m²	8, 22, 36, 50
with CF rescue	15 mg/m² q6h x 5 or more	(starts from hr 42)
TIT (MTX, HC, AraC)	(12, 12, 24 mg)	8, 22, 39, 50
Reinduction protocol II, starting 2 weeks after the end of protocol M		
Dexamethasone (orally)	10 mg/m²	1-21, then taper over 3x3 days
Vincristine (IV bolus)	1.5 mg/m² (max 2mg)	8, 15, 22, 29
Epirubicin (1-hr iv infusion)	30 mg/m²	8, 15, 22, 29
Asparaginase (IM)	5,000 IU/m²	8, 11, 15, 18
Cyclophosphamide (1-hr ivf)	1,000 mg/m²	36
Cytarabine (IV/SC)	75 mg/m²	38-41, 43-46
Mercaptopurine (orally)	60 mg/m²	36-49
TIT (MTX, HC, AraC)	(12, 12, 24 mg)	38, 45

Maintenance therapy (until 2 years from start of treatment)
6-MP 50 mg/m² p.o. daily and MTX 20 mg/m² p.o. weekly, pulses every 9 weeks with Vincristine 1.5 mg/m² i.v. d 57, 63 & Dexa 6 mg/m² p.o. d 57-63, q9w x 6

* Adjustment of time schedule can be made for clinical condition and marrow recovery

\# HD-MTX 24-hour infusion: 10% of the dose iv infusion over 30 minutes, and then 90% as a 23.5-hour continuous iv infusion, CF rescue starts at hr 42 after starting MTX infusion. MTX level should be measured at hr 42, if ≧1 μ M (or hr 48, if ≧0.4 μ M), measured daily and increase and extend leucovorin dose till MTX level < 0.1 μ M.

TIT dose adjusted for age<3 (TIT given at 8-12 hours before starting 24-hour HD-MTX)

TIT	<1yr	1-2yr	2-3yr	>3yr
MTX	6	8	10	12
HC	6	8	10	12
AraC	12	16	20	24

£ Additional doses of TIT at days 8, 22 for CNS-positive patients

TPOG 10 B-NHL (based on NHL-BFM 95 protocols)

Patient Eligibility:

1.Burkitt's or Burkitt's – like lymphoma

2.Diffuse large B-cell lymphoma

Exclusion Criteria:

1. Immunodeficiency related/ Post-transplantation lymphoma (PTLD)

2.Primary mediastinal large B-cell lymphoma (PMBL)

Treatment Plan:

1.Patients will be further stratified according to the risk criteria and treated accordingly

Risk Group	Definition	Therapy Courses
R1	Stage I + II, completely resected	A B
R2	Stage I + II, not resected Stage III and LDH < 500 U/L	V A B A B
R3	Stage III and LDH ≥ 500 ~ <1000 U/L And CNS-neg.	V AA BB CC AA BB
R4	Stage III+IV+B-ALL and LDH≥1000 U/L or/and CNS-pos.	V AA BB CC AA BB CC

TPOG 10 B-NHL

Drug	Dose	Days when administration
Cytoreductive Prephase V		
Dexamethasone (orally/IV)	5 mg/m²	1,2
Dexamethasone (orally/IV)	10 mg/m²	3-5
Cyclophosphamide (IV)	200 mg/m²	1,2
Course A		
Dexamethasone (orally)	10 mg/m²	1-5
Vincristine IV	1.5mg m² (max 2mg)	1
Ifosfamide (IV 1h)	800 mg/m²	1-5
MTX (4-hour infusion)	1g/m²	1
TIT (MTX, HC, AraC)	(12, 12, 24 mg)	1
Cytarabine (IV 1h)	150 mg/m² q12h	4,5
Etoposide (IV 1h)	100 mg/m²	4,5
Course B		
Dexamethasone (orally)	10 mg/m²	1-5
Cyclophosphamide (1-hr ivf)	200 mg/m²	1-5
Vincristine IV	1.5mg m² (max 2mg)	1
MTX (4-hour infusion)	1g/m²	1
TIT (MTX, HC, AraC)	(12, 12, 24 mg)	1
Epirubicin (IV 1h)	25 mg/m²	4,5
Course AA & BB (the same as A & B), except		
MTX (24-hour infusion) *	5g/m²	1
Course CC		
Dexamethasone (orally)	20 mg/m²	1-5
Vincristine (IV)	1.5 mg/m² (max 2mg)	1
Cytarabine (IV 3h)	3g/m² q12h	1,2
Etoposide (IV 2h)	100 mg/m² q12h	3-5
TIT (MTX, HC, AraC)	(12, 12, 24 mg)	5

