



中山醫學大學附設醫院

淋巴瘤診療指引 (Diffuse Large B-cell Lymphoma)

本臨床指引參考台灣國家衛生研究院、與美國NCCN版本

淋巴瘤多專科醫療團隊編修

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修訂內容

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<p>P15-16</p>	<p>七、化學治療原則(Principles of chemotherapy)^{4,5}</p> <p>第一線用藥^{4,5}</p> <table border="1"> <thead> <tr> <th>Regimen^{4,5}</th> <th>*Dosage^{4,5}</th> <th>Reference^{4,5}</th> </tr> </thead> <tbody> <tr> <td>RCHOP^{4,5}</td> <td>Rituximab 375 mg/m² i.v. on day 1^{4,5} Cyclophosphamide 750 mg/m² i.v. on day 1^{4,5} Doxorubicin 50 mg/m² i.v. on day 1^{4,5} Vincristine 1.4 mg/m² i.v. on day 1(maximum dose of 2 mg)^{4,5} Prednisone 100mg p.o. daily on day1-5^{4,5}</td> <td>McKevey EM. cancer 1876;38:1484-1493 Lenz G. J clin Oncol 2005;23:1984-1992. 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一、前言

淋巴瘤，是指由淋巴組織所衍生出的惡性腫瘤。淋巴瘤的臨床表現，常常是不正常的淋巴結腫大，有時還會合併發燒，體重減輕，夜間盜汗等症狀，也就是所謂的B症狀 (B Symptom)。這樣的腫瘤，因其具有不正常增生與分化的特性，所以淋巴瘤基本上都是惡性的。為了在名稱上不會混淆，惡性淋巴瘤反而能更精準的讓病人了解其罹患疾病的特性。

淋巴瘤大致上可分為兩大類，一是何杰金氏淋巴瘤 (Hodgkin lymphoma)，一是非何杰金氏淋巴瘤 (Non-Hodgkin lymphoma)。約莫80%的淋巴瘤屬於非何杰氏金淋巴瘤，而何杰金氏淋巴瘤佔約20%。何杰金氏淋巴瘤與非何杰金氏淋巴瘤的區別在於組織型態的差異。何杰金氏淋巴瘤的癌細胞常常會出現如貓頭鷹眼狀的細胞型態，這類的細胞，我們稱之為Reed-Sternberg Cell (RS cell)。其癌細胞的免疫組織染色，會呈現陽性的 CD15以及CD30。何杰金氏淋巴瘤的組織分類，根據世界衛生組織 (WHO) 的分類，可區分為兩大類，Lymphocyte predominant, nodular以及典型 (classic) 何杰金氏淋巴瘤。而典型何杰金氏淋巴瘤又細分為五大類，分別是 Lymphocyte-rich classic HL, Nodular sclerosis, Mixed Cellularity, Lymphocyte depleted, 以及無法分類的典型何杰金氏淋巴瘤

非何杰金氏淋巴瘤分類上則相對較複雜。依照其細胞來源，我們簡單的將非何杰金氏淋巴瘤區分為B細胞與T細胞兩大類。非何杰金氏淋巴瘤臨床的分類可以將淋巴瘤分為低惡性度 (Indolent)，高惡性度 (Aggressive)，簡單的說，如果低惡性度的淋巴瘤不治療，病人尚可存活數月甚至數年，如果高惡性度的淋巴瘤不治療，病人恐怕只可存活數月。最近世界衛生組織重新將非何杰金氏淋巴瘤做了分類，

二、組織病理分類與分化

2017年WHO淋巴瘤分類 (Classification of lymphoma)

