Guidelines

Chinese guidelines for diagnosis and treatment of malignant lymphoma 2018 (English version)

National Health Commission of the People's Republic of China

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1. Overview

Lymphoma is one of the most common malignancies in China. According to the report from the Chinese National Cancer Center, the incidence of lymphoma in China is 5.94/100,000 in 2014, and the estimated incidence of 2015 is 6.89/100,000. Due to the complexity of pathological classification in lymphoma and related distinctions in treatment, in order to improve standardization of diagnosis and therapy in lymphoma and to cooperate the safeguards for the supply of anti-tumor medicine, here we are updating and revising Chinese guidelines for diagnosis and treatment of malignant lymphoma (2015 edition).

2. Diagnosis of lymphoma

The diagnosis of lymphoma should integrate clinical manifestation with physical, laboratory, imaging and pathological examinations.

2.1 Clinical manifestations

The manifestation of lymphoma includes systemic and local symptoms. Systemic symptoms include fever of unknown origin, night sweating, weight loss, skin itching and fatigue. Local symptoms depend on the primary and invaded sites of lesions. Lymphoma may originate from any organ or tissue of the body, and it is usually divided into two categories — from lymph node and extra lymph node. The most common manifestation is painless progressive lymphadenectasis. Patients with the above symptoms should be paid attention to, and be referred to superior hospitals or tumor hospitals as soon as possible.

2.2 Physical examination

Special attention should be paid to the enlargement of lymph nodes in different regions, the size of liver and

spleen, accompanying signs and general state, etc.

2.3 Laboratory examination

Laboratory tests include complete blood count, liver and kidney function, lactate dehydrogenase (LDH), β2 microglobulin, erythrocyte sedimentation rate, and infection screening of human immunodeficiency virus (HIV), hepatitis B and hepatitis C virus etc. For primary gastric mucosa-associated marginal zone B-cell lymphoma, *Helicobacter pylori* (Hp) staining should be routinely performed. For patients with NK/T cell lymphoma, EB virus DNA titer in peripheral blood should be detected. For patients with risk of central nervous system involvement, lumbar puncture, and routine, cytological and biochemical examinations of cerebrospinal fluid should be performed.

2.4 Imaging examination

Common methods of image examination: computed tomography (CT), nuclear magnetic resonance (MRI), positron emission tomography-CT (PET-CT), ultrasound and endoscopy.

2.4.1 CT

It is still the most commonly used imaging method for staging, re-staging, efficacy evaluation and follow-up of lymphoma. For patients without contraindication for iodine contrast agent, enhanced CT scan should be used as far as possible.

2.4.2 MRI

MR imaging should be preferred for lesions in the central nervous system, bone marrow and muscles. For lesions in liver, spleen, kidney, uterus and other parenchymal organs, MR imaging could be selected or preferred, especially for those who are not suitable for enhanced CT scan, or as a further examination for suspicious lesions found by CT.

2.4.3 PET-CT

It is the best method for staging and re-staging, efficacy evaluation and prognosis prediction of lymphoma, except indolent subtypes. For the following situations, PET-CT is recommended.

(a) Routine examination for primary staging and re-staging of Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL) subtypes with high affinity for fluorodeoxyglucose (FDG), and evaluation of remission with Deauville five-point scale (*Appendix 1*). However, for NHL subtypes with low affinity for FDG, enhanced CT scan is still the first choice for primary staging.

(b) Mid-term efficacy evaluation if clinical indications of imaging available. However, it is still in clinical research, and it needs cautions to change the regimen according to mid-term PET-CT results.

(c) For HL and the majority of diffuse large B cell lymphoma (DLBCL), if PET-CT indicates explicit involvement of bone marrow, bone marrow biopsy is not necessary any more.

(d) Reference for biopsy site selection during the transformation from indolent lymphoma to more aggressive pathological subtypes.

(e) In terms of efficacy and prognosis prediction, PET-CT is better than other methods.

2.4.4 Ultrasound

A routine examination for diagnosis and follow-up of lesions in superficial lymph nodes and organs (such as testis, thyroid, breast, etc.), but not for staging. It is optional for abdominal and pelvic lymph node examination and is a supplement to CT and MRI for examination of liver, spleen, kidney, uterus and other abdominal and pelvic parenchymal organs, especially when enhanced CT scan is not applicable. For excision biopsy of superficial lymph nodes, it is helpful to improve the accuracy of biopsy to select lymph nodes with abnormal sonogram. Ultrasound-guided puncture biopsy should also be used for pathological diagnosis of deep lymph nodes, liver and mediastinum.

2.4.5 Isotope bone scan

Lymphoma patients with bone invasion lack characteristic changes of systemic bone imaging. Therefore, it is difficult to distinguish from bone metastases, multiple myeloma, bone tuberculosis, fibrous dysplasia, hyperparathyroidism and infections. Medical history, laboratory examinations and other imaging examinations are required for such cases. Conventional bone scan (99Tcm-MDP) has limited value in the evaluation of primary HL patients, but it is superior to CT in the follow-up and prognosis evaluation of primary bone lymphoma after treatment.

2.5 Other specific examinations

(1) Patients suspected of gastrointestinal tract involvement

should undergo gastroscopy and enteroscopy.
(2) Routine electrocardiogram examination; echocardiographic examination is preferred for patients with cardiovascular diseases, elderly or prospective use of anthracyclines.
(3) Pulmonary function tests should be performed for patients who intend to use bleomycin and have basal pulmonary lesions.

2.6 Pathological examinations

Pathological examination is the principal means of diagnosis of lymphoma. For lymph node lesions, the whole lymph node should be excised as far as possible. If lymph node lesions are superficial, neck, supraclavicular and axillary lymph nodes are the first choices. Core needle puncture is only used for patients who cannot effectively and safely obtain excision of the whole or partial lesion. For the primary diagnosis, excision of the whole or partial lesion should be the first choice. For relapsed patients, pathological diagnosis can be made by core needle puncture if excision of the lesion is not applicable.

Pathological diagnosis of lymphoma requires comprehensive application of morphology, immunohistochemistry, genetic and molecular biological technologies, and flow cytometry etc., and none of the single method could be the "gold standard".

2.6.1 Morphology

It is very important in pathological diagnosis of lymphoma. Different types of lymphoma have characteristic and diagnostic morphological features.

2.6.2 IHC

It can be used to distinguish the immunophenotype of lymphoma cells, such as B or T cell, or NK/T cell, differentiation and maturation of lymphoma cells. Differential diagnosis of different pathological subtypes was made through combination of related IHC markers.

2.6.3 Fluorescence *in situ* hybridization (FISH)

Identification of specific chromosome breaks, translocations, or amplifications, and guiding the auxiliary diagnosis of lymphoma with specific chromosome abnormality, such as Burkitt lymphoma (BL) related t (8; 14) translocation, follicular lymphoma (FL) related t (14; 18) translocation, extranodal mucosa associated lymphoid marginal zone lymphoma (MZL) related t (11; 18) translocation, mantle cell lymphoma related t (11; 14) translocation, and double or triple hit high-grade B-cell lymphoma related *MYC* (8q24), *BCL2* (18q21) and *BCL-6* (3q27) rearrangement, etc.

2.6.4 Antigen receptor gene rearrangement of lymphocytes

Monoclonal rearrangement of lymphocyte receptor gene is the main feature of lymphoma cells. It could be used as evidence to identify monoclonal or polyclonal proliferation of lymphocytes, and lymphoma that cannot be diagnosed by IHC. It is an important supplement to morphology and IHC assays.

2.6.5 Others

Others include FISH, Next-generation sequencing (NGS), flow cytometry etc., as a significant supplement to routine pathological diagnosis.

With the development of new technology and progress in pathological research, some changes have taken place in the pathological diagnosis of lymphoma. In the 2017 revision of the World Health Organization (WHO) classification of lymphoid neoplasms, anaplastic large cell lymphoma (ALCL) is classified into ALK positive ALCL, ALK negative ALCL and breast implant-associated ALCL. Some ALCL with rearrangements at the locus containing DUSP22 and IRF4 in chromosome 6p25 have a superior prognosis, while a small subset with TP63 rearrangements are very aggressive. Whereas angioimmunoblastic T-cell lymphoma (AITL) and nodal peripheral T-cell lymphoma (PTCL) with phenotype of follicular helper T cells (TFH) are regarded as one category.

3. Staging of lymphoma

Revised Ann-Arbor staging (2014 edition) (*Appendix 2*) is applicable for HL and primary nodal NHL, but not some primary extranodal NHL, such as chronic lymphocytic leukemia (CLL), cutaneous T-cell lymphoma, extranodal NK/T-cell lymphoma, nasal type (ENKTL), and primary gastrointestinal, central nervous system lymphoma. These NHLs originated from special extranodal organs and sites, usually have their own staging system.

4. Radiotherapy of lymphoma

Radiotherapy is an important component of comprehensive treatment of lymphoma. How to choose the radiation beam, radiation field and dosage during the process,

depends on the purpose of treatment and related conditions for each case. Photon, electron and proton beams can be used to achieve reasonable coverage of the target area and maximum protection of normal tissues. Complex radiotherapy technologies, such as intensity modulated radiation therapy (IMRT), breath holding and breathing gating, image guidance and proton therapy, could improve outcomes significantly in specific circumstances. They are especially recommendable for patients with purpose of cure and expectation of long-term survival.

According to the purpose and function, indications for radiotherapy of lymphoma are classified as (a) radical treatment; (b) part of comprehensive treatment; (c) salvage therapy for intolerance of chemotherapy, resistant or residual lesions; and (d) palliative treatment.

Radiotherapy field settings consist of total lymphoid irradiation (TLI) and sub-total lymphoid irradiation (STLI). TLI usually includes mantle field + hoe field + pelvic field (splenic irradiation is also needed in patients without splenectomy). STLI may omit part of field, and it is not applicable for HL treatment any more currently. Involved field radiotherapy (IFRT) only includes the entire lymph node region of the involved lymph node before chemotherapy. With the development of imaging diagnosis and conformal radiotherapy technique, IFRT is replaced by more accurate involved-node radiotherapy (INRT) or involved-site radiotherapy (ISRT) in HL and aggressive lymphoma.

Radiotherapy dose: Radical dose for HL is 36–40 Gy, and it reduces to 20–30 Gy when complete remission (CR) is achieved after chemotherapy. The radical dose for NHL with low-grade malignancy is 24–30 Gy. The dose for consolidation radiotherapy of DLBCL after CR with chemotherapy is 30–40 Gy, and the consolidation dose after partial remission (PR) is 40–50 Gy. The radical dose for ENKTL is 50–56 Gy.

5. Summary of comprehensive treatment of lymphoma

Lymphoma is a group of malignant tumors with different clinical features, diagnostic criteria and therapies. Lymphoma diagnoses require identification of pathological subtypes and molecular markers for prognosis. Stage of patients is defined with imaging diagnostic techniques. Prognosis evaluation is based on the integration of clinical manifestations, laboratory examinations, and related criteria for prognostic risk. Comprehensive therapy reasonable medical treatment (chemotherapy, targeted therapy and/or immunotherapy), radiotherapy and surgery are comprehensively performed in order to maximize the chance of cure or progression-free survival (PFS), to optimize life quality of patients (*Appendix 3*, *4*).

6. Treatment of lymphoma with Traditional Chinese Medicine

Nowadays, the treatment of lymphoma with Traditional Chinese Medicine mainly relieves the adverse reactions after medical treatment and radiotherapy, improves appetite, physical strength and immunity as adjuvant therapy. It plays a supportive role in treatment of end-stage patients.

Methods: Oral decoction, Chinese patent medicine and its external application, acupuncture, etc.

7. Clinical features, diagnosis and treatment of common lymphoma pathological types

7.1 HL

HL is an uncommon malignancy involving lymph nodes and lymphatic system, mainly in males, with the ratio of males to females being 1.4:1–1.3:1. The onset age of this disease shows a typical bimodal distribution in developed countries in Europe and America, ranging from 15 to 39 years old and over 50 years old, respectively. In East Asian region including China, the age of onset is mainly in early adulthood (aged 30–40 years), showing a unimodal distribution.

