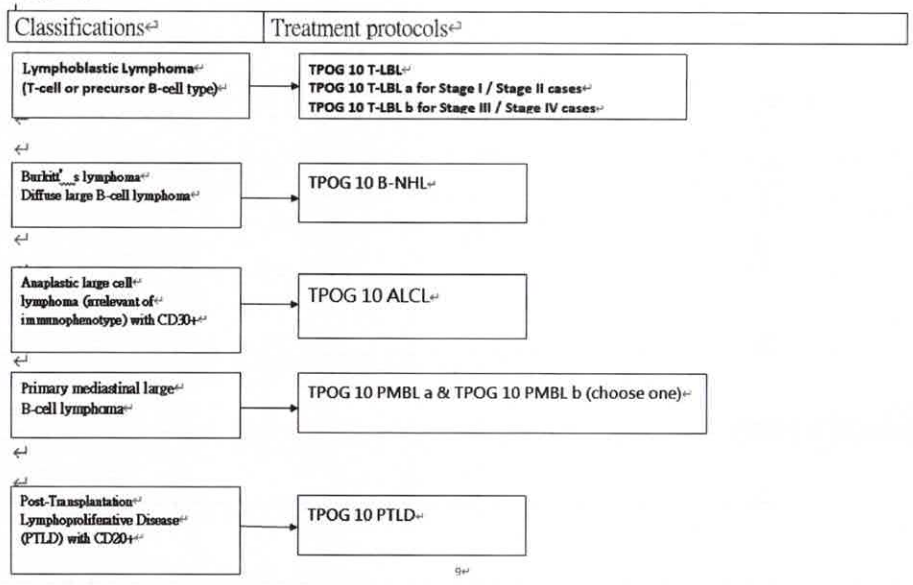
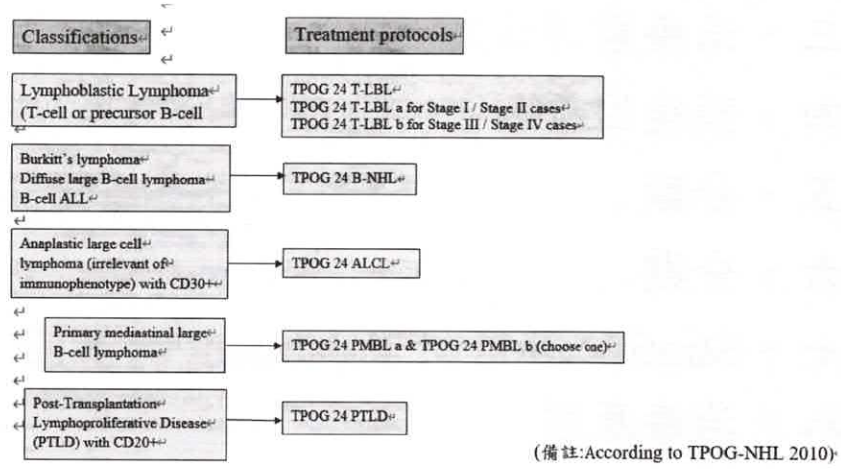
中山醫學大學附設醫院

兒童非何杰金氏淋巴瘤診療指引

2025/10/20 Version 3.0
2024/11/25 Version 2.0
2023/11/27 Version 2.0
2022/11/28 Version 2.0
2021/11/25 Version 2.0
2020/11/26 Version 2.0
2019/07/24 Version 2.0
2018/07/04 Version 1.0

本臨床指引參考TPOG與兒童癌症多專科醫療團隊編修

癌症委員會主任委員	癌症委員會執行長	癌症中心主任	抗癌藥物安全小組	團隊負責人

<table>
<tr>
<td>9-29</td>
<td>本P.9-26內容，八、治療原則的內容依TPOG-NHL 2024 protocols版修訂
 
</td>
<td>八、治療原則，由於TPOG-NHL 治療指引已由TPOG-NHL 2010 protocols版修訂為TPOG-NHL 2024 protocols版，相關內容因此進行大幅調整。
 

(備註:According to TPOG-NHL 2010)</td>
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<tr>
<td>30</td>
<td>九、反應評估</td>
<td>增修內容:
International Pediatric NHL Response Criteria
(Adapted from Sandlund JT, et al. International Pediatric Non-Hodgkin Lymphoma Response Criteria. Clin Oncol. 2015;33(18):2106-11.)
Supporting International Pediatric NHL Response Criteria
(Adapted from Sandlund JT, et al. International Pediatric Non-Hodgkin Lymphoma Response Criteria. Clin Oncol. 2015;33(18):2106-11.)</td>
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</table>

一、目的

提昇國內兒童 non-Hodgkin lymphoma (NHL)之治療成績。遵照兒童 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。