Mature B-cell neoplasms

Chronic lymphocytic leukemia/small lymphocytic lymphoma

Monoclonal B-cell lymphocytosis*

B-cell prolymphocytic leukemia

Splenic marginal zone lymphoma

Hairy cell leukemia

ˆ Splenic B-cell lymphoma/leukemia, unclassifiable

▲ Splenic diffuse red pulp small B-cell lymphoma

▲ Hairy cell leukemia-variant

 Lymphoplasmacytic lymphoma

▲ Waldenström macroglobulinemia

Monoclonal gammopathy of undetermined significance (MGUS), IgM*

Mu heavy-chain disease

Gamma heavy-chain disease

Alpha heavy-chain disease

Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*

Plasma cell myeloma

Solitary plasmacytoma of bone

Extraosseous plasmacytoma

Monoclonal immunoglobulin deposition diseases*

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue
(MALT lymphoma)

Nodal marginal zone lymphoma

▲Pediatric nodal marginal zone lymphoma

Follicular lymphoma

▲In situ follicular neoplasia*

▲Duodenal-type follicular lymphoma*

Pediatric-type follicular lymphoma*

Large B-cell lymphoma with IRF4 rearrangement*

Primary cutaneous follicle center lymphoma

Mantle cell lymphoma

▲In situ mantle cell neoplasia*

Diffuse large B-cell lymphoma (DLBCL), NOS

▲Germinal center B-cell type*

▲Activated B-cell type*

T-cell/histiocyte-rich large B-cell lymphoma

Primary DLBCL of the central nervous system (CNS)

Primary cutaneous DLBCL, leg type

EBV1 DLBCL, NOS*

EBV1 mucocutaneous ulcer*

DLBCL associated with chronic inflammation

Lymphomatoid granulomatosis

Primary mediastinal (thymic) large B-cell lymphoma

Intravascular large B-cell lymphoma

ALK-large B-cell lymphoma

Plasmablastic lymphoma

Primary effusion lymphoma
HHV8-positive DLBCL, NOS*
Burkitt lymphoma
Burkitt-like lymphoma with 11q aberration*
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements*
High-grade B-cell lymphoma, NOS
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

Mature T and NK neoplasms

T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells
Aggressive NK-cell leukemia
Systemic EBV1 T-cell lymphoma of childhood*
Hydroa vacciniforme-like lymphoproliferative disorder*
Adult T-cell leukemia/lymphoma
Extranodal NK-/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma*
Indolent T-cell lymphoproliferative disorder of the GI tract*
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides

Sézary syndrome

Primary cutaneous CD301 T-cell lymphoproliferative disorders

Lymphomatoid papulosis

Primary cutaneous anaplastic large cell lymphoma

Primary cutaneous gd T-cell lymphoma

Primary cutaneous CD81 aggressive epidermotropic cytotoxic T-cell lymphoma

Primary cutaneous acral CD81 T-cell lymphoma*

Primary cutaneous CD41 small/medium T-cell lymphoproliferative disorder*

Peripheral T-cell lymphoma, NOS

Angioimmunoblastic T-cell lymphoma

Follicular T-cell lymphoma*

Nodal peripheral T-cell lymphoma with TFH phenotype*

Anaplastic large-cell lymphoma, ALK1

Anaplastic large-cell lymphoma, ALK2*

Breast implant–associated anaplastic large-cell lymphoma*

Hodgkin lymphoma

Nodular lymphocyte predominant Hodgkin lymphoma

Classical Hodgkin lymphoma

Nodular sclerosis classical Hodgkin lymphoma

Lymphocyte-rich classical Hodgkin lymphoma

Mixed cellularity classical Hodgkin lymphoma

Lymphocyte-depleted classical Hodgkin lymphoma

Posttransplant lymphoproliferative disorders (PTLD)

Plasmacytic hyperplasia PTLD

Infectious mononucleosis PTLD

Florid follicular hyperplasia PTLD*

Polymorphic PTLD

Monomorphic PTLD (B- and T-/NK-cell types)