7.1.1 Clinical features

Lymphadenopathy is the initial symptom in 90% of HL patients, mostly starting from a group of involved lymph nodes in cervical and inguinal area. As the disease progresses, it can gradually spread to other lymph node regions, and in advanced stage, spleen, liver and bone marrow can also be involved. Most patients have no obvious systemic symptoms at first diagnosis, and 20%–30% of patients can be accompanied by B symptoms, including unexplained fever, drenching and recurrent night sweats, weight loss as well as pruritus, fatigue and other symptoms.

7.1.2 Pathological classification and diagnosis

According to the revised edition (2017) of WHO

classification of lymphoma, HL is divided into classical HL (cHL) and nodular lymphocyte-predominant HL (NLPHL), which is less common accounting for 10% of cases. The cHL can be divided into four histological subtypes, which are nodular sclerosis type, lymphocyte-rich type, mixed cellularity type and lymphocyte-depleted type.

HL originates from germinal center B lymphocytes, and its morphological features are defined by destruction of normal tissue structure and heteromorphic large cells like Reed-Sternberg (R-S) cells scattering in the inflammatory cellular background. Classical R-S cell features binucleated or multinucleated giant cell with abundant cytoplasm and large prominent and eosinophilic nucleoli. When the cell appears as a symmetrical dual nucleus, it is called mirror image cell. Malignant cells in nodular lymphocyte-predominant HL is called lymphocyte predominant (LP) cell which in the past was named lymphocytic-histocytic (L-H) cells or popcorn cells as the nuclei are large, folded and "popcorn-like". LP is surrounded by PD-1 positive T cells. Increasing evidence has suggested the overlap between NLPHL with complete diffuse growth pattern and T-cell/ histocytic cell-rich large B-cell lymphoma.

The routinely tested IHC markers for HL diagnosis include CD45 (LCA), CD20, CD15, CD30, PAX5, CD3, MUM1, Ki-67 and EBV-EBER. cHL often appears as CD30 (+), CD15 (+) or (−), PAX5 weak (+), MUM1 (+), CD45 (−), CD20 (−) or weak (+), CD3(−), BOB1(−), OCT2(−/+), EBV-EBER (+) in some cases. NLPHL shows CD20 (+), CD79α (+), BCL6 (+), CD45 (+), CD3 (−), CD15 (−), CD30 (−), BOB1 (+), OCT2 (+), EBV-EBER (−). For differential diagnosis, appropriate markers should be added to identify ALCL or DLBCL, etc. Therapeutic and prognostic markers include PD-1, PD-L1, P53, and so on.

Marrow cytology inspection shows that nuclear cells proliferate actively, eosinophil increase in partial cases. If tumor cells infiltrate bone marrow, HL specific R-S cells can be found there. The positive rate of R-S cell is rather low by detection of bone marrow puncture cytology smear with only about 3%, while bone marrow biopsy can reach to 9%−22%. If there is mixed cell hyperplasia and small lymphocytes showing a flow-like structure, it may suggest the development of cHL, which should be paid attention to.

7.1.3 Treatment principles

(1) NLPHL

(a) IA/IIA stage (non-bulky disease): observation or regional radiotherapy. (b) IB/IIB stage and IA/IIA stage (bulky diseases): regional radiotherapy ± chemotherapy ± Rituximab. (c) III/IV stage: chemotherapy ± Rituximab ± regional radiotherapy.

ABVD regimen (doxorubicin + bleomycin + vinblastine + dacarbazine), CHOP regimen (cyclophosphamide + doxorubicin + vincristine + prednisone), CVP regimen (cyclophosphamide + vinblastine + prednisone) and others ± rituximab treatments can be used for first-line chemotherapy.

(2) cHL

(a) I and II stage: 2−6 cycles chemotherapy + IFRT or ISRT. For early-stage favorable disease, ABVD (2−3 cycles) followed by 20−30 Gy involved-field RT (IFRT) or involved-site RT (ISRT) is the standard treatment, and patients not reaching CR can be appropriately increased radiation exposure dose; for patients suffering from complete metabolic response (CMR) after chemotherapy, prolonged chemotherapy to 6 cycles is required if ISRT is not selected. Unfavorable patients with non-bulky diseases is suggested for 4-cycle ABVD, followed by 30 Gy IFRT; If PET-CT evaluation is positive (not reaching CMR) after 2 cycles ABVD regimen, followed 2 cycles of BEACOPPesc and 30−36 Gy IFRT or INRT regimen is suggested. For patients with early-stage unfavorable HL with large mediastinal mass and lymph node diameter >5 cm or with B symptoms, the radiation dose should be increased properly, or 2 cycles of BEACOPPesc followed by 2 cycles of ABVD and IFRT regime is suggested if not reaching CR with ABVD regime 4−6 cycles followed by IFRT. (b) III and IV stage: 8 cycles of ABVD can be selected, and patients not getting CR or with bulky diseases can select IFRT; 6 cycles of BEACOPPesc can be another treatment choice, if not reaching CMR assessed by PET-CT after chemotherapy, IFRT is suggested to follow. Patients aged over 60 years can choose regimes not including bleomycin, like AVD.

For patients not receiving any treatment before, first-line chemotherapies include ABVD regime, Stanford V (doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin and prednisone, weekly) or BEACOPPesc (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) regime. Refractory or relapse patients can select second-line therapy including DHAP (dexamethasone, cisplatin, high-dose cytarabine), DICE (dexamethasone, ifosfamide, carboplatin, etoposide), ESHAP (etoposide, methylprednisolone, high-dose

cytarabine, cisplatin), GDP (gemcitabine + cisplatin + dexamethasone), GVD (gemcitabine, vinorelbine, liposomal doxorubicin), ICE (ifosfamide, carboplatin, etoposide), IGEV (ifosfamide, gemcitabine, vinorelbine), mini-BEAM (carmustine, cytarabine, etoposide, melphalan), MINE (etoposide, ifosfamide, mesna, mitoxantrone), etc. For young patients with good general conditions, high-dose chemotherapy combined with autologous hematopoietic stem cell transplantation (HDC/AHSCT) as consolidation treatment is suggested after rescue treatment remission, and the locations without radiation at initial treatment could be irradiated. For relapse/refractory patients, programmed cell death protein 1 (PD-1) can be selected as the rescue treatment. Anti-CD30 antibody (brentuximab vedotin, BV) is an option for relapse/refractory patients with CD30 positive.

7.1.4 Prognostic factors of HL (*Appendix 5.1*)

(1) Unfavorable prognosis factors of early-stage HL: the prognostic factors of early HL were slightly different in different groups.

(2) Unfavorable prognosis factors of advanced-stage HL: the International Prognostic Score (IPS): (a) Albumin level below 40 g/L; (b) Hemoglobin level below 10^5 g/L; (c) Male gender; (d) Aged 45 years or older; (e) Stage IV disease; (f) Leukocytosis (white blood cell count $>15\times10^9$/L); (g) Lymphocytopenia (lymphocyte count <8% of the white blood count and/or lymphocyte count $<0.6\times10^9$/L).

(3) Early PEI-CT evaluation results: PET negativity at the end of 2−3 cycles treatment has been shown to be a significant favorable factor in patients with no matter early-stage or advanced-stage disease at the time of diagnosis.

7.2 NHL

7.2.1 DLBCL

DLBCL are the most common lymphoid neoplasms in adults, accounting for approximately 30%−40% of NHLs in Western countries, and 35%−50% in China.

(1) Clinical manifestations

The median age at diagnosis of DLBCL is about 50−60 years, and males are slightly more than females. DLBCL patients exhibit various clinical manifestations according to the location of primary site and severity of the lesion. Most of DLBCL patients appear as painless lymphadenopathy at the beginning. However, the proportion of lesions outside the lymph nodes could reach 40%−60%, which can be originated from any extranodal tissues and organs. The pathogenesis of DLBCL is invasive and presents as a rapidly increasing mass. About 1/3 of DLBCL patients have B symptoms, and more than 50% of DLBCL patients have elevated lactate dehydrogenase (LDH). Moreover, about 50% of patients are diagnosed with stage III−IV disease and extensive extranodal invasion.

(2) Pathological diagnosis and classification

The main pathological feature of DLBCL is the diffuse growth of abnormal lymphoid cells, which destroys the normal structure of lymph nodes. DLBCL includes a variety of variants and subtypes (*Appendix 6*).

The regular IHC markers to diagnose DLBCL include CD19, CD20, PAX5, CD3, CD5, CD79α, CyclinD1, Ki-67. The typical immunophenotype exhibits as CD19 (+), CD20 (+), PAX5 (+), and CD3 (−). Furthermore, in order to explore the origin of cell (GCB or non-GCB), Han's classification (CD10, BCL-6, MUM-1) or Choi classification (GCET1, FOXP1, CD10, BCL-6, MUM-1) can be used to determine GCB *vs.* non-GCB origin. Then, several markers (CD30, CD138, ALK, etc.) also can be added for differential diagnosis. Moreover, it is recommended that all DLBCL patients routinely detect EBER to identify EBV-positive DLBCL (non-specific). In addition, all DLBCL patients are also suggested to routinely detect BCL-2, BCL-6 and C-MYC immunohistochemistry. Patients especially with GCB-like immunophenotype along with the extensive expression of C-MYC and either BCL-2 or BCL-6 by IHC and the Ki-67 index more than 80% positive should undergo FISH testing for the detection of C-MYC, BCL-2, and BCL-6 gene rearrangements. If there is no condition for FISH testing, MYC protein (cut-off value is 40%) and BCL-2 protein (cut-off value is >50%) is known as double-expression (DE) lymphoma, which indicates a poor prognosis. In addition, prognostic and therapeutic related indicators also include PD-1, PD-L1, P53, etc.

Bone marrow hemocytology: When DLBCL cells infiltrate to bone marrow, it can be seen that the volume of tumor cell is large, the chromatin is rough, the nucleolus is multiple, but not obvious, and the cytoplasm presents grayish blue with a few vacuoles.

(3) Prognostic indicators

The International Prognostic Index (IPI) is currently identified as the most common and useful scoring system to predict the prognosis of DLBCL patients. IPI scores are based on five independent adverse prognostic factors, including age >60 years, stage III−IV disease, extranodal

involvement >1, Eastern Cooperative Oncology Group performance status (ECOG PS) score ≥2, serum LDH level >upper limit of normal, each poor prognostic factor is 1 point. 0–1 point is divided into low-risk group, 2 points is divided into low-medium risk group, 3 points is divided into high-medium risk group, 4–5 points is divided into high-risk group. For patients treated with rituximab, a modified IPI prognostic index (Revised IPI, R-IPI) can be used. This system contains the same five independent adverse prognostic factors as IPI, with a poor prognostic factor of 1 point. 0 point is a very good prognosis, 1–2 points a a good prognosis, 3–5 points is a poor prognosis. Furthermore, for patients aged ≤60 years, an age-adjusted IPI (aaIPI) can be used. aaIPI has three adverse prognostic factors, including stage III–IV disease, serum LDH level >upper limit of normal, ECOG PS score ≥2, which 0 point is classified as low risk, 1 point is classified as low to medium risk, 2 points is classified as medium to high risk, and 3 points is classified as high risk. In recent years, the National Comprehensive Cancer Network (NCCN)-IPI prognosis system which further stratifies age and LDH based on IPI can more accurately predict the prognosis of patients. NCCN-IPI is also composed of the above five poor prognostic factors. However, the age factor is divided into three groups, including age >40 years old and ≤60 years old (1 point), age >60 years old and ≤75 years old (2 point), age >75 years old (3 point). In addition, serum LDH levels are divided into two groups, including >1 and ≤3 folds (1 point), and >3 fold (2 points). Extranodal involvement was defined as the involvement of bone marrow, central nervous system, liver, digestive tract, or lung. Furthermore, the prognostic factor of NCCN-IPI also contains ECOG PS score is ≥2 points and stage III–IV disease. The highest score is 8 points, NCCN-IPI score 0–1 is divided into low-risk group, score 2–3 is divided into low-medium risk group, score 3–4 is divided into medium-high risk group, score ≥6 is divided into high-risk group (*Appendix 5.2*).