' MTX 24-hour infusion: 10% of the dose iv infusion over 30 minutes, and then 90% as a 23.5-hour continuous iv infusion in courses AA & BB; leucovorin 15 mg/m² iv starts at hr 42 after starting MTX infusion q6h for 5 times in courses AA & BB, 3 times in courses A & B; measure MTX level at hr 42 or 48, if ≧1 μ M at hr 42 or ≧0.4 μ M at hr 48, measure it daily, and increase and extend leucovorin dose till MTX level < 0.1 μ M.

♦ Vincristine is not given in patients of branch R1.

* For CNS disease, administer chemotherapy intraventricularly via Ommaya reservoir (implanted before the 2nd course). MTX 2mg & HC 2mg on Days 2-5, AraC 3mg on day 6 of course AA/BB, MTX & HC on days 3-6, and AraC on day 7 of course CC.

TIT is given 24 hour after starting MTX infusion in all course A/B, AA/BB; TIT & intraventricular dose adjusted for age<3 yr:

TIT	<1y	1-2y	2-3y	>3y
MTX	6	8	10	12
HC	6	8	10	12
AraC	12	16	20	24

I.Vent.	<1y	1-2y	2-3y	>3y
MTX	1.5	2	2.5	3
HC	1.5	2	2.5	3
AraC	15	20	25	30

Special Notes:

1.Patients in risk groups R2, R3, and R4 receive a 5-day cytoreductive prephase before the first course A (AA) is administered. All patients in R3/ R4 have to receive Rasburicase (1.5mg/vial) 0.1-0.2mg /kg/day intravenously (take the whole vial near the proper dosage) during the first days of cytoreductive chemotherapy (max. 5 doses). Note:G6PD deficiency is contraindication. Hydration (without sodium bicarbonate) is administered at 3L/m2. Chemotherapy can be initiated between 4 and 24 hours of the day 0 rasburicase dose.

2. For patients of risk groups R3 + R4 receiving MTX 5g/m2 (AA/BB), the guidelines for HD-MTX administration and following leucovorin rescue are the same as those for the TPOG 10 T-LBL protocol. For course A/B, MTX 1g/m2 will be infused over 4 hours, measure the MTX level at 42 hours after the start of MTX infusion, give leukovorin 15mg/m2 q6h for 3 doses at hr 42, 48, and 54 after the start of MTX infusion. if the MTX level is >1μM at hr 42 (or ≧0.4μM at hr 48), it should be monitored daily and leucovorin dose should be increased and extended till the MTX level falls <0.1μM.

3. Conditions for starting the second and subsequent courses are as follows: platelet levels higher than 50x109/L and neutrophil counts higher than 0.5 x 109/L after the nadir of postchemotherapeutic cytopenia. For patients of risk groups R3 and R4, granulocyte colony-stimulating factor 5 g/kg /day subcutaneously is recommended after the first 2 therapy courses. The minimal interval between the first day of two successive courses is 2 weeks.

4.In CNS-positive patients, a device for intraventricular application of chemotherapy is implanted before the second course. MTX 3 mg and hydrocortisone 3 mg are administered intraventricularly on days 2, 3, 4, and

5, and cytarabine 30 mg is given on day 6 of courses AA and BB. In course CC, MTX 3 mg and hydrocortisone 3 mg are administered on days 3, 4, 5, and 6; cytarabine 30 is given on day 7

6.For patients in risk groups R3 + R4 with residual tumor after the fifth course of therapy, a second-look operation will be performed. If viable lymphoma tissue is detected, use megadose chemotherapy with autologous stem cell rescue (autologous stem cell transplantation [ASCT]). If no viable lymphoma tissue is found, therapy will be continued with the last course CC in risk group R4, while patients in risk group R3 will not receive any further therapy.

7. For relapsed/refractory B-cell NHL and B-ALL, may try R-ICE regimen for 1-3 cycles, depending upo response. (Griffin et al; PBC 2009;52:177).