Classical Hodgkin lymphoma PTLD

Histiocytic and dendritic cell neoplasms

Histiocytic sarcoma

Langerhans cell histiocytosis

Langerhans cell sarcoma

Indeterminate dendritic cell tumor

Interdigitating dendritic cell sarcoma

Follicular dendritic cell sarcoma

Fibroblastic reticular cell tumor

Disseminated juvenile xanthogranuloma

Erdheim-Chester disease*

三、分期

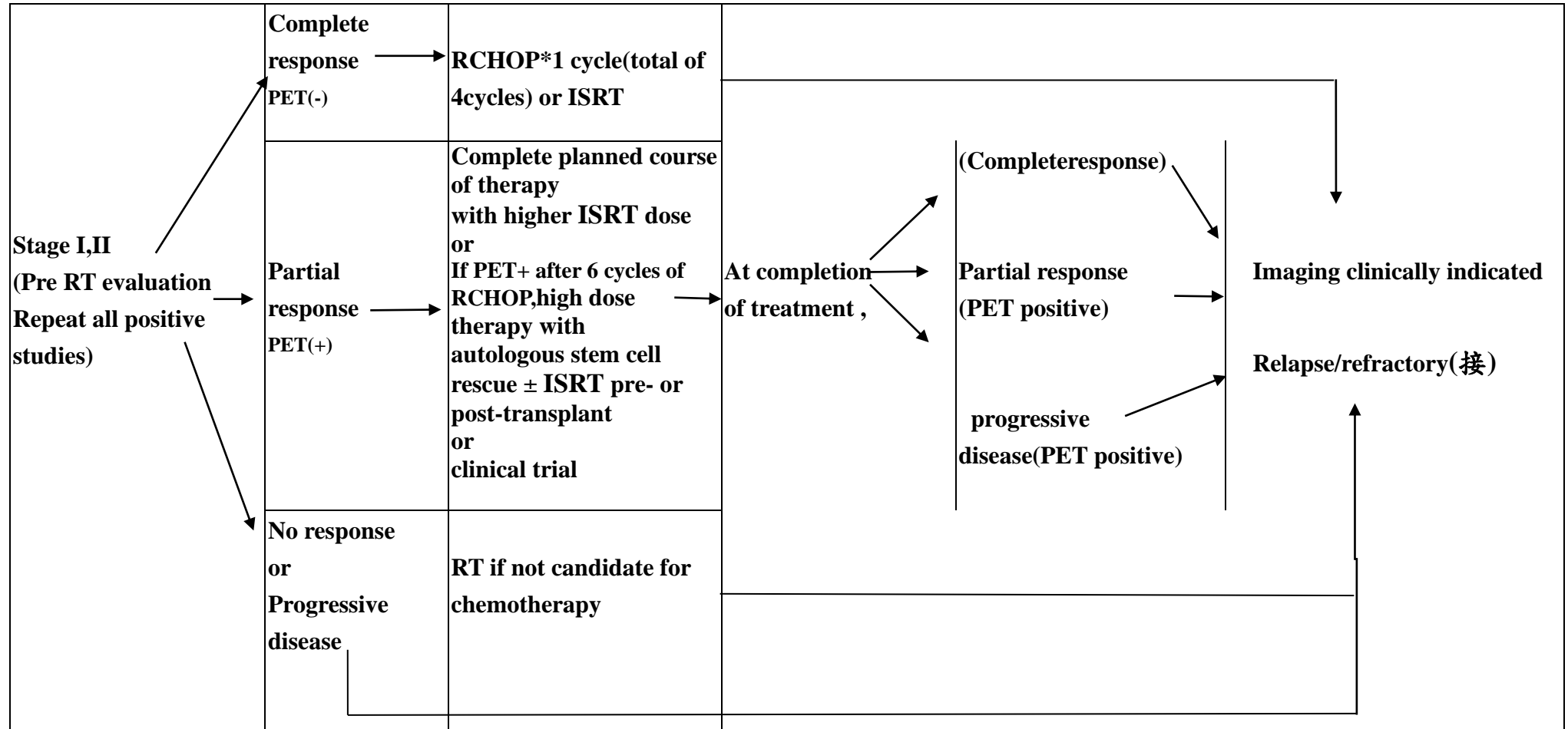
淋巴瘤的分期，是依照 Ann Arbor Staging System 來分期。淋巴瘤一般分為四期，簡單的說，當淋巴瘤只侵犯單一區域淋巴結時，稱為第一期。當淋巴瘤侵犯兩個區域以上淋巴結，且在橫膈膜同側時，稱為第二期。當淋巴瘤侵犯兩個區域以上淋巴結，且在橫膈膜異側時，稱為第三期。當淋巴瘤侵犯淋巴組織以外的地方，或是侵犯肝臟或骨髓時，則稱為第四期。這樣分期的目的，是為了決定治療方式與評估預後。簡單的說，三，四期病患的預後一般來說比一、二期的病患差。