(4) Principle of treatment

The principle of treatment of DLBCL is multidisciplinary treatment based on medical treatment. Medical treatment includes chemotherapy and immunotherapy. Treatment strategies should be based on different factors such as age, IPI score, and disease stage. For patients with high tumor burden, a low dose of induction therapy can be given before the start of regular chemotherapy. The drugs of induction therapy could include prednisone ± vincrinstine to avoid the occurrence of tumor lysis syndrome. For patients with or infected with Hepatitis B virus (HBV), peripheral blood HBV-DNA titer should be closely monitored and appropriate antiviral therapy should be selected.

(a) Initial treatment of stage I and II: For patients with no large masses in stage I and II, R-CHOP regimen chemotherapy can be selected for 3–4 cycles + radiotherapy, or R-CHOP regimen for 6 cycles ± radiotherapy. For patients with large lumps in stage I and II, R-CHOP regimen can be chosen for 6–8 cycles ± radiotherapy.

(b) Initial treatment of stage III and IV: Patients in stage III and IV could select to participate in a clinical trial, or receive 6–8 cycles of R-CHOP regimen thermotherapy. Treatment strategies can be developed and adjusted according to the results of PET-CT examinations which could be performed before and at the end of treatment. Patients who did not achieve complete remission (CR) after chemotherapy are treated with ISRT for residual lesions. Patients with post-chemotherapy efficacy evaluation of CR or uncomfirmed complete remission (CRu) after the initial treatment should be received 30–40 Gy of radiotherapy, while patients with efficacy evaluation of PR after initial treatment should be performed 40–50 Gy of radiotherapy.

(c) Weak patients over the age of 80 years: The initial treatment could select the R-miniCHOP regimen. For patients with left ventricular dysfunction, RCEPP, RCDOP, DA-EPOCH-R, RCEOP and RGCVP regimens could be selected.

(d) Central nervous system (CNS) prevention: patients with 4–6 risk factors for CNS invasion (risk factors include: age >60 years old, elevated serum LDH level, stage III or IV, ECOG PS score >1, extranodal lesions >1, kidney or adrenal gland involvement), lesions involving the paranasal sinus and paravertebral, HIV-associated lymphoma, primary testicular and breast DLBCL, the risk of CNS invasion might increase. Therefore, these patients should be considered the CNS prevention. However, the methods of the CNS prevention are currently controversial. Intrathecal injection of 4–8 doses of methotrexate and/or cytarabine, or systemic application of 3–3.5 g/m^2 methotrexate could be selected for prophylactic treatment.

(e) First-line consolidation therapy: HDC/AHSCT can be considered in young and high-risk patients who have achieved CR after treatment.

(f) Rescue treatment: For patients who are suitable for HDC/AHSCT, the available rescue chemotherapy regimens include: DICE, DHAP, ESHAP, GDP, ICE and

MINE. The rescue chemotherapy regimens ± rituximab was used for induction therapy, then HDC/AHSCT was performed after remission. For patients who are not suitable for HDC/AHSCT, the rescue treatment options include: bendamustine monotherapy, CEPP regimen, CEOP regimen, DA-EPOCH regimen, GDP regimen, GemOx regimen. These regimens mentioned above can be combined with rituximab. Moreover, rituximab monotherapy or palliative radiotherapy can also be used. A portion of patients can only receive the best supportive care. In addition, allogenic hematopoietic stem cell transplantation may also be considered for appropriate patients.

(5) Special primary site DLBCL

1) Primary central nervous system DLBCL: It refers to DLBCL originating in the brain or eyes, excluding dural lymphoma, intravascular large B-cell lymphoma, lymphoma secondary to central nervous system invasion and immune deficiency lymphoma. The primary central nervous system DLBCL is less than 1% of NHL, accounting for about 2%–3% of primary brain tumors. The medium age of this disease is about 60 years old, and males are slightly more than females.

(a) Clinical manifestations: 50%–80% of patients have focal symptoms, generally accompanied by changes in mental and reactional levels. Patients also have nausea, vomiting, headache and other symptoms due to the elevated intracranial pressure. In addition, pia mater lesions could cause headaches and asymmetrical cranial nerve dysfunction. Intraocular lymphoma manifests as blurred vision, visual field defects, etc.

(b) Diagnosis: Imaging findings present the central nervous system nodules or masses. MRI is the preferred method of examination. It can be seen that the lesions exhibit a low signal or equal signal in the T1-weighted image, and the T2-weighted image shows a high signal, usually accompanied by edema. The pathological examination is still necessary for the diagnosis of this disease. The pathological samples can be obtained by stereotactic needle biopsy or craniotomy. Cerebrospinal fluid cytology is also acceptable when tumor biopsy is not available, and cerebrospinal fluid flowcytometry can be used as an auxiliary diagnostic tool. Diseases that need to be identified with primary central nervous system DLBCL include demyelinating disease, subacute infarction, intracranial space-occupying lesions caused by infection, gliomas, and metastases. In particular, it should pay attention to the identification of disease with similar imaging findings and hormonal therapies, such as multiple sclerosis and neurological sarcoidosis.

The perivascular infiltration of the primary central nervous system DLBCL is significantly obvious. The morphology of the tumor cells is similar to that of the centroblast, which basically originate from the non-germinal center B-cells, and the proportion of Ki-67 positive cells often exceeds 90%. The immunohistochemical antibodies of this disease for pathological diagnosis are same as that of DLBCL.

(c) Principles of treatment: The treatment of this disease is mainly based on medical treatment. Corticosteroids can quickly relieve patients' symptoms; however, disease often recur in the short term without chemotherapy or radiotherapy. Moreover, corticosteroids are not recommended prior to biopsy, except when intracranial hypertension is life-threatening. Chemotherapy is the most important treatment, and the principle of using drug is to penetrate the blood-brain barrier. The preferred chemotherapy regimen should contain a high-dose methotrexate regimen that can be combined with rituximab to effectively prolong patients' survival. Moreover, consolidation therapy can be performed in patients who have achieved CR/CRu after first-line treatment, including HDC/AHSCT, high-dose cytarabine +/– etoposide. Radiotherapy is recommended for patients who are resistant to chemotherapy or do not achieve CR. Relapse or refractory patients can select high-dose methotrexate ± rituximab regimen (remission period ≥12 months), temozolomide ± rituximab regimen, regime containing high-dose cytarabine, topotecan, pemetrexed, etc. For patients who are effective to rescue treatment could consider HDC/AHSCT.

Radiotherapy can effectively shrink the tumor and relieve patients' symptoms, and can prolong the survival time of patients compared with simple supportive treatment. The methods of radiotherapy generally include whole brain irradiation and local tumor area irradiation. However, the recurrence rate of radiotherapy alone is high and the performance of radiotherapy alone might cause certain neurotoxicity. Therefore, radiotherapy alone is limited to patients who cannot receive chemotherapy. Moreover, radiotherapy can be used as a consolidation treatment after chemotherapy. However, for elderly patients who have achieved CR after chemotherapy (>60 years old), there are some controversies about the advantages and disadvantages of consolidation radiotherapy. In addition, the role of surgery is limited to biopsy, and there is no benefit in the

complete removal of the tumor.

(d) Prognosis: The disease has a high degree of malignancy. The median survival time of different treatment strategies are 2–3 months for supportive therapy, 3–5 months for surgery alone, 12–16 months for radiotherapy alone, and 25–84 months for chemotherapy regime contained high dose of methotrexate, respectively. The most important prognostic factors are age and physical status.

2) Primary testicular DLBCL: The primary testicular DLBCL accounts for 3%–9% of testicular tumors, and accounts for 1%–2% of NHL. Moreover, DLBCL is the most common pathological type of primary testicular lymphoma with the rate of 80%–90%. In addition, the disease is the most common testicular malignancy in males over 60 years old, with a median age at diagnosis of 65 years old.

(a) Clinical manifestations: Most patients present testicular painless mass or swelling, while a few of patients appear as scrotal pain. About 20% of patients have both tests affected, and 35% of patients are involved with the contralateral testis during the course of disease. Patients with retroperitoneal lymphadenopathy may present with abdominal pain and ascites. B symptoms are usually seen only in patients with advanced disease. The disease is prone to extranodal organs involvement, including the central nervous system, skin, subcutaneous tissue, Webster's ring, lung, pleura, etc. The main presentations of ultrasound is increased testicular volume, smooth appearance, localized testicular or diffuse hypoechoic area, clear or unclear borders. Additionally, color ultrasound shows abundant blood supply, and normal testicular blood vessels can pass through the lesion.

(b) Principles of treatment: Primary testicular DLBCL should receive comprehensive treatment, including surgery, radiotherapy and immunochemotherapy. Moreover, patients with this disease should be performed orchiectomy and high spermatic ligation. Then patients should receive immunochemotherapy combined with contralateral testicular prophylactic radiotherapy and central nervous system prevention treatment after operation. In addition, patients with stage II disease should also receive regional lymph node irradiation.

(c) Prognosis: The disease may still recur 10–14 years after the initial treatment. Poor prognositic factors include advanced age, advanced stage, elevated LDH, B symptoms, high IPI score, and without surgery or radiotherapy.

3) Primary mediastinal DLBCL: Primary mediastinal DLBCL is common in young adults with the median age at diagnosis of 35 years old, and females are slightly more than males. Tumor cells of this disease originate from thymic B cells, and the gene expression profiles are unique and similar to cHL. Unlike most DLBCL, 70% of primary mediastinal DLBCLs express CD23 and PD-L1. Moreover, the expression of CD30 and CD23 suggests the diagnosis of primary mediastinal DLBCL.

(a) Clinical manifestations: The clinical symptoms and signs are associated with a rapidly increasing mediastinal mass, which could cause superior vena cava compression syndrome, hydropericardium, pleural effusion, etc. At the initial treatment, the lesions are usually limited, mainly located in the anterior superior mediastinum, which might be associated with supracondylar, cervical and hilar lymph nodes. After recurrence, lesions often involved with extensive extranodal organs or tissues. Additionally, patients with stage I–II disease account for about 80%, while patients with stage III–IV disease is rare.

(b) Principles of treatment: The option of chemotherapy strategies is still controversial. The alternative options include R-DA-EPOCH, R-CHOP continuous R-ICE, etc. For patients with early-stage disease, chemotherapy and sequential radiotherapy is preferred. However, female patients with no large lumps and negative PET-CT might not consider the performance of radiotherapy. Owing to the application of CT for evaluation, residual mass lesions are usually existing, however, it is impossible to identify whether the tumor remains. Therefore, it is suggested to use PET-CT for evaluation at the end of chemotherapy. Additionally, treatment of relapsed or refractory primary mediastinal DLBCL patients is based on relapsed or refractory DLBCL.

(c) Prognosis: The prognosis of this disease is better than that of non-specific DLBCL, and the 5-year overall survival (OS) treated with R-DA-EPOCH regimen can achieve more than 90%. Poor prognostic factors include older age, poor general condition, advanced stage, etc.

7.2.2 FL

FL is the most common indolent lymphoma in Europe and America, accounting for 20%–30% of NHL. The incidence of FL in Asia, including China, is low, less than 10% of NHL. The median age of onset was about 60 years old.

(1) Clinical manifestations

The main manifestations were multiple lymph node enlargement, which also involved bone marrow, peripheral

blood, spleen, Wechsler's ring, gastrointestinal tract and soft tissues. Primary extranodal cases were rare. Terminally ill patients are more common, accounting for about 70%.

(2) Pathological diagnosis

Morphological manifestations were the proliferation of follicular central cells and centroblasts, most of which were follicular nodular growth. According to the number of centroblasts, FL was divided into three grades: 0–5 centroblasts in each view of highly magnifying lens of microscopes were grade 1, 6–15 centroblasts were grade 2, 15 or more were grade 3. Grade 3 could be further divided into grade 3a and grade 3b, of which grade 3b showed that centroblasts were patchy distribution or lacked of centroblasts. IHC markers for FL diagnosis included CD19, CD20, PAX5, CD3, CD10, BCL-2, BCL-6, LMO2, CD21 and Ki-67, also inculed the markers for differential diagnosis, such as CLL/small lymphocytic lymphoma (SLL) and mantle cell lymphoma (MCL), such as CD23, CD5 and cyclin D1. FL often has t (14;18) translocation and Bcl-2 protein overexpression, which makes it difficult to diagnose. FISH can be used to detect BCL2 expression when necessary.