二、背景

TPOG-NHL 2010 protocols 自 2010 年推出，用於治療國內兒童 NHL，至今已 13 年餘。近 10~20 年間世界各國兒童 NHL 的治療架構並無太大改變，大多是以 BFM or LMB protocol 為主軸，加上一些微調。此外，有越來越多的標靶藥物已在歐美拿到適應症，可當第一線或第二線以上之成人 NHL 的治療，近年來也有部分標靶藥物取得治療兒童 NHL 的適應症。

因此，根據我們 TPOG-NHL 2010 protocols 的經驗、醫學文獻搜尋、2018 年 9 月在荷蘭鹿特丹舉行的第 6 屆 CAYANHL 國際會議、以及 2022 年 10 月在美國紐約舉行的第 7 屆 CAYANHL 國際會議中的資訊，以下簡單列出一些結論與建議，當作推出全新的兒童 NHL 治療方案之依據：

1. Rituximab 在 inter-B-NHL Ritux 2010 trial 的結果中，已證明其對兒童 mature B-cell lymphoma (BL & DLBCL)治療有顯著幫助。此 trial 以 LMB protocol 當主軸，對象是 high risk mature B-NHL，有接受化療 + rituximab 6 的病人其 EFS 比單純化療的病人增加了 10% (93.9% vs. 82.3%) [1]。也因此美國 FDA 與歐洲 EMA 相繼核准 rituximab 可治療兒童 B-NHL。在 Reduce the burden of oncological therapy (REBOOT) trial 中，也是以 LMB protocol 當主軸，針對 good risk mature B-NHL 的病人，在

induction 和 consolidation 中加入 rituximab (共 4 doses)，並降低 doxorubicin 劑量(60 mg/m^2；25 mg/m^2)，目前 OS 與 EFS 都是 100%。新的 TPOG 24 B-NHL 方案中將把 rituximab 放入療程中，其餘沒有新增變更。

2. PMBCL 在成人目前以 DA-EPOCH-R 6-8 cycles 的治療效果最佳，5 年的 EFS 達 93%，且減少 radiation [2]。然而在兒童使用的治療效果似乎沒有成人的成績理想：美國與加拿大的多中心研究中，使用 DA-EPOCH-R 6 cycles 的兒童病人，其 3 年的 EFS 為 81.4% [3]。德國 B04 trial 與 HL-BFM registry 中，使用 DA-EPOCH-R 6 cycles 的病人，其 5 年的 EFS 為 84% [4]。而 inter-B-NHL Ritux 2010 trial 中，PMBCL 病人使用 DA-EPOCH-R 6 cycles，4 年的 EFS 為 67% [5]。倒是法國 LMB 2001 trial 以 LMB protocol 當主軸，在 reduction、induction、consolidation、以及 maintenance 都加入 rituximab (共 6 doses)，其中 PMBCL 病人的 5 年 EFS 高達 95% [6]。因 TPOG 10 PMBL 的治療成績不錯，因此我們將維持原方案，開放 DA-EPOCH-R 與 R-CHOP 讓顧問醫師選擇，累積個案數夠多後，也能夠比較這兩種方案治療成果的差別。

3. B-LBL 治療方面這幾年在國際間比較沒有新的改變，而 T-LBL 倒是有一些新的治療方向。COGALL0434 trial 中，發現 nelarabine 對於 T-LBL 並沒有改善治療成績 [7]。而在 COGALL1231 trial 中，induction 與 delayed intensification 療程中加入 bortezomib 有顯著改善 T-LBL 的 4 年 PFS (86.4% vs. 76.5%)與 OS (89.5% vs. 78.3%)，不過對於 induction failure 的個案，治療效果仍然不佳 [8]。新的 TPOG 24 LBL 會分出 pB-LBL 與 T-LBL，TPOG 24 pB-LBL 與 TPOG 10 T-LBL 維持一樣，而 TPOG 24 T-LBL 將在 induction 與 delayed intensification 療程中加入 bortezomib。

4. ALCL 99 protocol 最新的追蹤報告顯示 10 年的 PFS 為 70%，長期的成績與過去 BFM protocols 並無太大差別，但其顯示在 SR 與 HR 病人使用 MTX 3g/m2 over 3 hours 而不用 IT、以及 VHR 病人使用 weekly vinblastine 並不會增加治療失敗的風險 [9]。在 COG ANHL12P1 trial 中以 ALCL 99 為主軸，第一個 arm 是在每個療程的第 1 天多給予 brentuximab，其 2 年的 EFS 與 OS 分別為 79%與 97%，結論是加上 brentuximab 可減少治療中的 relapse，且整體的治療成績略有進步 [10]；第二個 arm 是在每個療程中有 21 天的 crizotinib，其 2 年的 EFS 與 OS 分別為 76.8%與 95.2%，結論是加上 crizotinib 亦可減少治療中的 relapse，且整體的治療成績略有進步，但有增加 thromboembolic events [11]。因此新的 TPOG 24 ALCL 仍維持與 TPOG 10 ALCL 一樣的療程，雖然 brentuximab 目前台灣健保不給付在兒童 ALCL 一線治療，但可向兒癌基金會申請補助，因此顧問醫師們可放心使用。