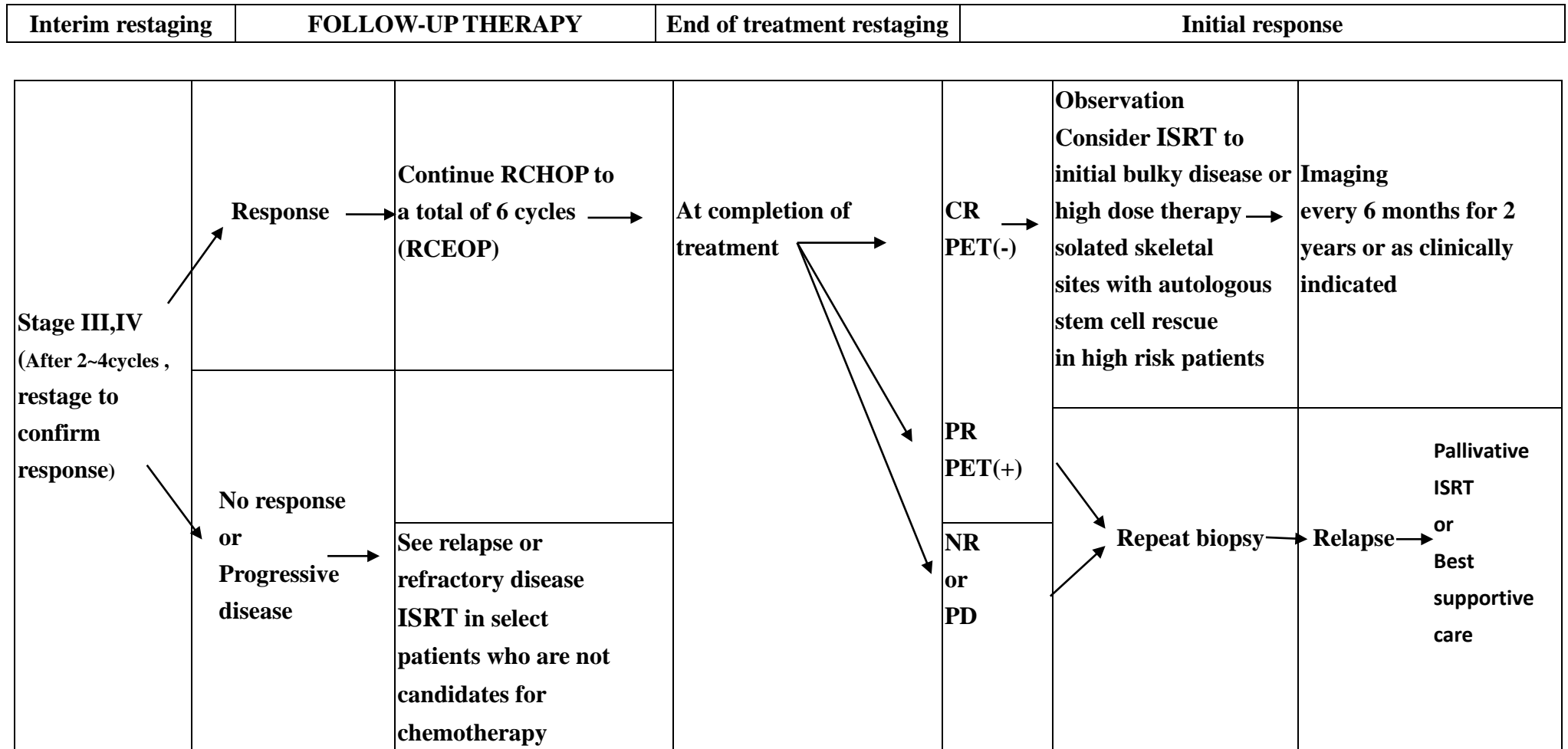
四、淋巴瘤臨床指引

Workup-主要檢查	Stage	Fist-line therapy	
<ul style="list-style-type: none"> ·Physical Exam ·Performance status ·B symptoms ·CBC/DC ·LDH ·Uric acid ·Comprehensive metabolic panel ·CT scan with contrast or PET-CT ·Bone marrow biopsy± aspiration ·Calculation of international prognostic index (IPI) ·Hepatitis B、C testing ·echocardiogram ·Beta-2-microglobulin <optional> ·Discussion of fertility issues and sperm banking(optional) 	Stage I,II	Nonbulky <7.5cm <ul style="list-style-type: none"> → smIPI 0 → → smIPI 1 → 	RCHOP x3cycles+ ISRT Or RCHOP x6 cycles± ISRT RCHOP(RCEOP) x 4cycles Or RCHOP(RCEOP) x 4cycles followed by rituximab x 2cycles(if IPI=0)
		Bulky ≥7.5cm → smIPL0-1 →	RCHOP(RCEOP) x 3-4 cycles± ISRT
	Stage III, IV	Clinical trial or RCHOP	Interim restaging after 2-4cycles

Pre-R/T Evaluation (End of first-line chemoimmunotherapy)	F/U therapy	End-of-treatment restaging	FOLLOW-UP
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Stage I (smlPI 0; Non-bulky; <7.5cm)





五、復發的評估

Relapse/Refractory disease	Additional therapy	RESPONSE #2	Consolidation/Additional therapy	Relapse or greater #2