A new classification of duodenal-type follicular lymphoma (DTFL) was proposed in the revised WHO classification in 2017, which has a good prognosis and needs to be differentiated from FL in other gastrointestinal anatomical sites. The newly proposed large B-cell lymphoma with *IRF4* gene rearrangement often occurs in Waldeyer's ring and cervical lymph nodes, which is common in children and young people. Histological manifestations are consistent with classical FL. The prognosis is relatively good when epidemic histochemistry showed that IRF4+, CD10+, BCL6+ and molecular detection showed that *IRF4* gene rearrangement. In addition, the former *in situ* FL was replaced by *in situ* follicular neoplasms.

Bone marrow cytology: When tumor cells involve bone marrow, the proliferation of nucleated cells can be obviously active. FL cells were mainly increased with larger lymphocytes than normal cells. The nucleus is round or irregular, the nuclear chromatin is finer, the nucleolus is obscure, the cytoplasm is rich, pale blue, and some of the FL cells are vacuolar degeneration. The diagnosis of FL is mainly based on histopathology. When FL leukemia occurs, a certain number of FL cells can be seen in bone marrow or peripheral blood.

(3) Treatment

Grade 1–2 FL belongs to indolent lymphoma, and the treatment strategies are as follows. The treatment of grade 3 FL is equivalent to DLBCL.

(a) Early FL: Radiotherapy, immunochemotherapy ± radiotherapy, rituximab ± chemotherapy or observation and waiting are the recommended treatments for grade I and II FL. The choice of specific treatment should be based on patient's age, general condition and willingness to treat, combined with evidence-based medical evidence. Patients with a large mass greater than 7 cm should be treated as advanced FL.

(b) Late FL: With the existing treatments, late FL is still considered to be an incurable disease. A number of studies have shown that for FL patients with advanced stage but low tumor burden, there is no difference in OS time between immediate treatment after diagnosis and administrate treatment after observation the therapeutic indications.

The standard first-line treatment for FL is rituximab combined with chemotherapy. Palliative radiotherapy for symptomatic sites and clinical trials can also be considered. Chemotherapeutic regimens have many options, none of which has been proven to significantly prolong OS of patients. Chemotherapy options include CHOP regimen, CVP regimen and BR regimen. For elderly and frail patients, single-drug rituximab or single-drug alkylating agents (such as nitrogen mustard phenylbutyrate, cyclophosphamide) + rituximab can also be used. For patients with initial treatment and high tumor burden, CR or partitial remission (PR) can be achieved after induction chemotherapy, and rituximab maintenance therapy is feasible.

The indications for the treatment of advanced FL are as follows: symptoms show that threat to organ function, secondary hematopenia, large mass and continuous progression of lesions. Clinical trials are also a good choice for these patients.

(c) Treatments of relapsed and refractory FL: For relapsed FL, observation and waiting can be preferred, and rescue treatments can be started when treatment indications appear. If the relapse or progression is more than 6 months after the last application of rituximab, it can also be treated with rituximab. According to the time of recurrence or progression after first-line treatment, alternative second-line rescue chemotherapy regimens include first-line chemotherapy regimen, fludarabine-containing combination regimens and all DLBCL second-line rescue regimens. For FL with rapid progress, histological type transformation should be excluded first. The clinical

manifestations of suspicious transformation include elevated LDH, uncontrolled rapid growth in an affected area, extranodal lesions or newly emerged B symptoms. For example, PET-CT examination showed a significant increase in the standard uptake value of an invaded site, we should be alert to the occurrence of histological type transformation, and we need to carry out tissue biopsy on the suspicious site of transformation to clarify the pathological type. Conversion of FL during recurrence or progression has poor prognosis. HDC/AHSCT or allogeneic hematopoietic stem cell transplantation may be considered for patients with remission after partial induction chemotherapy. Biopsy is recommended for the treatment of transformed lymphoma (the possible recurrence is a pre-transformed pathological type).

(d) Prognosis: Follicular lymphoma international prognostic index (FLIPI) has two scoring systems, FLIPI1 and FLIPI2, which contain five independent adverse prognostic factors. All patients are divided into three risk groups, 0–1 into low-risk group, 2 into medium-risk group, and (>3) into high-risk group. FLIPI1 was obtained by retrospective study and analysis of rituximab pre-marketing treatments. Five adverse prognostic factors were age >60 years old, >4 lymph node involvement, III–IV, elevated LDH and hemoglobin <120 g/L. The 10-year OS of low-risk, medium-risk and high-risk groups were 71%, 51% and 36%, respectively. FLIPI2 was treated with rituximab. Prospective study showed that five adverse prognostic factors were age >60 years old, the longest diameter of lymph node >6 cm, bone marrow invasion, increase of β2 microglobulin and hemoglobin <120 g/L. Five-year OS of low-risk, middle-risk and high-risk patients were 98%, 88% and 77%, respectively, and 5-year PFS were 79%, 51% and 20%, respectively (*Appendix 5.3*).

7.2.3 MZL

MZL is a type of indolent lymphoma that originates from the marginal zone and comprises of 3 distinct subtypes: extranodal MZL (EMZL), nodal MZL (NMZL), and splenic MZL (SMZL), among which EMZL, also known as mucosa-associated lymphoid tissue (MALT) lymphoma, is the most common subtype and it is also the most common indolent lymphoma subtype in China. The prognosis of MALT lymphoma is superior to NMZL and SMZL.

The cause of MZL is associated with persistent immune stimulation due to chronic infection or inflammation [e.g. gastric MALT lymphoma is associated with Hp infection; thyroid MALT lymphoma is associated with Hashimoto's thyroiditis; parotid MALT lymphoma is associated with Sjgren's syndrome (SS); and NMZL and SMZL are associated with hepatitis C viral infection].

Due to the lack of specific immunological markers, exclusion method is mainly used for the pathological diagnosis of MZL and the main exclusion subtypes are other types of small B-cell lymphoma. CD21 and CD23 are often used to reflect an expanded follicular dendritic cell network. Pathological morphology often appears as small lymphocytic clonal hyperplasia, causing the widening of marginal zone, atrophy of the germinal center, visible follicular implantation phenomenon and lymphatic epithelial lesions. κ and λ are recommended to use in differential diagnosis of MALT lymphoma or NMZL with plasma cell differentiation.

Bone marrow cytology: nucleated cell proliferation is markedly active; villus lymphocytes are significantly increased; the percentage of both granular and erythroid cells are reduced, and the number of megakaryocytes is variable.

(1) MALT lymphoma

The most common primary site of MALT lymphoma is the gastrointestinal tract, of which gastric accounts for approximately 80%–85%. About 2/3 of the patients have a limited-stage, while the other patients have an extensive-stage, and bone marrow invasion is about 10%–15%.

1) Primary gastric MALT lymphoma

(a) Clinical manifestations: The common symptoms include indigestion, acid reflux, abdominal pain, weight loss, etc., while B symptom is uncommon. The proportion of gastric bleeding and perforation are 20%–30% and 5%–10%, respectively. Stage I and II patients account for 80%–90%, and 90% patients are Hp positive. Endoscopic appearance can vary from erythema, erosion to ulceration, etc.

(b) Pathological diagnosis: Gastroscopic biopsy is an essential examination and routine HE staining is required. The typical morphology of MALT lymphoma is small lymphocyte dense proliferation, infiltration and destruction of mucosal epithelium, leading to the formation of lymphatic epithelial lesions. The common IHC markers include CD3ε, CD5, CD10, CD19, CD20, PAX5, CD23 and Cyclin D1. Patients excluded as FL, CLL/SLL and MCL, can be diagnosed as MALT lymphoma by the combination of morphology and B cell phenotype detection of t (11;18) translocation by FISH or PCR can be used to determine whether the gastric MALT lymphoma is Hp-dependent, indicating resistance condition of anti-Hp treatment. DLBCL accompanied with MALT lymphoma

should be diagnosed if large transformed lymphocytes show solid or flaky hyperplasia.

(c) Principle of treatment: For Hp positive patients, anti-Hp therapy is the preferred treatment, followed by gastroscopy to further confirm the Hp clearance, but patients with t (11;18) translocation need further radiotherapy after anti-Hp therapy. For Hp negative patients or Hp positive patients with failed anti-Hp therapy, radiotherapy is preferred. Patients who are not suitable for radiation therapy may consider single-agent rituximab treatment. Stages III and IV Patients with no treatment indications can choose "watch and wait", while patients with indications for treatment can refer to the treatment principle of advanced FL. Surgical treatment is limited to special cases such as bleeding, perforation, etc.

2) Non-gastric MALT lymphoma

(a) Clinical manifestations: Non-gastric MALT lymphoma presents an inert process with a similar prognosis to primary gastric MALT lymphoma. The common involved-sites include salivary glands, lungs, head and neck, eye appendages, skin, thyroid, breast, etc.

(b) Principle of treatment: For stage I and II patients, radiotherapy is preferred, but those suffering serious complications due to radiotherapy may consider "watch and wait" or single-agent rituximab treatment. Stages III and IV patients refer to the treatment principle of advanced FL.

(2) NMZL

(a) Clinical manifestations: NMZL, accounting for 1.5%−1.8% in all lymphomas, distributing similarly in males and females, with a median age of onset of 60 years. Late lesions are common, mainly involving the lymph nodes and even the bone marrow and peripheral blood. Most patients present with painless multiple lymphadenopathy, but patients with MALT lymphoma or SMZL, accompanied by lymph node involvement, should be noted.

(b) Pathological diagnosis: The structural features are similar to the SMZL, and the immunophenotype is not specific, similar to other MZL subtypes.

(c) Principle of treatment: Refer to treatment principle of advanced FL.

(d) Prognosis: The 5-year OS is 60%−80%, and the prognosis refer to FLIPI in details.

(3) SMZL

(a) Clinical manifestations: SMZL, accounting for 2% in all lymphomas, distributing similarly in males and females, with a median age of onset of 50 years. The common involved-sites include spleen, splenic hilar lymph nodes and even bone marrow, peripheral blood and liver. The most common symptom is splenomegaly, occasionally accompanied by autoimmune thrombocytopenia, anemia, visible hair cells in the peripheral blood. Hepatitis C virus should be included in laboratory tests.

(b) Pathological diagnosis: The tissue structure is similar to NMZL, but the immunophenotype is not specific. Patients who are excluded as CLL/SLL, MCL, FL, may be diagnosed as SMZL if abnormal small lymphocytes involve in the bone marrow or peripheral blood, accompanied by splenomegaly.

(c) Principle of treatment: For patients with no symptoms, progressive hematopenia, and splenomegaly, "watch and wait" is preferred. For patients with splenomegaly and positive HCV infection, anti-hepatitis C treatment is recommended if there are no contraindications. For patients with splenomegaly, but negative for hepatitis C virus, clinical symptoms should be considered when choosing a treatment plan. For those without symptoms, "watch and wait" is recommended, while for those with symptoms, simple splenectomy or rituximab monotherapy is preferred. Patients who have progressed after the above treatments, could refer to the principles of treatment of advanced FL.

(d) Prognosis: Patients with large lumps and poor general condition have a poor prognosis.

7.2.4 CLL/SLL

CLL and SLL are indolent B-cell malignancies that are often considered to be different clinical presentations of one disease. SLL usually has no leukemia-like appearance, while CLL is mainly composed of bone marrow and peripheral blood invlvement. The International Workshop on Chronic Lymphocytic Leukemia (IWCLL) defines SLL as having lymphadenopathy and/or splenomegaly, no hemocytopenia due to bone marrow invasion, and B cell count in peripheral blood less than 5×10^9/L. SLL needs to be confirmed by histopathology of lymph node biopsy, while flow cytology is usually sufficient to diagnose CLL, requiring lymph node biopsy and bone marrow biopsy for difficult diagnosis. The diagnosis of CLL should meet the following criteria: the presence of monoclonal B cell lymphocytes in peripheral blood $\geq5\times10^9$/L; characteristic mature small lymphocytes in peripheral blood increased significantly, atypical lymphocytes and naive lymphocytes in lymphocytes ≤55%; the typical immunophenotypes were CD19+, CD5+, CD23+, CD20 weak+, CD43+/−, CD10−,

CyclinD1−; Flow cytology confirmed that B cells were clonal abnormalities.