5. 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 的 subtype 中以 PTCL-NOS 占多數，但大規模之治療結果分析仍然很缺乏。ECHELON-2 trial 中，針對 CD30 (+) 的 PTCL 成人使用 brentuximab + 化療(CHOP)的病人，其 5 年的 PFS 比單用化療(CHOP)的病人高(51.4% vs. 43%)，在 subtype 分析中，brentuximab + 化療對 PTCL-NOS 的預後無顯著改善 [12]。在成人 R/R PTCL，pralatrexate 有適應症可用來當 salvage therapy，但在一個 2 期臨床試驗中，使用第一線 pralatrexate + 化療(CEOP)並無改善 PTCL 的治療成績，而 subgroup 分析中，在 CR/PR/SD 情況下做 HDCT-SCT 的成人病人，其 2 年的 PFS 比沒做 HDCT-SCT 的病人來的顯著優異(63% vs. 17%) [13]。由於國際間仍沒有一定的療程，因此目前 TPOG 24 NHL 方案中也沒有明定。

6. PTLD 的治療策略並無新的變革，減少或停用免疫抑制是最基本的治療。在 localized PTLD 單獨使用 Rituximab 4 就可能達到緩解。在 COG ANHL0221 trial 中，使用 rituximab + low dose cyclophosphamide + prednisolone 治療 EBV (+) CD20 (+) PTLD，其 2 年的 EFS 與 OS 分別為 71%與 83% [14]。而德國 Ped-PTLD Pilot 2005 trial 中，先給 weekly rituximab 3 後評估治療反應：若腫瘤體積減少>25%，則再給 rituximab q3weeks 3；腫瘤體積減少 ≤25%的病人皆給予 mCOMP X 6 cycles。在 2014 年 ASH meeting 的報告：高達 64%病人只接受 rituximab 治療，不需要額外化療，整體 5 年的 EFS 與 OS 分別為 67%與 83%。 因此新的 TPOG 24 PTLD 仍維持與 TPOG 10 PTLD 一樣的療程。

7. HSCT 目前仍是兒童 R/R NHL 主要的鞏固治療。T-LBL 通常是 early relapse/progression，其對於 re-induction 後的反應是重要的預後因子，且再達到 2nd remission 後建議要做 allo-HSCT，以 TBI-based conditioning 為佳。R/R B-NHL 在有 rituximab 做 re-induction 治療後，成績有顯著進步。R/R DLBCL 若起初治療不含 rituximab，使用 R-CYVE、R-ICE、R-DHAP 等的 re-induction，70-80%可達 CR。建議在 CR 後做 R-BEAM + auto-HSCT。但 R/R BL 的治療成績則很差，使用 VICI、ICI、NT 等的 re-induction，成績較其他療程好。此外，一定要做 HSCT 才有機會治癒，且 HSCT 前是否能達到 CR 是關鍵，allo-HSCT 可能優於 auto-HSCT，但尚未有定論。R/R PMBCL 預後很差，若 radiotherapy 和 salvage chemotherapy 達到 remission 後，應盡快做 HSCT (allo-SCT or auto-SCT 皆可)。R/R ALCL 根據發生的時間有不同的治療方案：治療中 relapse，建議 re-induction 後盡快接 allo-HSCT；late relapse (診斷後 1 年後)，可用 vinblastine monotherapy。

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

Staging of pediatric NHL

International Pediatric Non-Hodgkin Lymphoma Staging System	
Stage I	Single tumor with exclusion of mediastinum and abdomen (N; EN; B or S: EN-B, EN-S)
Stage II	Single EN tumor with regional node involvement ≥ Two N areas on same side of diaphragm Primary GI tract tumor (usually in ileocecal area), ± involvement of associated mesenteric nodes, that is completely resectable (if malignant ascites or extension of tumor to adjacent organs, it should be regarded as stage III)
Stage III	≥ Two EN tumors (including EN-B or EN-S) above and/or below diaphragm ≥ Two N areas above and below diaphragm Any intrathoracic tumor (mediastinal, hilar, pulmonary, pleural, or thymic) Intra-abdominal and retroperitoneal disease, including liver, spleen, kidney, and/or ovary localizations, regardless of degree of resection (except primary GI tract tumor [usually in ileocecal region] ± involvement of associated mesenteric nodes that is completely resectable) Any paraspinal or epidural tumor, regardless of whether other sites are involved Single B lesion with concomitant involvement of EN and/or nonregional N sites

Stage IV	Any of the above findings with initial involvement of CNS (stage IV CNS), BM (stage IV BM), or both (stage IV combined) based on conventional methods

Abbreviations: B, bone; BM, bone marrow; EN, extranodal; N, nodal; S, skin.