Classifications	Treatment protocols
Lymphoblastic Lymphoma (T-cell or precursor B-cell type)	**TPOG 10 T-LBL** **TPOG 10 T-LBL a for Stage I / Stage II cases** **TPOG 10 T-LBL b for Stage III / Stage IV cases**
Burkitt' s lymphoma Diffuse large B-cell lymphoma	**TPOG 10 B-NHL**
Anaplastic large cell lymphoma (irrelevant of immunophenotype) with CD30+	TPOG 10 ALCL
Primary mediastinal large B-cell lymphoma	**TPOG 10 PMBL a & TPOG 10 PMBL b (choose one)**
Post-Transplantation Lymphoproliferative Disease (PTLD) with CD20+	**TPOG 10 PTLD**

TPOG 10 ALCL(base on EICNHL-ALCL99 PROTCOL)

Patient Eligibility:

1.CD30+ Anaplastic large cell lymphoma (irrelevant of immunophenotype)

Exclusion Criteria:

1. Isolated skin disease
2. Completely resected stage I disease
3. CNS involvement

TPOG 10 ALCL: Chemotherapy Dose and Schedule in Each Course(administered every 3 wk)

Course and Drug	Dose and Schedule
Prephase	
Dexamethasone	5 mg/m^2 on days 1 and 2; 10 mg/m^2 on days 3 to 5
Cyclophosphamide	200 mg/m^2 on days 1 and 2
Triple intrathecal injection	Day 1
Course A	
Dexamethasone	10 mg/m^2 on days 1 to 5
Methotrexate	3 g/m^2 in 3-hour infusion on day 1
Ifosfamide	800 mg/m^2 on days 1 to 5
Cytarabine	150 mg/m^2 x 2 on days 4 and 5
Etoposide	100 mg/m^2 on days 4 and 5
Course B	
Dexamethasone	10 mg/m^2 on days 1 to 5
Methotrexate	3 g/m^2 in 3-hour infusion on day 1
Cyclophosphamide	200 mg/m^2 on days 1 to 5
Doxorubicin	25 mg/m^2 on days 4 and 5

* Leucovorin rescue (15 mg/m^2 every 6 hours) starting at 24 hours of start of MTX infusion and ending when the methotrexate level was < 0.15 μm/L.

Special Notes:

1. Completely resected stage I disease: treat as R1 branch of 10 B-NHL protocol:A+B (omit IT)
2. CNS disease at diagnosis will be treated as R4 course of protocol TPOG 10 B-NHL: V+AA+BB+CC+AA+BB+CC, and use intraventricular chemotherapy via Omaya reservoir as CNS treatment for R4 patients with initial CNS involvement.
3. Primary refractory or relapse patients may try Vinblastine 6mg/m2 iv weekly as solo therapy or combined with other more intensive therapy followed by HSCT or not.

Classifications	Treatment protocols
Lymphoblastic Lymphoma (T-cell or precursor B-cell type)	**TPOG 10 T-LBL** **TPOG 10 T-LBL a for Stage I / Stage II cases** **TPOG 10 T-LBL b for Stage III / Stage IV cases**
Burkitt' s lymphoma Diffuse large B-cell lymphoma	**TPOG 10 B-NHL**
Anaplastic large cell lymphoma (irrelevant of immunophenotype) with CD30+	TPOG 10 ALCL
Primary mediastinal large B-cell lymphoma	**TPOG 10 PMBL a & TPOG 10 PMBL b (choose one)**
Post-Transplantation Lymphoproliferative Disease (PTLD) with CD20+	**TPOG 10 PTLD**

TPOG 10 PMBL a & TPOG 10 PMBL b (choose one)

Patient Eligibility:

Primary mediastinal large B-cell lymphoma (PMBL)

TPOG 10 PMBL a : DA-EPOCH-R for 6-8 cycles (based on dose-adjusted EPOCH protocol)

EPOCH: Etoposide, Prednisolone, Vincristin, Cyclophosphamide，Epirubicin (Table 1)

DA: Dose-Adjusted (dose-adjustment paradigm as in Table 2:based on twice weekly CBCs to achieve limited neutropenia lower than 500/L)

R: Rituximab: 375mg/m2 iv infusion (day 0); (in N/S 500ml slowly infusion initially after premedication with acetaminophen vena solucortef increase rate gradually over 5-6h)

Table 1. EPOCH starting dose level (level 1)