CLL/SLL, in Europe and the United States, is one of the most common type of leukemia, accounting for 7%−10% of NHL. In comparison, Asian populations have a significantly lower incidence of disease. The incidence of CLL/SLL accounts for about 1%−3% of NHL in China. The median age of onset was 65 years old, and the ratio of male to female was 1.5−2:1.

(1) Clinical manifestations

Lesions usually involve peripheral blood, bone marrow, lymph nodes and liver and spleen. Clinical manifestations are diverse, most patients can be asymptomatic, and some may have fatigue, autoimmune anemia, infection, hepatosplenomegaly and lymphadenopathy.

(2) Pathological diagnosis

Typical CLL/SLL cells are singular, diffuse infiltration, with pseudo-follicle formation, and nuclear chromatin granules are characteristics, showing the proliferation center. IHC phenotype: CD5+, CD23+, CD43+/−, CD10−, CD19+, CD20 weak+. Other markers, such as Cyclin D1, CD10, and BCL-6, can be specifically targeted for differential diagnosis. The appearance of proliferative foci could be easily misdiagnosed as reactive hyperplasia, and there are monoclonal B-cell lymphocytosis (MBL) in early stage.

Cytological diagnosis

Blood: RBC and HGB are mostly normal in early stage, and can be reduced in late stage. WBC increased, mostly (30−100)×10^9/L; the number of lymphocytes continuously increases, and mainly consists of differentiated CLL lymphocytes, often more than 50%, up to 80%−90%. Its morphology is similar to normal lymphocytes, but the nucleus is irregular, presenting as deep incision or nuclear fissure; the nuclear chromatin irregularly aggregated, with small cytoplasm, grayish blue and no particles. Broken cells (e.g., basket cells) are more common; a small number of young lymphocytes increase, usually less than 2%. Thrombocytopenia can be seen in late stage. If there is no extramedullary tissue infiltration, the CLL phenotype monoclonal lymphocytes in peripheral blood must be ≥ 5×10^9/L.

Bone marrow

Bone marrow nucleated cells are significantly or extremely active. Lymphocytes are highly proliferative, mainly composed of abnormal mature small lymphocytes, accounting for more than 40%, and even up to 90%. The size and shape of the cells are basically as same as those in peripheral blood. The morphological abnormalities are not obvious. The nucleus shows deep incisions or fissures, and the nuclear chromatin irregularly aggregated, with nucleolus absence or not obvious. There was a small amount of cytoplasm and no particles. It can also be mixed with some medium to large lymphocytes. Primary and young lymphocytes are generally less than 5%. Increased numbers of young lymphocytes are associated with disease progression. When the young lymphocytes are more than 55%, it can be diagnosed as promymphocytic leukemia (PLL). The granulocyte, erythroid and megakaryocytic cells were significantly reduced. When the patient is accompanied by hemolysis, the young erythrocytes may significantly proliferate.

(3) Staging

The Lugano staging system is utilized for patients with SLL; CLL refers to the Rai and Binet staging systems (*Appendix 2.2*).

(4) Treatment

(a) SLL: Phase I patients use local radiotherapy; patients with stage II−IV can wait for treatment if there is no indication for treatment, and refer to the treatment principles of CLL when there are indications for treatment.

(b) CLL: Low-risk and intermediate-risk patients with stage 0−II of Rai can watch and wait if there is no indication for treatment; when there are indications for treatment, according to FISH test and *p53* gene mutation results, general state of patients and comorbidities, select the corresponding treatment programs. If high-risk patients with stage III−IV have progressive cytopenia, follow the FISH test and *p53* gene mutation results, general patient status and comorbidities, choose the appropriate treatment program. Attention should be paid to the supportive treatment of CLL, such as the treatment of tumor lysis syndrome, infection, and autoimmune cytopenia.

(c) Treatment indications: Suitable for clinical trials; obvious disease-related symptoms such as severe fatigue, night sweats, weight loss and non-infectious fever; threatening organ function; continuously enlarged masses, such as splenomegaly beyond the left costal margin 6 cm, lymph node diameter >10 cm; lymphocyte count >200−300×10^9/L, or the presence of leukocyte stasis symptoms; progressive anemia and progressive thrombocytopenia.

(d) First-line treatment options: Patients <65 years old or ≥ 65 years old, without *del(17p)/p53* gene mutation or severe comorbidities, are recommended for FCR regimen, FR

regimen, bendamustine +/– rituximab, Ibrutinib, high-dose methylprednisolone + rituximab and other treatments. Patients ≥65 years old or <65 years old with comorbid disease, are recommended for Ibrutinib, bendamustine +/– rituximab, chlorambucil + rituximab, high-dose methylprednisolone + rituximab, chlorambucil monotherapy, rituximab monotherapy and other regimens. Frail patients with severe comorbidities who are unable to tolerate steroid therapy, may choose Ibrutinib, chlorambucil + rituximab, high-dose methylprednisolone + rituximab, rituximab single monoclonal antibody, single-agent chlorambucil. After remission, patients with minimal residual tumors (MRD) $\geq 10^{-2}$ may be considered for lenalidomide maintenance therapy.

Patients with *del(17p)* gene mutations have poor efficacy in the above immunochemotherapy regimen and are recommended to participate in clinical trials. Recommended first-line treatments include: ibufibrate, high-dose methylprednisolone + rituximab, and lenalidomide maintenance therapy for patients with MRD $\geq 10^{-2}$ after remission. Allogeneic hematopoietic stem cell transplantation is considered for young patients with donors.

(e) Treatment options for patients with relapse and resistance: If the duration of remission after treatment is ≥2 years, continue to use the previous treatment plan. If the remission period after treatment is less than 2 years, immunochemotherapy or targeted drug combinations that have not been applied in the previous first-line treatment scheme can be selected according to the results of FISH detection and *p53* gene mutation, age and comorbidities. Firstly, we recommend molecular targeted drugs and their combinations, including Ibrutinib, rituximab +PI3K inhibitor (Idelalisib), new CD20 monoclonal antibody (Ofatumumab, Obinutuzumab), bcl-2 inhibitor (Venetoclax), and lenalidomide, etc. After treatment remission, lenalidomide maintenance therapy can be considered.

(5) Prognosis

SSL/CLL patients survive for 2–15 years. The factors associated with poor prognosis include late stage, del(11q) and del(17p) changes, *p53* gene mutation, the proportion of CD38 positive tumor cells ≥30% or ZAP70 positive cells ratio ≥20% or immunoglobulin heavy chain variable region (IGHV) mutation rate ≤2%, CD49d ≥30%, complex karyotype (≥3 chromosomal abnormalities), etc. CLL-IPI prognostic staging system integrates cytogenetics, IGHV mutation status, β2-microglobulin, age, staging and other factors, which can be utilized to stratify the prognostic risk of CLL.

7.2.5 MCL

MCL accounts for approximately 5%–10% of NHL. MCL predominates in males over females with a ratio of around 2–3:1, the median age at diagnosis is around 65 years old. The natural course of this disease can be divided into aggressive and indolent MCL. The classic variant of MCL accounts for the majority with aggressive behavior. And this variant resembles indolent MCL to therapy, thus this disease is considered incurable. The OS of patients with prior combined chemotherapy is about 3–5 years. But in recent years, with the rapid progress of HDC/AHSCT and new pharmacological research, the OS has improved significantly. A small proportion of patients with indolent MCL, so called leukemic non-nodal MCL, with less molecular genetic variations, have no mutation or lack of *p53* gene and appear non-expression or low expression of SXO11. Similarly, to the course of indolent lymphoma, this disease presents with a good prognosis.

(1) Clinical features of MCL

Frequently involving lymph nodes, bone marrow, gastrointestinal tract, spleen and Waldeyer's ring. About 70% patients present with stages IV disease at diagnosis. The bone marrow infiltration rate can be 50%–100%. With lower gastrointestinal involvement (80%–90%), and upper gastrointestinal involvement (about 40%), digestive tract involvement under endoscope presents with multiple polypoid lesions.

(2) Pathological diagnosis

Tumor cells of MCL are small, medium or large size lymphocytes with similar morphological characteristics and irregular nuclear surface. The main architectural patterns of these cells are mantle zone, nodular and diffuse. Given its poor prognosis, it is, therefore, of significance to conduct differential diagnosis, distinguishing from CLL/SLL, FL and MZL. The commonly used IHC markers are CD20, PAX5, CD3, CD10, CD23, MUM-1, SOX11 and CD138. Cyclin D1+ expression and CD5+ expression can be observed in most patients. While Cyclin D1– expressed, diagnosis of MCL is difficult and other available evidence is essential. Detection of t (11;14) using FISH presents with great sensitivity and specificity in the diagnosis of MCL. Furthermore, according to the revised version of WHO Lymphoma Classification (2017), MCL can be divided into two types: the classic variant of MCL, SOX11 positive and no or less IGHV mutation. This type

of MCL shows high invasiveness and poor prognosis, or appears blastoid variants and pleomorphic cells with greater invasiveness and *p53* mutation. Leukemic non-nodal MCL, the other type, frequently involving peripheral blood, bone marrow and spleen, presents with SOX11 negative expression and IGHV mutation, with an indolent clinical traits and good prognosis. But poor prognosis can be found with *p53* gene mutation.

Bone marrow cytology

With bone marrow infiltration, various amounts of abnormal lymphocytes increasing can be observed in bone marrow smear. These tumor cells vary in size, and mainly have a circular or mild irregular nucleus frequently with a big and abnormal nucleolus. The chromatin is finely dispersed. Rich and pale blue cytoplasm can be observed in these cells.

(3) Treatment

Overall detections and accurate staging are needed for the patients with MCL to guide treatment options. The patients with blastoid variants and symptoms of central nervous system should conduct cerebrospinal fluid examination and brain MRI. For patients with stages I–II MCL, endoscopy examination is necessary to exclude gastrointestinal involvement.

(a) Treatment options: A widely used regimen for stages I–II patients of classic variant of MCL is the combination of chemotherapy and rituximab plus radiotherapy, or radiotherapy alone. Patients with stage II MCL accompanying masses, or with stages III–IV MCL, may benefit from stratified treatment strategy: for patients older than 60–65 years, or with a poor condition and not suitable for HDC/AHSCT, the regimen of chemotherapy plus rituximab can be used to prolong survival; for patients younger than 60–65 years, with a good condition and suitable for HDC/AHSCT, the induction treatment of rituximab plus high-dose cytarabine should be used. HDC/AHSCT is needed after releasing and the patients may further benefit from maintenance treatment with rituximab. Leukemic non-nodal MCL and *in situ* MCL, two subtypes newly added by Classification of Tumors of Haematopoietic and Lymphoid Tissues (2016 edition), have a slow course and are considered incurable. Thus, immediate treatments of these diseases are unnecessary, and watchful waiting approach is generally recommended. With therapeutic indications such as rapid progression of symptoms and courses or severe tumor loads, treatment is necessary.

(b) First-line treatment: Without standard treatment options, it is advisable for patients with MCL to conduct clinical trials. For elder patients with poor condition and not suitable for HDC/AHSCT, reduced-intensity regimens are recommended, including COP, CHOP, R-CHOP, VR-CAP, B-R and reduced-dose R-Hyper-CVAD/R-MA alternative therapeutic strategy. Intensified chemotherapeutic regimens are recommended to induce releasing for younger patients, HDC/AHSCT as the first-line consolidation therapy and then using rituximab 3 years as maintenance treatment. Advisable treatment regimens include CALGB regimen, R-Hyper-CVAD/R-MA alternative therapy, R-CHOP/R-ICE alternative therapy, NORDIC/R + HD-Ara-C alternative therapy and R-CHOP/R-DHAP alternative therapy. Novel targeted drugs like ibrutinib combined with rituximab (IR) followed by R-Hyper-CVAD/R-MA, are expected to improve the model of the first-line therapy of MCL.