七、Stratification of Treatment by NHL Subtypes

1. TPOG 24 pB-LBL & T-LBL (based on NHL-BFM 95 protocols)
2. TPOG 24 B-NHL (based on NHL-BFM 95 protocol)
3. TPOG 24 ALCL (based on EICNHL-ALCL99 protocol)
4. TPOG 24 PMBLa & TPOG 24 PMBLb (choose one)
5. TPOG 24 PTLD

八、治療原則

Classifications	Treatment protocols
Lymphoblastic Lymphoma (T-cell or precursor B-cell	TPOG 24 T-LBL TPOG 24 T-LBL a for Stage I / Stage II cases TPOG 24 T-LBL b for Stage III / Stage IV cases
Burkitt's lymphoma Diffuse large B-cell lymphoma B-cell ALL	TPOG 24 B-NHL
Anaplastic large cell lymphoma (irrelevant of immunophenotype) with CD30+	TPOG 24 ALCL
Primary mediastinal large B-cell lymphoma	TPOG 24 PMBL a & TPOG 24 PMBL b (choose one)
Post-Transplantation Lymphoproliferative Disease (PTLD) with CD20+	TPOG 24 PTLD

(備註:According to TPOG-NHL 2010)

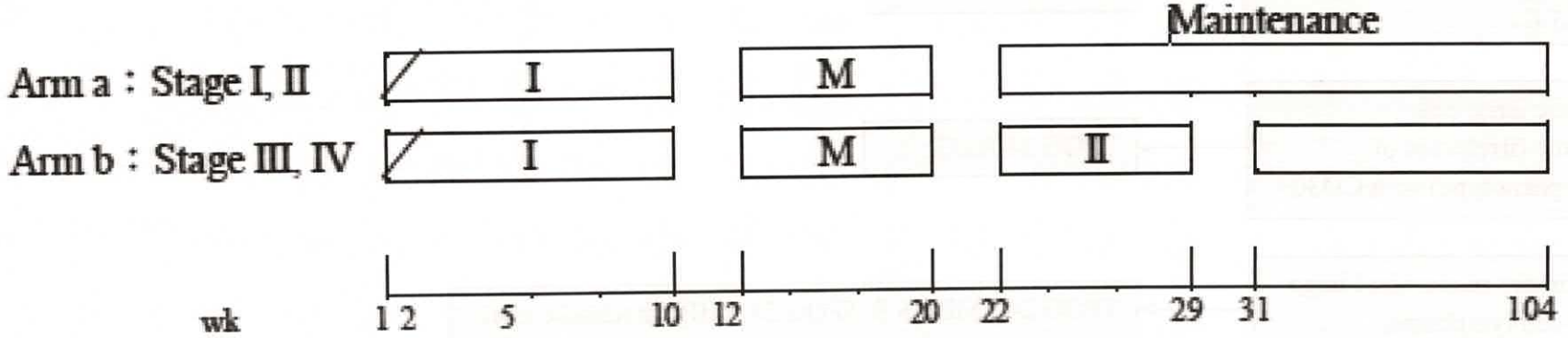
TPOG 24 T-LBL(based on NHL-BFM 95 protocols)

Patient Eligibility:

- Lymphoblastic lymphoma (precursor B-cell or T-cell)

Treatment Plan:

- Arm a (TPOG 24 pB-LBLa/T-LBLa) for Stage I / Stage II cases
- Arm b (TPOG 24 pB-LBLb/T-LBLb) for Stage III / Stage IV cases



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 MTX level falls <0.1μM..

2. CNS-directed treatment will be mainly based on frequent intrathecal injections without routine cranial radiation.
3. Patients with a persistent tumor after induction protocol I may receive either local radiotherapy (30 Gy) or surgical resection.
4. Proteasome inhibitor bortezomib will be added on TPOG 10 T-LBL backbone for T-LBL.
5. For relapsed/refractory T-LBL, allogeneic HSCT is suggested based on the results from many groups. Combination of nelarabine with etoposide and cyclophosphamide followed by allogeneic HSCT showed acceptable activity and toxicities in children, adolescents, and young adults with first relapse of T-LBL. (Whitlock JA, et al. Pediatr Blood Cancer. 2022;69(11):e29901.)