Drug	Dose	Route	Treatment days
Infused agents			
Etoposide	50 mg/m2/day	CIV	1, 2, 3, 4 (96 hours)
Epirubicin	10 mg/m2/day	CIV	1, 2, 3, 4 (96 hours)
Vincristine	0.4 mg/m2/day	CIV	1, 2, 3, 4 (96 hours)
Bolus agents			
Cyclophosphamide	750 mg/m2/day	IV	5
Prednisolone	60 mg/m2/bid	Oral	1, 2, 3, 4, 5
G-CSF	5 g/kg/day	SC	6 to ANC>. 5x109/L past nadir
Next cycle			Day 21

Table 2. EPOCH dose-adjustment paradigm

Nadir measurements	Dose-adjustment
If Nadir ANC at least 0.5x109/L	20% increase in etoposide, epirubicin, and cyclophosphamide above last cycle
If Nadir ANC less than 0.5x109/L Same dose(s) as last cycle on 1 or 2 measurements	Same dose(s) as last cycle
If Nadir ANC less than 0.5x109/L on at least 3 measurements	20% decrease in etoposide, epirubicin, and cyclophosphamide below last cycle
Or	
If Nadir platelet count less than 25x109/L on 1 measurement	20% decrease in etoposide, epirubicin, and cyclophosphamide below last cycle
1.Measurements of ANC and platelet nadir are based on twice weekly CBC only. 2.Dose adjustments above starting dose level (level 1) apply to etoposide, epiubicin and cyclophosphamide. 3.Dose adjustments below starting dose level (level 1) apply to cyclophosphamide only.	

TPOG 10 PMBLa & TPOG 10 PMBLb(choose one)

TPOG 10 PMBLb (based on R-CHOP)

R: rituximab 375mg/m2 iv infusion (day 0)

CHOP:cyclophosphamide 750 mg/m2 on day 1, epirubicin 50 mg/m2 on day 1, vincristine 1.4 mg/m2 on day 1,prednisolone 60mg/m2 on days1-5, every 21 days for 6-8 cycles . CHOP will be delayed 1 week for ANC<1500/uL and a platelet count <100,000/uL, and then administer at full dose with G-CSF support.

Special Note:

1.Use bactrium twice daily for 3 days per week to prevent Pneumocystis pneumonia.

2.Radiation therapy to mediastinum if residual tumor exists after 8 cycles of above chemotherapy.

Classifications	Treatment protocols
Lymphoblastic Lymphoma (T-cell or precursor B-cell type)	**TPOG 10 T-LBL** **TPOG 10 T-LBL a for Stage I / Stage II cases** **TPOG 10 T-LBL b for Stage III / Stage IV cases**
Burkitt' s lymphoma Diffuse large B-cell lymphoma	**TPOG 10 B-NHL**
Anaplastic large cell lymphoma (irrelevant of immunophenotype) with CD30+	TPOG 10 ALCL
Primary mediastinal large B-cell lymphoma	**TPOG 10 PMBL a & TPOG 10 PMBL b (choose one)**
Post-Transplantation Lymphoproliferative Disease (PTLD) with CD20+	**TPOG 10 PTLD**

TPOG 10 PTLD

Patient Eligibility:

Post-Transplantation Lymphoproliferative Disease (PTLD) with CD20-positive

Treatment Plan:

1.Step 1: Immune suppression reduction or withdrawal; if not effective,

2.Step 2: Rituximab 375mg/ m2 IVF weekly monotherapy, assess treatment response after 3 weeks, patients showing >25% reduction in tumor volume receive 3 further Rrituximab infusion on a protracted schedule (3-4wk interval). All others will be stratified to receive other chemotherapy regimen including vincristin, cyclophophamide, low dose MTX and Prednisolone (mCOMP)

3.Another option: for higher risk patients with more advanced or fulminant PTLD defind as feverhypotension and >2 organ system failure: Treatment consists of cyclophosphamide 600 mg/m2 IVx1day, predsisone1mg/kg iv/po bid x 5 days every 3 weeks for 6 cycles and rituximab 375 mg/m2 IV weekly x 6.

4. Patients not responding may try more intensive regimen for B-cell NHL accordingly.

九、治療反應評估

1.In TPOG 10 T-LBL group, tumor response will be evaluated at day 42 and at the end of Induction protocol I. Subsequent evaluation is performed at the beginning of reinduction protocol II, and at 1-2 month intervals thereafter until the end of maintenance therapy.