Relapse / Refractory disease	Intention to proceed to transplant	Second- line therapy	Complete response or Partial response	High dose therapy with autologous stem cell rescue ±ISRT or Clinical trial or allogeneic stem cell-transplant in selected casescc or Palliative
	No Intention to proceed to transplant	Clinical trial or Second- line therapy or Palliative ISRT or Best supportive care	No response	Clinical trial or Palliative ISRT or Best supportive care

六、International prognostic Index (IPI)

All patients: Age > 60 years Serum LDH > 1X normal Performance status 2-4 Stage III or IV Extranodal involvement > 1 site	International Index, All patients: Low 0 - 1 Low intermediate 2 High intermediate 3 High 4 - 5
Age-adjusted International prognostic Index (IPI)	
Patients ≤ 60 years Stage III or IV Serum LDH > 1X normal Performance status 2-4	International Index, Patients ≤ 60 years: Low 0 Low intermediate 1 High intermediate 2 High 3
STAGE-MODIFIED INTERNATIONAL PROGNOSTIC INDEX (smIPI)	
STAGE I OR II PATIENTS:	International Index, Stage I or II patients
Age > 60 years Serum LDH > normal Performance status 2-4 Stage II or IIE	Low 0 or 1 High 2-4

七、化學治療原則(Principles of chemotherapy)