TPOG 24 pB-LBL Schema

Drugs	Dose	Days when administration
Induction protocol I, week 1-9		
Prednisolone (orally)	60 mg/m^2	1-28, then taper over 3x3 days
Vincristine (IV bolus)	1.5 mg/ m^2 (max 2mg)	8, 15, 22, 29
Epirubicin (1-hr iv infusion)	20 mg/ m^2	8, 15, 22, 29
Asparaginase (IM)	5,000 IU/ m^2	12,15,18,21,24,27,30,33
Cyclophosphamide (1-hr ivf)	1,000 mg/ m^2	36, 64
Cytarabine (IV/SC)	75 mg/ m^2	38-41,45-48,52-55,59-62
Mercaptopurine (orally)	60 mg/ m^2	36-63
TIT§(MTX, HC, AraC)	(12, 12, 24 mg)	1, 12, 33, 45, 59
TIT£(MTX, HC, AraC)	(12, 12, 24 mg)	1, 8, 12, 22, 33, 45, 59
Consolidation protocol M, starting 2 weeks after the end of protocol I		
Mercaptopurine	25 mg/ m^2	1-56
MTX (24-hour infusion)¢	5 gm/ m^2	8, 22, 36, 50
with CF rescue	15 mg/ m^2 q6h x 5 or more	(starts from hr 42)
TIT§(MTX, HC, AraC)	(12, 12, 24 mg)	8, 22, 36, 50
Reinduction protocol II, starting 2 weeks after the end of protocol M		
Dexamethasone (orally)	10 mg/ m^2	1-21, then taper over 3x3 days
Vincristine (IV bolus)	1.5 mg/ m^2 (max 2mg)	8, 15, 22, 29
Epirubicin (1-hr iv infusion)	30 mg/ m^2	8, 15, 22, 29

Asparaginase (IM)	5,000 IU/ m^2	8, 11, 15, 18
Cyclophosphamide (1-hr ivf)	1,000 mg/ m^2	36
Cytarabine (IV/SC)	75 mg/ m^2	38-41, 45-48
Mercaptopurine (orally)	60 mg/ m^2	36-49
TIT§(MTX, HC, AraC)	(12, 12, 24 mg)	38, 45
Maintenance therapy (until 2 years from start of treatment)		
Mercaptopurine (orally)	60 mg/ m^2	1-63
MTX (orally)	20 mg/ m^2	1, 8, 15, 22, 29, 36, 43, 50, 57
Vincristine (IV bolus)	1.5 mg/m2 (max 2mg)	1,57
Dexamethasone (orally)	6 mg/m2	57-63

*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 $\geqq 1\mu M$ (or hr 48, if $\geqq 0.4\mu M$), measured daily and increase and extend leucovorin dose till MTX level $< 0.1\mu M$.

TPOG 24 T-LBL Schema

Drugs	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)	20 mg/m2	8, 15, 22, 29
Bortezomib (IV)	1.3 mg/m2	8, 11, 15, 18
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, 12, 33, 45, 59
TIT£(MTX, HC, AraC)	(12, 12, 24 mg)	1, 8, 12, 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, 36, 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
Bortezomib (IV)	1.3 mg/m2	8, 11, 15, 18
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, 45-48
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)		
Mercaptopurine (orally)	60 mg/m2	1-63
MTX (orally)	20 mg/m2	1, 8, 15, 22, 29, 36, 43, 50, 57
Vincristine (IV bolus)	1.5 mg/m2 (max 2mg)	1, 57
Dexamethasone (orally)	6 mg/m2	57-63

*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 $\geqq 1\mu M$ (or hr 48, if $\geqq 0.4\mu M$), measured daily and increase and extend leucovorin dose till MTX level $< 0.1\mu M$.

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

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

£TIT schedule for CNS-positive patients

TPOG 24 B-NHL (based on NHL-BFM 95 protocols)

Patient Eligibility:

- Burkitt's or Burkitt's-like lymphoma
- Diffuse large B-cell lymphoma
- B-cell ALL

Exclusion Criteria:

- Lymphoproliferative disease associated with primary immunodeficiency
- Posttransplant lymphoproliferative disease (PTLD)
- Primary mediastinal large B-cell lymphoma (PMBL)

Treatment Plan:

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

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

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 24 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 0.5 109/L after the nadir of postchemotherapeutic cytopenia. For patients of risk groups R3 and R4, granulocyte colony-stimulating factor 5 μg/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
5. 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.
6. Patients will be administered 2, 2, 5, 6 doses of rituximab with R1, R2, R3, and R4 group, respectively.
7. For relapsed/refractory B-cell NHL and B-ALL, the ICE regimen is now the preferred option in r/r

pediatric B-NHL, with the advantages of no further anthracycline exposure and acceptable extra-hematological toxicity. Rituximab in combination with ICE (R-ICE) was proven effective and safe in COG and Japan studies. (Griffin TC, et al. Pediatr Blood Cancer. 2009;52(2):177-81. Osumi T, et al. Pediatr Blood Cancer. 2016;63(10):1794-9.)