2. In TPOG 10 B-NHL group, tumor response will be evaluated after the first two therapy courses, and subsequent evaluation at the beginning of every therapy course, later in 4-week intervals during the first year and in 2- month intervals during the second year.

3.Complete response is defined as disappearance of lymphoma cells in BM or CSFor complete regression of local tumor proved by imaging studies or second-look surgery.

4.Initial tumor failure is defined as persistence of lymphoblasts in the BM and/or CSF and/or as incomplete regression of local tumor followed by progression during chemo-therapy.

5. Relapse is defined as recurrence of lymphoma at any site after complete disappearance of lymphoblasts from the blood, CSF, and BM, as well as disappearance of all tumor mass on clinical examination, imaging methods (ultrasonography, x-ray, CT, or MRI)or second-look surgery.

十、追蹤檢查

時程 / 檢查項目	化療前	第1年	第2年	第3年	第4~5年	超過5年
Physical Examination	★	每隔1個月	每隔2個月	每隔3個月	每隔6個月	每隔12個月
CBC+DC+LDH	★	每隔1個月	每隔2個月	每隔3個月	每隔6個月	每隔12個月
Bone marrow A+B Gallium Scan/ Bone Scan/PET	★	每隔6個月	每隔6個月	每隔12個月	每隔12個月	每隔12個月
T4+TSH+FT4		每隔6個月(經放療者)				
FSH+LH		每隔12個月(經放療者)				
Chest X-ray	★	每隔1個月	每隔2個月	每隔3個月	每隔6個月	每隔12個月
CT/MRI (primary site)	★	每隔3個月	每隔3個月	每隔 6 個月	每隔12個月	
PFT		每1年檢測一次，追蹤5年				
Cardia Echo/EKG	★	每1年檢測一次，追蹤10年				

十一、安寧緩和照護原則

若預期疾病難以治癒時，病人存活期小於 6 個月便適合安寧療護(Pomeranz & Brustman, 2005；Waldrop & Rinfrette, 2009) 。若藉由症狀、檢驗數據、及確切的腫瘤診斷，證實臨床上該惡性腫瘤已經廣泛侵犯、或進展快速；功能分數（Palliative Performance Scale）低於 70%；拒絕進一步腫瘤治癒性治療，或者在治療之下仍持續惡化者，即可轉介緩和醫療團隊（彭等，2006）。

十二、文獻查證

1.Bernardo V; Richardson J; Knapp K; Pat Flynn P.Guidelines for the Use of Antifungal Agents. SJCRH2011.
2.Döring M, Müller C, Johann PD, et al. Analysis of posaconazole as oral antifungal prophylaxis in pediatric patients under 12 years of age following allogeneic stem cell transplantation. BMC Infect Dis 2012;12:263
3.Kurt B, Flynn P, Shenep JL, et al. Prophylactic antibiotics reduce morbidity due to septicemia during intensive treatment for pediatric acute myeloid leukemia. Cancer 2008; 113:376-82.
4.Yeh TC, Liu HC, Hou JY, et al. Severe infections in children with acute leukemia undergoing intensive chemotherapy can successfully be prevented by ciprofloxacin, voriconazole, or micafungin prophylaxis. Cancer 2014; 120:1255- 62.
5.Inaba H, Gaur AH, Cao X, et al. Feasibility, efficacy, and adverse effectsof outpatient antibacterial prophylaxis in children with acute myeloid leukemia. Cancer 2014; 120:1985-92.

十三、完治率定義

癌別	期別	完治率定義
惡性淋巴腫瘤-非何杰金氏症（T 細胞）	I/II	T 細胞淋巴芽細胞性淋巴癌依 TPOG NHL-2010 治療計畫的引導期、鞏固期、再引導期，之後再接受 2 年的維持期化療，四階段療程結束即算完成治療。
	III/IV	依 TPOG NHL-2010 治療計畫的引導期、鞏固期、再引導期，之後再接受 2 年的維持期化療，四階段療程結束即算完成治療。
惡性淋巴腫瘤-非何杰金氏症（B 細胞）	I/II	依 TPOG NHL-2010 治療計畫，完成 2-4 個循環的化學治療，即算完成治療。
	III	依 TPOG NHL-2010 治療計畫，完成 5 個循環的高強度化學治療，即算完成治療。
	IV	依 TPOG NHL-2010 治療計畫，完成 6 個循環的高強度化學治療，即算完成治療。