第一線用藥

Regimen	*Dosage	Reference
RCHOP	Rituximab 375 mg/m ² i.v. on day 1 Cyclophosphamide 750 mg/m ² i.v. on day 1 Doxorubicin 50 mg/m ² i.v. on day 1 Vincristine 1.4 mg/m ² i.v. on day 1(maximum dose of 2 mg) Prednisone 100mg p.o. daily on day1-5	McKelvey EM. cancer 1976;38:1484-1493.Lenz G. J clin Oncol 2005;23:1984-1992. Hiddemann W.Blood 2005;106:3725-3732
RCEOP	Rituximab 375 mg/m ² i.v. on day 1 Cyclophosphamide 750 mg/m ² i.v. on day 1 Epirubicin 50 mg/m ² i.v. on day 1 Vincristine 1.4 mg/m ² i.v. on day 1(maximum dose of 2 mg) Prednisone 100mg p.o. daily on day1-5	
DA-EPOCH ±Rituximab	Rituximab (Rituxan) 375 mg/m ² IV over 3 hours once on day 1 Etoposide (Vepesid) 50 mg/m ² /day IV over 96 hours, started on day 1 <u>(total dose per cycle: 200 mg/m²)</u> Vincristine (Oncovin) 0.4 mg/m ² /day IV over 96 hours, started on day 1 <u>(total dose per cycle: 1.6 mg/m²; dose was not capped)</u> Cyclophosphamide (Cytoxan) 750 mg/m ² IV over 2 hours once on day 5 Doxorubicin (Adriamycin) 10 mg/m ² /day IV over 96 hours, started on day 1 <u>(total dose per cycle: 40 mg/m²)</u> Prednisone (Sterapred) 60 mg/m ² /dose PO twice per day on days 1 to 5	Giulino-Roth L, O'Donohue T, Chen Z, Bartlett NL, LaCasce A, Martin-Doyle W, Barth MJ, Davies K, Blum KA, Christian B, Casulo C, Smith SM, Godfrey J, Termuhlen A, Oberley MJ, Alexander S, Weitzman S, Appel B, Mizukawa B, Svoboda J, Afify Z, Pauly M, Dave H, Gardner R, Stephens DM, Zeitler WA, Forlenza C, Levine J, Williams ME, Sima JL, Bollard CM, Leonard JP. Outcomes of adults and children with primary mediastinal B-cell lymphoma treated with dose-adjusted EPOCH-R. Br J Haematol. 2017 Dec;179(5):739-747. doi: 10.1111/bjh.14951. Epub 2017 Oct 29. PMID: 29082519; PMCID: PMC6650639.

Pola-R-CHP	<p>Polatuzumab vedotin(Polivy)1.8mg/kg IV over 1.5 hours once on day1</p> <p>Rituximab (Rituxan) 375 mg/m2 IV over 3 hours once on day1</p> <p>Cyclophosphamide (Cytosan) 750 mg/m2 IV over 2 hours once on day 5</p> <p>Doxorubicin (Adriamycin) 10 mg/m2/day IV over 96 hours, started on day 1 (total dose per cycle: 40 mg/m2)</p> <p>Prednisone (Sterapred) 60 mg/m2/dose PO twice per day on days 1 to 5</p>	<p>Tilly H, Morschhauser F, Sehn LH, Friedberg JW, Trněný M, Sharman JP, Herbaux C, Burke JM, Matasar M, Rai S, Izutsu K, Mehta-Shah N, Oberic L, Chauchet A, Jurczak W, Song Y, Greil R, Mykhalska L, Bergua-Burgués JM, Cheung MC, Pinto A, Shin HJ, Hapgood G, Munhoz E, Abrisqueta P, Gau JP, Hirata J, Jiang Y, Yan M, Lee C, Flowers CR, Salles G. Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma. N Engl J Med. 2022 Jan 27;386(4):351-363. Epub 2021 Dec 14</p>
註: patients >80 of age with comorbidities R-mini CHOP		

第二線用藥

Regimen	*Dosage	Reference
DHAP±Rituximab	<p>Cisplatin 80-100 mg/m² CIVI over 24 h on day 1</p> <p>Cytarabine 2000 mg/m² i.v. q12h x2 dose on day 2</p> <p>Dexamethasone 40 mg/m² p.o./i.v. daily on day 1-4</p> <p>Repeat cycle every21-28 d</p>	Velasquez WS. Blood 1988;71:117-122.
ESHAP±Rituximab	<p>Etoposide 40 mg/m² i.v. daily on days 1-4</p> <p>Methylprednisolone 500 mg/m² i.v. daily on days 1-5</p> <p>Cytarabine 2000 mg/m² CIVI on day 5</p> <p>Cisplatin 25 mg/m² i.v. daily on days 1-4</p> <p>Repeat cycle every21-28 d</p>	Velasquez WS. J clin Oncol 1994;12:1169-1176.
ICE±Rituximab	<p>Ifosfamide 5000 mg/m² CIVI over 24h on day 2</p> <p>Mesna 5000 mg/m² CIVI over 24h on day 2</p> <p>Carboplatin AUC 5 i.v. on day 2(maximum dose of 800 mg)</p> <p>Etoposide 100 mg/m² i.v. daily on days 1-3</p>	<p>Moskowitz CH0J clin oncol 1999;17:3776-3785.</p> <p>Kewalramans T. blood 2004;103:3684-3688</p>