8. Although there are no data on the efficacy of rituximab in children already treated upfront, rituximab is added to all salvage regimens, irrespective of a previous exposure to the drug, and the R-ICE regimen remains the most used treatment in pediatric patients with r/r B-NHL.
9. Numerous novel therapies are currently being tested in adults with r/r B-NHL, mostly in DLBCL, with promising results. The small number of children with r/r BNHL limits the possibility of obtaining consistent results.

TPOG 24 B-NHL Schema

Drugs	Dose	Days when administration
Cytoreductive Prephase V		
Dexamethasone (orally/IV)	5 mg/m^2	1,2
Dexamethasone (orally/IV)	10 mg/ m^2	3-5
Cyclophosphamide (IV)	200 mg/ m^2	1,2
Course A		
Rituximab (IV)	375 mg/ m^2	0
Dexamethasone (orally)	10 mg/ m^2	1-5
Vincristine IV	1.5mg m^2 (max 2mg)	1
Ifosfamide (IV 1h)	800 mg/ m^2	1-5
MTX (4-hour infusion)	1g/ m^2	1
TIT§(MTX, HC, AraC)	(12, 12, 24 mg)	1
Cytarabine (IV 1h)	150 mg/ m^2 q12h	4,5
Etoposide (IV 1h)	100 mg/ m^2	4,5
Course B		
Rituximab (IV)	375 mg/ m^2	0
Dexamethasone (orally)	10 mg/ m^2	1-5
Cyclophosphamide (1-hr ivf)	200 mg/ m^2	1-5
Vincristine IV	1.5mg m^2 (max 2mg)	1
MTX (4-hour infusion)	1g/ m^2	1

TIT§(MTX, HC, AraC)	(12, 12, 24 mg)	1
Epirubicin (IV 1h)	25 mg/ m^2	4,5
Course AA & BB (the same as A & B), except		
MTX (24-hour infusion) ¢	5g/ m^2	1
Course CC		
Rituximab (IV)	375 mg/ m^2	0
Dexamethasone (orally)	10 mg/ m^2	1-5
Vincristine IV	1.5mg m^2 (max 2mg)	1
Cytarabine (IV 3h)	3 g/ m^2 q12h	1,2
Etoposide (IV 2h)	100 mg/m2 q12h	3-5
TIT§(MTX, HC, AraC)	(12, 12, 24 mg)	5

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

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

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

TPOG 24 ALCL(base on EICNHL-ALCL99 PROTCOL)

Patient Eligibility:

- CD30+ Anaplastic large cell lymphoma (irrelevant of immunophenotype)

Exclusion Criteria:

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

Treatment Plan:

Special Notes:

- Completely resected stage I disease: treat as R1 branch of TPOG 24 B-NHL protocol without rituximab: A+B & omit IT).
- CNS disease at diagnosis will be treated as R4 course of protocol TPOG 24 B-NHL protocol without rituximab: V+AA+BB+CC+AA+BB+CC, and use intraventricular chemotherapy via Ommaya reservoir as CNS treatment for R4 patients with initial CNS involvement.
- Brentuximab is not covered by National Health Insurance in Taiwan at present, but will be reimbursed by Childhood Cancer Foundation of R.O.C. The administration of brentuximab (1.8 mg/kg) on day 1 of each cycle.
- 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.

TPOG 24 ALCL Schema

Course and Drug	Dose and Schedule
Prephase	
Dexamethasone	5 mg/ m^2 on days 1 and 2; 10 mg/m2 on days 3 to 5
Cyclophosphamide	200 mg/ m^2 on days 1 and 2
Triple intrathecal injection	Day 1
Course A	
Brentuximab vedotin	1.8 mg/kg on day 1
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	
Brentuximab vedotin	1.8 mg/kg on day 1
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

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)

TPOG 24 PMBLb : R-CHOP for 6-8 cycles (on page 21)

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 days 1-5, every 21 days for 6-8 cycles. CHOP will be delayed 1 week for ANC<1500/μL and a platelet count <100,000/μL, and then administer at full dose with G-CSF support.

Special Notes:

- ✧ Use Bactrim twice daily for 3 days per week to prevent *Puenmocystis* pneumonia infection.
- ✧ Radiation therapy to mediastinum if residual tumor exists after 8 cycles of above chemotherapy

TPOG 24 PMBLa Schema

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/ m^2/day		CIV	1, 2, 3, 4 (96 hours)
Vincristine†	0.4 mg/ m^2/day		CIV	1, 2, 3, 4 (96 hours)
	Bolus agents			
Cyclophosphamide	750 mg/ m^2/day		IV	5
Prednisolone	60 mg/ m^2/day		PO	1, 2, 3, 4, 5
	Biologic agents			
Rituximab	375mg/m^2		IV	1
G-CSF	5 μg/kg/day		SC	6 to ANC>0.5 10^9/L past nadir
Next cycle‡			Day 21	

*Etoposide, epirubicin, and vincristine could be mixed in the same solution (daily dose of the 3 drugs mixed in 0.9% normal saline around 300ml/m2 via PICC or Port-A central catheter daily infusion for 4 days)

†The vincristine dose will be not routinely capped, reduce 25% dose for grade 2 motor neuropathy, and 50% for grade 3 motor/sensory neuropathy.