(c) Second-line treatment: Without standard treatment options, regimens that show no cross resistance with the above first-line treatment are feasible, including B-R therapy containing bendamustine, R-BAC therapy, and FCR and FMR therapy are also effective. Allogenic stem cell transplantation is considered for second-line consolidation therapy. Novel targeted drugs, like bortezomib, lenalidomide and ibrutinib and its combination regimens, are also recommended.

(4) Prognosis

IPI for aggressive lymphomas, identified from the survival data of aggressive lymphomas, can be used as a prognostic indication of MCL, although with poor efficiency. Simplified version of the Mantle Cell Lymphoma International Prognostic Index (MIPI), which can better stratify the prognosis of MCL, is widely used. Other bad prognostic factors contain Ki-67, p53 and blastoid variant. Ki-67 is the most important biological prognostic factor independent of MIPI. By including Ki-67 and MIPI, the so-called MIPI-c can better stratify the prognosis of MCL, which is also recommended (*Appendix 5.4*).

7.2.6 BL

BL is a highly invasive NHL, which can be divided into three variants: local epidemic, sporadic and immune deficiency correlation. BL accounts for about 3%–5% of NHL and about 40% of children's NHL.

(1) Clinical characteristics

Epidemic BL mainly occurs in equatorial Africa and Northeastern Brazil, with the peak onset age of 4–7 years old, male to female ratio of 2:1, more involved jaw bones,

and EBV positive rate of >95%. Sporadic BL is scattered all over the world, mainly in children and young people, with a male to female ratio of 3:1 to 2:1. The abdominal involvement is more common in BL, and the positive rate of EBV is less than 30%. Most of the immune deficiency-related types occur in acquired immune deficiency syndrome (AIDS) patients, often involving lymph nodes and bone marrow. BL is a tumor with the shortest cell multiplication cycle which grows rapidly. Extranodular invasion of BL is common, of which head and neck, abdomen, bone marrow and central nervous system are the most commonly affected sites.

(2) Pathological diagnosis

Typical BL morphology shows diffuse proliferation of medium size neoplastic B cells, obvious mitosis and apoptosis, and common starry sky phenomenon. Tumor cells originate from germinal centers, and IHC immunophenotypes often presents as sIgM+, single light chain +, CD19+, CD20+, CD22+, C-MYC+, CD10+, Bcl-6 +, Bcl−, CD5−, CD23−, MUM-1 and TdT−. The proliferation index is very high, and the positive rate of Ki-67 is nearly 100%. Even if morphological and immunophenotypes all suggest typical BL, FISH should also be applied for MYC detection, of which t (8;14) accounts for about 80%, t (2;8) and t (8;22) for about 15%. The differential diagnosis includes high-grade B-cell lymphoma with MYC, BCL-2, and/or BCL-6 rearrangement and Burkitt-like lymphoma with 11q abnormality. EBV-EBER detection is necessary for BL, but more sporadic patients are found in China, and EBV-EBER negative is more common.

Bone marrow cytology

Bone marrow hyperplasia is obviously active or hyperactive. The typical BL cells are medium to large lymphocytes, which tend to be distributed in piles with different sizes, and the nuclei of leukemic cells are large, mostly round or irregular. The nuclear chromatin is coarse granular, and there are one or more obvious nucleoli of different sizes. The number of cytoplasm is uncertain, strongly basophilic and contains a large number of lipid vacuoles of different sizes, and vacuoles can also be seen in the nucleus. The degenerated cells are more common in the smear, and the proliferation of granulocytic and erythroid cells are inhibited.

(3) Treatment

Chemotherapy is the main treatment, but the curative effect of CHOP regimen is not ideal, and high-dose intensive treatment could improve the curative effect. Combining with rituximab can improve long-term survival rate of patients, especially for patients over 60 years old. Prophylactic treatment of central nervous system should be carried out to prevent the occurrence of tumor lysis syndrome. Depending on high- or low-risk classification, BL chemotherapy regimens may include: CODOX-M (low-risk group), CODOX-M/IVAC (high-risk group), dose-adjusted EPOCH or Hyper-CVAD/HD-MA regimens. R-ICE, R-GDP, R-IVAC and other regimens can be used in second-line chemotherapy, and HDC/AHSCT or allogeneic hematopoietic stem cell transplantation can be considered in patients with complete remission.

(4) Prognosis

Sporadic, adult, late staging, high LDH, bone marrow invasion and HIV positive are the adverse prognostic factors of BL.

7.2.7 Lymphoblastic lymphoma (LBL)

LBL accounts for 3%−4% of adult NHL and about 40% of childhood NHL, which is a highly invasive lymphoma. It can be divided into T-LBL and B-LBL derived from T cells and B cells, respectively. T-LBL accounts for more than 80% of LBL and B-LBL accounts for about 10%−15% of LBL. LBL and acute lymphoblastic leukemia (ALL) are the same disease with different clinical manifestations and different stages of development. The ratio of primitive and immature lymphocytes in bone marrow ≥25% is defined as ALL according to WHO classification.

(1) Clinical manifestations

Typical clinical manifestations of T-LBL are cough and shortness of breath caused by a huge mass in the anterior mediastinum, which can be accompanied by pleural effusion, bone marrow and central nervous system invasion. B-LBL is often characterized by enlarged lymph nodes, with skin or bone invasion.

(2) Pathological diagnosis

In terms of cell morphology, LBL is mainly characterized by diffuse growth of medium-sized tumor cells, round, irregular or twisted nucleus, indistinct nucleolus, few cytoplasm, fine chromatin and easy mitosis. The LBL immunophenotype is characterized by TdT (+), which can also increase the determination of CD99 and CD10 to assist in the differentiation of mother cells. The immunophenotype of B-LBL is sIg−, cIg+, CD10+, CD19+, CD20− or +, PAX5+. The immunophenotypes of T-LBL are CD3ε +/−, CD2+, CD4+, CD8+, CD1α+/− and

CD7+. CD7 and CD43 can not be used as markers of T lymphocytes alone. When the cells are immature, it is necessary to increase the detection of CD34, CD117, MPO and Lys in order to distinguish acute myeloid leukemia. Since LBL is derived from immature lymphocytes, tumor cells can simultaneously express markers of B or T lymphocytes, and even express molecular markers of NK or myeloid cells, therefore this situation is not uncommon and should be noted in particular. When the lesion occurs in the mediastinum, additional epithelial-related markers (such as AE1/AE3 and CK19) and clonal rearrangement of T/B cell genes are needed to differentiate and diagnose thymus tumor. B-LBL is often associated with some specific genetic abnormalities, such as *BCR-ABL1*, *ETV6-RUNX1* and *KMT2A* rearrangements. Relevant genetic examination is recommended if conditions permit.

Bone marrow cytology

The proliferation of nucleated cells in bone marrow is usually hyperactive or obviously active, mainly with primary and juvenile lymphocyte hyperplasia, often accompanied by morphological abnormalities. The prolymphocyte is round, elliptic or caudate. The nuclei are mostly round and large, with uneven chromatin thickness and irregular arrangement, and pits, folds, cuts and cracks can be seen in the nuclei. The cell mass is less and the nucleoplasma ratio is high. Granulocyte proliferation is significantly inhibited and granulocytes decreased significantly, or even disappeared. The proliferation of erythroid cells is also significantly suppressed, and juvenile erythrocytes are rare or absent. Most of the megakaryocytes are significantly reduced or not seen, and platelets were rare. The number of degenerating cells increases obviously. Mitotic cells are readily visible. It is found that when there are eosinophils infiltrating around the lymphoma cells in T-LBL, the 8p11.2 cytogenetic abnormalities of eosinophilic granulocytosis and myeloid hyperplasia associated with *FGFR1* gene should be ruled out.

Hemogram

Most of the white blood cell count is increased, a few can be as high as 100×10^9/L.

(3) Treatment

Patients with whether I or IV stage should be treated as systemic diseases. LBL patients should adopt the treatment scheme of ALL. For young adult patients, the therapeutic effect of ALL treatment scheme for children is better than that for adults. The treatment process includes induction therapy, consolidation and reinforcement, maintenance therapy and so on. In order to prevent tumor lysis syndrome, glucocorticoid plus cyclophosphamide can be pretreated. VDCLP regimen or Hyper-CVAD/HD-MA regimen is recommended for induction therapy. Lumbar puncture and intrathecal injection should be started as soon as possible to prevent the invasion of the central nervous system. Consolidation and intensive therapy should be continued after induction therapy reaches complete remission. For patients without bone marrow invasion, HDC/AHSCT may be considered as soon as possible after consolidation chemotherapy. Patients after HDC/AHSCT should be treated with MTX combined with 6-mercaptopurine (6-MP) or 6-thioguanine (6-TG) for a total treatment period of at least 2 years. Patients with high risk of initial treatment and refractory recurrence can choose allogeneic hematopoietic stem cell transplantation. Patients with t (9;22)/BCR-ABL positive can be treated with chemotherapy combined with imatinib, and L-asparaginase (L-ASP) can no longer be used in the chemotherapy regimen. It is recommended that imatinib be used continuously until the end of maintenance therapy.

(4) Prognosis

The prognosis of children's LBL is significantly better than that in adults. Other adverse prognostic factors included high leukocyte count, central nervous system involvement, long time to complete remission, residual lesions after induction chemotherapy. Some gene abnormalities are associated with poor prognosis, such as t (9;22), t (4;11), t (8;14), complex karyotype, subdiploid or nearly 3-ploid, while patients with t (12;21) has a better prognosis.

7.2.8 Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)

PTCL is a group of lymphoid malignancies originating from post-thymic mature T lymphocytes, which has many subtypes, PTCL-NOS is the most common one. PTCL-NOS accounts for 7%–10% of all NHL in European and American countries, while the incidence rate in Asian countries accounts for 15%–22% of all NHL, which is significantly higher than that in European and American countries. The diagnosis of PTCL-NOS can only be confirmed after excluding other independent types of T-cell lymphoma, because it is not specific in morphology, immunology, genetics and clinical manifestations.

(1) Clinical manifestations

The median age of onset of PTCL-NOS was 55 years old, which was common in middle-aged and elderly people, with no significant gender difference. Superficial lymph

node enlargement was the most common symptom, and half of patients had B symptoms. Outside the knot often involves in skin and the subcutaneous tissue, liver, spleen, digestive tract, thyroid gland and bone marrow, etc. Most patients were diagnosed with III, IV period at their first visit.

(2) Pathological diagnosis

PTCL-NOS is the tumor at the stage of mature (peripheral) T cell development. Histopathology shows a mixed background of abundant small endothelial hyperplasia, epithelioid histiocytosis, and inflammatory cell infiltration. Tumor cells are diverse and varied, and are composed of small, medium or large cells, most of which are medium to large cells. The characteristics of PTCL-NOS also include pale cytoplasm, pleomorphic and irregular nuclei, abundant or vesicular chromatin, prominent nucleoli, and mitotic appearance. Common immunophenotypes of PTCL-NOS contain CD3+, CD4+, CD5+, CD45RO+, CD7− and CD8−. Tumor cells often express T cell-related antigens, such as CD3ε and CD2, and lose one or more other mature T cell antigens (CD5 or CD7), which indicates that clonal proliferation of T cells was existed. Meanwhile, TCR gene of PTCL-NOS often presents as clonal rearrangement, which means TCR gene rearrangement can be used to assist diagnosis when it is difficult to distinguish it from reactive changes in lymphoid tissues. Attention should also be paid to differentiating follicular helper T-cell lymphomas of origin, such as AITL, peripheral T-cell lymphomas of lymph nodes with follicular helper T-cell phenotypes, and lymph node follicular T-cell lymphomas, etc. In addition, they resemble T cells and need to be identified, when the pleomorphism of DLBCL cells is obvious. Therefore, B-cell markers, such as CD20 and PAX5, are indispensable. Note the clonality of plasma cells in the presence of multiple plasma cell proliferation. PTCL-NOS includes three subtypes, which overexpress GATA3, TBX21 and cytotoxic genes, respectively. Among them, GATA3 type has poor prognosis.