	±rituximab 375 mg/m ² i.v. 48 h before start of cycle 1 and on day 1 of each cycle Repeat cycle every 14-15 d	
Polatuzumab vedotin-piiq ± bendamustine ± rituximab	Polatuzumab vedotin-piiq (Polivy) 1.8mg/kg i.v. at 90min repeat cycle every 21 d ± Benamustine 90mg/m ² /day on day1, day2 ± rituximab 375 mg/m ² i.v. on day 1 Total 6 cycle	Morschhauser F, Flinn IW, Advani R, et al. Polatuzumab vedotin or pinatuzumab vedotin plus rituximab in patients with relapsed or refractory non-Hodgkin lymphoma: final results from a phase 2 randomised study (ROMULUS). Lancet Haematol 2019;6:e254-e265. Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. J Clin Oncol 2020;38:155-165.
RB	Rituximab 375 mg/m ² i.v. on day 1 Bendamustine 90-120mg/m ² day 1-2	

*化學治療原則劑量會依病患體能狀況，調整劑量。

八、放射線治療原則 (Principles of radiation)

Non-Hodgkin's lymphoma

Disease	Indication	Target area	Dose	Note
Diffuse large B	Stage I~II, CR ^a Non-bulky ^b	Locoregional RT	30-36Gy	1. testicular lymphoma should include contralateral testis to 30-36Gy
	Stage I~II, CR ^a Bulky	Locoregional RT	30-36Gy ^a	2. Refractory -40-55Gy
	Stage I~II, PR ^c	Locoregional RT	36-50Gy	3. RT as primary treatment(without chemoimmunotherapy) : 40-55Gy

a: complete response from previous chemotherapy (5-PS 1-3)

b : with adverse effects such as elevated LDH, stage II, age > 60y, performance status ECOG > 2

c: partial response from previous chemotherapy (5-PS 4)

九、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、實證醫學

Categories of Evidence and Consensus :

Category 1: There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

Category 2A: There is uniform NCCN consensus, based on lower- level evidence including clinical experience, that the recommendation is appropriate.

Category 2B: There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 3: There is major NCCN disagreement that the recommendation is appropriate.

All recommendations are category 2A unless otherwise noted.

十一、參考文獻

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3. Velasquez WS. Blood 1988;71:117-122.
4. Velasquez WS. J clin Oncol 1994;12:1169-1176.
5. Moskowitz CH0J clin oncol 1999;17:3776-3785.
6. Kewalramans T. blood 2004;103:3684-3688
7. BLOOD, 19 MAY 2016 x VOLUME 127, NUMBER 20:2376
8. Giulino-Roth L, O'Donohue T, Chen Z, Bartlett NL, LaCasce A, Martin-Doyle W, Barth MJ, Davies K, Blum KA, Christian B, Casulo C, Smith SM, Godfrey J, Termuhlen A, Oberley MJ, Alexander S, Weitzman S, Appel B, Mizukawa B, Svoboda J, Afify Z, Pauly M, Dave H, Gardner R, Stephens DM, Zeitler WA, Forlenza C, Levine J, Williams ME, Sima JL, Bollard CM, Leonard JP. Outcomes of adults and children with primary mediastinal B-cell lymphoma treated with dose-adjusted EPOCH-R. Br J Haematol. 2017 Dec;179(5):739-747. doi: 10.1111/bjh.14951. Epub 2017 Oct 29. PMID: 29082519; PMCID: PMC6650639.