‡Begin on day 21 if the ANC is at least 1×10^9/L and the platelet count is at least 100×10^9/L.

Table 2. EPOCH dose-adjustment paradigm

Nadir measurements	Dose-adjustment
If Nadir ANC at least $0.5x10^9$/L	20% increase in etoposide, epirubicin, and cyclophosphamide above last cycle
If Nadir ANC less than $0.5x10^9$/L on 1 or 2 measurements	Same dose(s) as last cycle
If Nadir ANC less than $0.5x10^9$/L on at least 3 measurements	20% decrease in etoposide, epirubicin, and cyclophosphamide below last cycle
If Nadir platelet count less than 25x109/L on 1 measurement	20% decrease in etoposide, epirubicin, and cyclophosphamide below last cycle

*Measurements of ANC and platelet nadir are based on twice weekly CBC only.

†Dose adjustments above starting dose level (level 1) apply to etoposide, epirubicin and cyclophosphamide. Dose adjustments below starting dose level (level 1) apply to cyclophosphamide only.

TPOG 24 PMBLb Schema

Drug	Dose	Days of administration
Rituximab (IV)	375 mg/m^2	1
Cyclophosphamide (IV)	750 mg/m^2	1
Vincristine (IV)	1.4 mg/m^2	1
Epirubicin (IV)	50 mg/m2	1
Prednisolone (PO)	60 mg/m^2	1 – 5

(備註:According to TPOG-NHL 2010)

TPOG 10 PTLD

Patient Eligibility:

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

Treatment Plan:

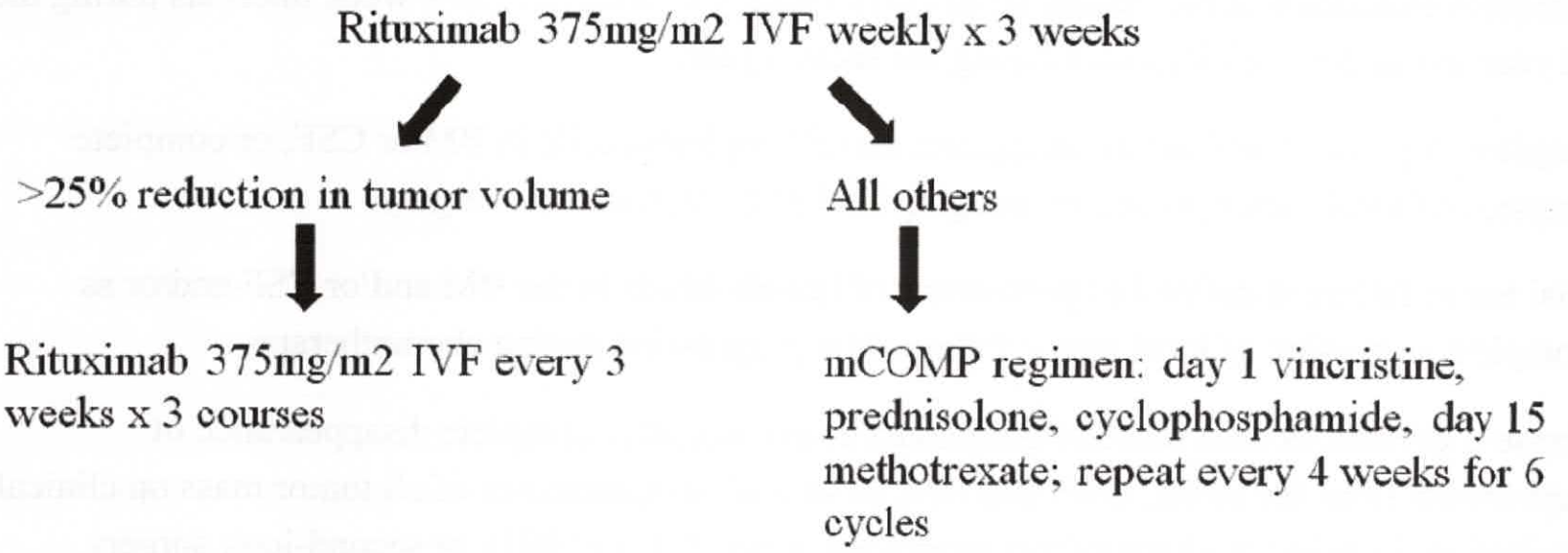
1. Step 1: Immune suppression reduction or withdrawal; if not effective,
2. Step 2: Rituximab 375mg/ m2 IVF weekly monotherapy, assess treatment response after 3 weeks, patients showing >25% reduction in tumor volume receive 3 further Rrituximab infusion on a protracted schedule (3-4wk interval). All 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/m^2 IVx1day, predsisone1mg/kg iv/po bid x 5 days every 3 weeks for 6 cycles and rituximab 375 mg/m^2 IV

or 6 cycles and rituximab 375 mg/m^2 IV weekly x 6.