Cytology of bone marrow

Proliferation of nucleated cells in bone marrow was mostly active, mainly lymphocyte hyperplasia. In most cases, ATL cells were over 10%, but up to 80%. Granulocytes, erythrocytes and megakaryocytes are often reduced.

(3) Treatment

(a) Treatment strategies. PTCL-NOS is a group of heterogeneous diseases, of which optimal treatment plan and strategy are still being explored. For IPI low-risk patients with low or moderate I, II period, the priority recommended to participate in clinical trials or 4–6 cycles of chemotherapy combined with local radiotherapy. For IPI high-risk patients with high dangerous I–IV period, first-line treatment to participate in clinical trials, or 6–8 cycles of chemotherapy joint or not combined with local radiotherapy. For patients with recurrent refractory PTCL-NOS, clinical trials, posterior therapy or palliative radiotherapy is given priority to recommended.

(b) First-line treatment scheme. Young patients with poor prognosis are recommended to participate in clinical trials. Alternative solutions include CHOP-21 day, CHOP-14 day, CHOEP, DA-EPOCH and Hyper-CVAD/MA. For patients who cannot tolerate anthracycline therapy, other regimens which contained gemcitabine should be considered. HDC/AHSCR or allogeneic hematopoietic stem cell transplantation should also be considered for young patients, which excluded ALK-positive anaplastic large cell lymphoma.

(c) Second-line treatment scheme. Clinical trials are still be recommended first. Otherwise, second-line rescue treatment, including local radiotherapy is performed. Sequential HDC/AHSCT or allogeneic hematopoietic stem cell transplantation is still the priority second-line treatment system strategy for patients with acquired CR or PR. The selection of second-line treatment scheme is determined by whether patients were planned adoption with HDC/AHSCT or allogeneic hematopoietic stem cell transplantation. Alternative single-drug regimens include sidarbenamine, bailiestat, romidixin, pratracta, gemcitabine, bendamustine, lenalidomide, bortezomib, and BV (targeting CD30 + PTCL only), etc. Alternative joint schemes include DHAP scheme, ESHAP scheme, GDP scheme, GemOx scheme and ICE scheme, etc.

(4) Prognosis

Overall prognosis of PTCL-NOS was worse than that of patients with invasive B-cell lymphoma, and the 5-year survival rate of PTCL-NOS was approximately 30%. The prognostic scoring system includes IPI and prognostic index for PTCL-NOS, and the PIT includes >60 years old, LDH increase, PS score ≥2 and bone marrow invasion (*Appendix 5.5*).

7.2.9 Mycosis fungoides/Sézary syndrome (MF/SS)

MF/SS are the most common cutaneous T cell lymphoma (CTCL), accounting for approximately 2%–3% of NHL. While MF accounts for 60% of CTCL, SS only accounts for 5%. MF is a primary cutaneous matural T-cell lymphoma with an indolent course. SS is considered as a

variant of erythrodermic leukemic MF with an invasive characteristic, featuring as obviously hematologic manifestations and lymphadenopathy.

(1) Clinical features

MF presents clinically with erythematous patches, plaques and tumors. Generally distributed in skins, pruritus can be found frequently in this disease. With a recurring course, the lesion can be limited to the skin, typically months to years, even decades. Lymph node and visceral organ involvement can be found in the later stage. Generalized erythroderma accounts for approximately 10% of MF skin lesions. SS typically features as generalized erythroderma with peripheral blood involvement, and Sézary cells can be detected in lesional tissues, lymph node and peripheral blood. The diagnosis of SS should be based on: absolute Sézary cell counts $\geq 1\times10^9$/L, CD4+/CD8+ ratio ≥10, the immunophenotypic analysis of the tumor cells as CD3+, CD4+, CD5+, CD45RO+, CD7− and CD8−, and evidence of T-cell clonal proliferation.

(2) Pathological diagnosis

A definitive diagnosis of MF may need years of observation and several biopsies. Atypical T cells of small regular size with irregular nuclei aggregate in epidermis and dermoepidermal junctions, infiltrating epidermis and forming Pautrier microabscesses as its feature. The main characteristics of SS are considered similarly as MF. Immunophenotype of MF presents with matural memory T cells, CD3ε+, CD4+, CD45RO+ and CD8−. Matural T cells with phenotype of CD4− and CD8+, as the evidence of clonal proliferation of T cells, are infrequently detected. This disease should be distinguished from lymphoma originated from helper follicular T cells. Pathological diagnosis at non-tumour stage is difficult, and it should be distinguished from non-atopic dermatitis. Clinical traits should be especially noticed.

(3) Staging

The Staging Criteria of Cutaneous T cell Lymphoma (*Appendix 6*).

(4) Treatment

While present treatment strategies for MF and SS are generally not curative, thus, stage of this disease is considered the main factor to guild therapy. Intense treatment should not be conducted in the early stage of skin lesions, and topical treatment or the combination of several topical treatments is recommended. Comprehensive treatments with systemic treatment as the main or clinical trials are recommended at the IIB, III and IV stages of the disease or with the refractory lesions. Treatment options contain therapy targeted at skin and systemic treatment, or the combination of both. Therapy targeted at skin includes topical corticosteroids, nitrogen mustard or solution, retinoid, phototherapy and electron beam therapy. Systemic treatment includes light therapy, cytokine therapy, targeted therapy, histone deacetylase inhibitors, monoclonal antibodies, systemic chemotherapy. Allogeneic hematopoietic stem cell transplantation is recommended in refractory patients or with a recurring course or in later stage of this disease.

(a) Therapy at the early stage: Patients with MF at their early stage have normal cellular immunity function. Topical treatments are advisable in most patients, and active or intense therapy too early can poorly improve prognosis. Therapy targeted at skin lesions includes topical corticosteroids (medium or high efficiency), nitrogen mustard or solution, retinoid (bexarotene gel and tazarotene gel). Phototherapy, using ultraviolet: psoralen ultraviolet A light for thick-plaques and narrow band ultraviolet B light for thin-plaques. Total skin electron beam therapy: recommended at patients with generalized skin lesions.

(b) Therapy at the later stage or in the refractory lesions: Refractory and invasive lesions or advanced stage of this disease can be observed in a limited number of patients. Aim of therapy is to release tumor load and symptom, and reduce the potential risk of transforming into invasive lymphoma. Regimens or drugs contain light therapy, interferon-α, Denileukin diftitox (1), Vorinostat, Romidepsin, Chidamide, Alemtuzumab, Bortezomib, Brentuximab Vedotin, monotherapy (Gemcitabine, Doxil, Pentostatin, Chlorambucil, CTX, VP-16, Temozolomide, MTX, Pralatrexate), combined therapy (CVP regimen, CHOP regimen, ESHAP regimen, EPOCH regimen). Therapy targeted at skin plus systemic treatment is recommended as combined therapy, or combined systemic treatment such as light therapy plus interferon-α or retinoid.

(5) Prognosis

Favorable prognosis can be found in most patients with MF, with a 5-year survival rate as nearly 90%. Factors that determine prognosis contain T-staging, involvement besides skin (lymph node and visceral organ) and ages (≥65 years old). Patients with SS frequently present with a poor prognosis, with median survivals of 2−4 years.

7.2.10 ENKTL

ENKTL is an EBV-associated lymphoma, and more than 90% of patients have EB virus positive tumor tissue. The

patients of ENKTL spread over Asia and South America, but rarely in Europe and America. ENKTL accounts for 9% of all NHL patients in China. Nasal cavity is the prototype of this type of lymphoma, which is also the most common primary site, followed by nasopharynx, tonsil, oropharynx and other upper respiratory digestive organs. Besides, it can also occur in skin, gastrointestinal tract, testicular and other extra-node organs. Amost 80%–90% of NK/T cell lymphomas are derived from NK cells, and 10%–30% are derived from cytotoxic T lymphocytes. Until now, no significant differences in clinicopathological features of diseases of different cell sources have been found, so they are named as NK/T cell lymphocytes. As most of the primary causes were external, ENKTL was used in WHO lymphoma classification revised in 2001, 2008 and 2017 version.

(1) Clinical features

Young males were more common patients at the initial diagnosis of ENKTL. B symptoms were common, and the patient is generally in good condition. The tumor was usually confined to the nasal cavity or directly invaded the adjacent structures or tissues, and fewer distant lymph nodes were invaded or metastasized outside the node. Patients diagnosed with early stage account for 70%–90%, and the stage III–IV was rare (approximately 10%–30%). IPI scores were mostly in low-risk group (0–1 point). The upper respiratory tract is the most common primary site, accounting for 80%–90%, mainly occurred in the nasal cavity, followed by the nasopharynx and tonsil, etc. The primary site outside the upper respiratory tract, which included the skin soft tissue and gastrointestinal tract, only accounts for 10%–25% of all patients.

(2) Pathological diagnosis

Pathological features of ENKTL were diffuse lymphoma cell infiltration with vascular centrality and destructive growth of blood vessels, resulting in tissue ischemia necrosis (common and a major cause of missed diagnosis) and mucosal ulcer. The IHC markers needed for diagnosis include CD3, CD56, CD2, CD4, CD5, CD7, CD8, CD45RO, CD20, PAX5, TIA-1, granzyme B, Ki-67 and EBV-EBER, etc. The typical ENKL immunophenotypes are CD2+、CD3+、CD56+、TIA-1+、granzyme B+ and EBV-EBER+. The diagnosis of EBV-EBER negative should be cautious. If CD56+, CD3+ and cytotoxic markers are expressed, patients can be diagnosed as ENKTL. If CD3− and CD56− are expressed, patients should be diagnosed as PTCL-NOS. ENKTL (60%–90%) had no TCR gene rearrangement. In addition, it should also be noted that ENKTL should be distinguished from undifferentiated carcinoma, and the detection of epithelial markers such as CK and EMA were also needed. The expressions of PD-1, PD-L1, CD30 and p53 are related to treatment and prognosis ENKT.

(3) Staging

Lugano staging system can be used to stage in patients with ENKTL, patients were divided into I, II, and IV period, III period lesions of patients was classified to IV period.

(4) Treatment

(a) For IE stage patients without any adverse prognostic factors (age <60 years old, ECOG 0–1 point, LDH with no abnormalities, stage I, no primary tumor invasion), it is recommended to use simple radiotherapy. Radiotherapy is performed by enlarging the affected site, radical treatment dose 50 Gy.

(b) For IE stage with any adverse prognostic factors and IIE patients, combined radiochemical therapy is recommended. Radiotherapy was performed by expanding the affected site irradiation, radical treatment dose was 50 Gy. Chemotherapy regimen including L-ASP, PEG-ASP or gemcitabine was recommended.

(c) For patients with advanced stage (III–IV periods), chemotherapy regimen containing L-ASP, PEG-ASP and gemcitabine was recommended, such as SMILE regimen or GDP regimen. The short-term efficacy of the regimen including L-ASP or PEG-ASP is better than that of other regimens, but prognosis of patients with stage III–IV is poor. The median survival is only 8–12 months, and the 5-year OS rate is still less than 30% even with the new regimen of chemotherapy, which was giving priority to clinical studies. For patients with CR and PR in advanced chemotherapy, the addition of radiotherapy may improve the prognosis.

Different primary site of ENKTL, CTV and radiation dose are critical factors to the success of radiotherapy for ENKTL, which are closely related to the local regional control rate and prognosis of tumor.

In the early stage, patients were treated with large field irradiation and 50 Gy radical dose, and the local regional control rate reached over 90%, and the 5-year survival rate was approximately 70%–80%. However, patients were treated with the small field low-dose (<50 Gy) irradiation, the local recurrence rate was up to 50%, and the 5-year survival rate was only 40%–50%. Abundant studies have proved that the local regional control rate of patients with radiotherapy is linearly correlated the 5-year PFS rate and OS rate, which suggested that patients treated with lower

than 50 Gy can significantly increase the risk of regional treatment failure and death.

(5) Prognostic factors

Currently, the prognostic models recommended by NCCN guidelines are KPI, PINK and PINK-E models. KPI includes B symptom, increased LDH, regional lymph node invasion, stage III–IV; PINK includes ages of patients over 60 years old, distant lymph node invasion, stage III–IV, and extrasal primary; PINK-E model was formed if PINK model factors were combined with plasma EBV-DNA levels.