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

TPOG 24 PTLD Schema

- Immune suppression reduction or withdrawal



九、治療反應評估

1. In TPOG 24 pB-LBL &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 24 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 CSF, or 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 chemotherapy.

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.

International Pediatric NHL Response Criteria

(Adapted from Sandlund JT, et al. International Pediatric Non-Hodgkin Lymphoma Response Criteria. Clin Oncol. 2015;33(18):2106-11.)

Criterion	Definition
CR	Disappearance of all disease (three designations)
CR	● CT or MRI reveals no residual disease or new lesions ● Resected residual mass that is pathologically (morphologically) negative for disease (detection of disease with more sensitive techniques described as supporting data [next table]) ● BM and CSF morphologically free of disease (detection of disease with more sensitive techniques described as supporting data [next table])
CRb	● Residual mass has no morphologic evidence of disease from limited or core biopsy (detection of disease with more sensitive techniques described as supporting data [next table]), with no new lesions by imaging examination ● BM and CSF morphologically free of disease (detection of disease with more sensitive techniques described as supporting data [next table]) ● No new and/or progressive disease elsewhere
CRu	● Residual mass is negative by FDG-PET; no new lesions by imaging examination ● BM and CSF morphologically free of disease (detection of disease with more sensitive techniques described as supporting data [next table]) ● No new and/or progressive disease elsewhere
PR	● 50% decrease in SPD on CT or MRI; FDG-PET may be positive (Deauville score or 4 or 5 with reduced lesional uptake compared with baseline); no new and/or PD; morphologic evidence of disease may be

	present in BM or CSF if present at diagnosis (detection of disease with more sensitive techniques described as supporting data [next table]); however, there should be 50% reduction in percentage of lymphoma cells
MR	● Decrease in SPD > 25% but < 50% on CT or MRI; no new and/or PD; morphologic evidence of disease may be present in BM or CSF if present at diagnosis (detection of disease with more sensitive techniques described as supporting data [next table]); however, there should be 25% to 50% reduction in percentage of lymphoma cells
NR	● For those who do not meet CR, PR, MR, or PD criteria
PD	● For those with > 25% increase in SPD on CT or MRI, Deauville score 4 or 5 on FDG-PET with increase in lesional uptake from baseline, or development of new morphologic evidence of disease in BM or CSF

BM, bone marrow; CR, complete response; CRb, complete response biopsy negative; CRu, complete response unconfirmed; CT, computed tomography; FDG, [18F]fluorodeoxyglucose; MR, minor response; MRI, magnetic resonance imaging; NHL, non-Hodgkin lymphoma; NR, no response; PD, progressive disease; PET, positron emission tomography; PR, partial response; SPD, sum of product of greatest perpendicular diameters.

Supporting International Pediatric NHL Response Criteria

(Adapted from Sandlund JT, et al. International Pediatric Non-Hodgkin Lymphoma Response Criteria. Clin Oncol. 2015;33(18):2106-11.)

Supporting Information	Description
BM involvement	Currently defined by morphologic evidence of lymphoma cells; this applies to any histologic subtype; type and degree of BM involvement should be specified*
BMm	● BM positive by morphology (specify percentage of lymphoma cells)
BMi	● BM positive by immunophenotypic methods (histochemical or flow cytometric analysis; specify percentage of lymphoma cells)
BMc	● BM positive by cytogenetic or FISH analysis (specify percentage of lymphoma cells)
BMmol	● BM positive by molecular techniques
CNS involvement	
CSF status	● CSF positivity is based on morphologic evidence of lymphoma cells; CSF should be considered positive when any number of blasts is detected; CSF may be unknown; as with BM, type of CSF involvement should be described whenever possible
CSFm	● CSF positive by morphology (specify No. of blasts/μL)
CSFi	● CSF positive by immunophenotype methods (histochemical or flow cytometric analysis; specify percentage of lymphoma cells)
CSFc	● CSF positive by cytogenetic or FISH analysis (specify percentage of lymphoma cells)
CSFmol	● CSF positive by molecular techniques
RM	
RMm	● Tumor detected by standard morphologic evaluation

RMi	● Tumor detected by immunophenotypic methods (immunohistochemical or flow cytometric analysis)
RMc	● Tumor detected by cytogenetic or FISH analysis
RMmol	● Tumor detected by molecular techniques

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）。

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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。