The prognostic models based on large sample data in China included age (>60 years old and ≤60 years old), ECOG score (≥2 points and 0–1 points), increased LDH, Ann Arbor stage (stage I, stage II, stage III–IV) and primary tumor invasion (PTI). PTI is defined as invasion of adjacent organs or tissues at any stage of primary tumor.

Biological prognostic factors include circulating blood EBV-DNA and Ki-67. Patients with high plasma EBV-DNA concentration accompanied by increased LDH, late stage, B symptoms and high IPI score, which is associated with tumor load.

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Appendix 1 Criteria for evaluation of efficacy of malignant lymphoma

Table A1 Deauville five-point scale

Point	Evaluation
1	No uptake of FDG
2	Slight uptake, but SUV below blood pool (mediastinum)
3	SUV above mediastinal, but below or equal to uptake in the liver
4	SUV slightly to moderately higher than liver
5	SUV markedly increase uptake or any new lesions (one response evaluation)
X	Any new lesions not overtly attributable to lymphoma

SUV, standarized uptake value.

Table A2 Cheson Response Criteria (CT/MRI)

Response category	Physical examination	Lymph nodes	Lymph nodes masses	Bone marrow
CR	Normal	Normal	Normal	Normal
CRu	Normal	Normal	Normal	Indeterminate
	Normal	Normal	>75% decrease	Normal or indeterminate
PR	Normal	Normal	Normal	Positive
	Normal	≥50% decrease	≥50% decrease	Irrelevant
	Decrease in liver/spleen	≥50% decrease	≥50% decrease	Irrelevant
Relapse/progression	Enlarging liver/spleen; new sites	New or increased	New or increased	Reappearance

CT, computed tomography; MRI, nuclear magnetic resonance; CR, complete response; CRu, uncomfirmed complete response; PR, partial response.

Appendix 2 Stage system of lymphoma

Appendix 2.1

Table A3 Ann-Arbor (Cotswolds revised) stage system

Stage I: Disease is present in only one group of lymph nodes (I), or in a single extranodal organ (IE)
Stage II: Disease is found in two or more groups of lymph nodes on the same side of the body with respect to the diaphragm (II). In addition, an extranodal organ may be involved (IIE)
Stage III: Disease is present in lymph node groups on both sides of the diaphragm (III), or occasionally with the involvement of an extranodal organ (IIIE). If the spleen or/and an extranodal organ is involved then the disease becomes stage III as well (IIIS or IIIES)
Stage IV: Disease is present in one or more extranodal organs diffusely and dissenminately, which could be with or without lymph node involvement
Group A: Patients have no systemic symptoms
Group B: Patients have systemic symptoms, including unexplained fever (>38 ℃ for 3 consecutive days or more), night sweets (7 consecutive days or more) or weight loss (10% or more of weight within 6 months)
E: Lymphoma involves the extranodal organs. When lymphoma involves single extranodal organ/tissue connected to lymph nodes or lymphatic tissue, it is recorded as each stage +E instead of stage IV (e.g. lymphoma infiltrates to the skin connected to lymph nodes of left neck, it is recorded as “IE”)
X: Large mass, tumor diameter >1/3 of the width of the thorax or maximum diameter of the fused tumor block >7.5 cm

Appendix 2.2 Rai and Binet stage system of chronic lymphocytic leukemia

Table A4 Rai stage system

Stage	Clinical manifestations	Risk stratification	Median survival time (month)
0	Lymphomcytosis, the number of peripheral blood lymphocyte >15×10^9/L, and lymphocyte ratio in bone marrow >40%	Low risk	>10^5
I	Stage 0 with lymph node enlargement	Intermediate risk	101
II	Stage 0–I with splenomegaly, hepatomegaly or both	Intermediate risk	71
III	Stage 0–II with hemoglobin <110 g/L or hematocrit <33%	High risk	19
IV	Stage 0–III with platelets <100×10^9/L	High risk	19

Table A5 Binet stage system

Stage	Clinical manifestations
Stage A	Hemoglobin ≥100 g/L, platelet ≥100×10^9/L, affected lymph node area <3
Stage B	Hemoglobin ≥100 g/L, platelet ≥100×10^9/L, affected lymph node area ≥3
Stage C	Hemoglobin <100 g/L and/or platelets <100×10^9/L, affected lymph node area does not count

Appendix 2.3

Table A6 TNMB stage system of Mycosis fungodies and Sézary syndrome

Stage	Clinical manifestations
Skin	
T1	Localized patches, papules, and/or plaques, <10% body surface area
T2	Patches, papules, and/or plaques, ≥10% body surface area
T3	One or more lumps are formed (diameter ≥1 cm)
T4	Fusional erythema ≥80% body surface area
Lymph nodes	
N0	No abnormal lymph nodes; no biopsy required
N1	Abnormal lymph nodes; histopathology shows Dutch level 1 or NCI LN 0–2
N2	Abnormal lymph nodes; histopathology shows Dutch level 2 or NCI LN 3
N3	Abnormal lymph nodes; histopathology shows Dutch level 3–4 or NCI LN 4
NX	Abnormal lymph nodes; no histological confirmation
Viscera	
M0	No viscus involvement
M1	Visceral involvement (required pathological diagnosis and indication of the affected organs)
MX	Visceral abnormalities; no histological diagnosis
Blood	
B0	No obvious blood involvement: atypical cells (Sézary cells) accounts for 5% of peripheral blood lymphocytes
B1	Low-load blood involvement: atypical cells (Sézary cells) accounts for >5% of peripheral blood lymphocytes, but do not reach B2 level
B2	High-load blood involvement: atypical cells (Sézary cells) ≥1,000/μL or CD4+/CD7− cell ratio ≥40% or CD4+/CD26− cell ratio ≥30%

Table A7 Clinical stage of Mycosis fungodies and Sézary syndrome

Stage	T	N	M	B
IA	1	0	0	0, 1
IIB	2	0	0	0, 1
IIA	1–2	1, 2	0	0, 1
IIB	3	0–2	0	0, 1
IIIA	4	0–2	0	0
IIIB	4	0–2	0	1
IVA_1	1–4	0–2	0	2
IVA_2	1–4	3	0	0–2
IVB	1–4	0–3	1	0–2

Appendix 2.4

Table A8 Lugano gastrointestinal lymphoma stage system

Stage	Definition
Stage IE	Lesions are limited to the gastrointestinal tract
IE1	Infiltrate to mucosa, submucosa
IE2	Infiltrate to muscularis propria, serosal layer
Stage II	Lesions spread to abdominal cavity
II1	Involvement of local lymph nodes
II2	Involvement of distant lymph nodes
Stage IIE	Penetration of serosa layer to adjacent organs or tissues
Stage IV	Disseminated involvement of extranodal organs or invasion of lymph nodes on upper side of diaphragm

Appendix 3

Table A9 Major new drugs and indications for treatment of lymphoma approved to market by US FDA but not in China

Drug name	Mechanism of action	FDA approved indications	Approved time to market
Alemtuzumab	Humanized CD52 monoclonal antibody	Alkylating agent and fludarabine resistant advanced CLL	May 2001
Belinostat	Histone deacetylase inhibitor	Relapse, refractory peripheral T-cell lymphoma	July 2014
Bendamustine	Bifunctional alkylating agent	1. CLL2. Indolent B-cell lymphoma	March 2008
Brentuximab vedotin	CD30 mAb coupled to cytotoxin MMAE	1. Autologous hematopoietic stem cell transplantation failed or not suitable for autologous hematopoietic stem cell transplantation, at least second-line treatment failed cHL	October 2011
		2. Consolidation treatment for patients with high risk of relapse or progression after autologous hematopoietic stem cell transplantation	
		3. ALCL that fails after first-line multi-drug combined chemotherapy	
		4. Relapse refractory pcALCL and MF expressing CD30	November 2017
		5. Combined with chemotherapy for previously treated stage III or IV cHL	March 2018
Idelalisib	Selective PI3Kδ (phosphatidylinositol 3-kinase) inhibitor	1. Combined with rituximab for relapsed CLL	July 2014
		2. FL and CLL with at least second-line treatment failure	
Ibrutinib	BTK inhibitor	1. MCL with at least first-line treatment failure	November 2013
		2. CLL failed in first-line chemotherapy	
		3. CLL with del (17p) gene mutations	
		4. Waldenstrom macroglobulinemia	
Lenalidomide	Immunomodulator	MCL failed in second-line chemotherapy	May 2013
Obinutuzumab	Humanized and glycosylated CD20 mAb	Combined with chlorambucil for initial treatment of CLL	November 2013
Ofatumumab	Fully humanized CD20 mAb	Refractory CLL with ineffective treatment of fludarabine	April 2014
Pralatrexate	Folate metabolism inhibitor	Recurrent or refractory PTCL	September 2009
Romidepsin	Histone deacetylase inhibitors	Cutaneous T-cell lymphoma failed in first-line treatment	November 2009
Vorinostat	Histone deacetylase inhibitors	Cutaneous T-cell lymphoma failed in second-line treatment	October 2006
Copanlisib	Selective PI3Kδ (phosphatidylinositol 3-kinase) inhibitor	FL with at least second-line treatment failure	September 15, 2017
Acalabrutinib	BTK inhibitor	CLL with at least first-line treatment failure	November 1, 2017
Yescarta	anti-CD19 CAR-T	Relapsed/refractory large B cell lymphoma	October 18, 2017
Nivolumab	PD-1 mAb	cHL that progressed after HDC/AHSCT or could not receive transplantation and progressed after previous three chemotherapies	May 17, 2016
Pembrolizumab	PD-1 mAb	Refractory cHL and cHL relapse after previous treatment with 3 or more regimens	March 14, 2017
Obinutuzumab	Humanized and glycosylated CD20 mAb	Combined with chemotherapy for previously untreated advanced FL	November 21, 2017

FDA, Food and Drug Administration; MMAE, monomethyl auristatin E; CLL, chronic lymphocytic leukemia; cHL, classical Hodgkin's lymphoma; ALCL, anaplastic large cell lymphoma; pcALCL, primary cutaneous anaplastic large cell lymphoma; MF, m11ycosis fungoides; MCL, mantle cell lymphoma; FL, follicular lymphoma; PTCL, peripheral T cell lymphoma.

Appendix 4

Table A10 Summary of adverse events associated with specific drugs for lymphoma treatment

Drug name	Adverse events	Mechanism	Treatment
Rituximab (CD20)	Transfusion reaction	Specific antigenic antibody reaction between rituximab and CD20 of lymphocyte	Pretreatment: acetaminophen and diphenhydramine 30 min before transfusion; Transfusion should be stopped once severe transfusion reaction occurs, and transfusion could be continued only if all symptoms disappear and laboratory results turn to normal, with an infusion speed less than half of the previous speed. Stopping treatment should be considered once the same reaction occurs.
	Cutaneous and mucous reaction (Stevens-Johnson syndrome, blister bullosa dermatitis and toxic epidermal necrolysis)	Delayed III type hypersensitivity (allergic reaction)	Methylprednisolone pulse treatment
	HBV reactivation	HBV reactivation can be found in drug therapy, thus severe results like fulminant hepatitis can be induced.	Patients who are expected to chemotherapy or riuximab should first test HBsAg. With a positive result, viral load detection and appropriate treatment should be conducted before tumor therapy. With HBV DNA ≤2,000 IU or chemotherapy less than one year, lamivudine or telbivudine can be used as antiviral therapy. Otherwise, entecavir or tenofovir as antiviral therapy
Anthracyclines	Delayed cardiotoxicity	Anthracyclineschelate iron ion to activate oxygen free radical, especially hydroxyl free radicals. Resulting lipid peroxidation of myocardial cell membrane and damaging cardiac mitochondria DNA	Detect and prevent cardiotoxicity resulted from anthracyclines; The maximal dosage should be controled: the maximum permissible accumulated dose is 450–550 mg/m^2; Radiotherapy or combined therapy should less than 350–400 mg/m^2; With EPI as 900–1,000 mg/m^2, less than 800 mg/m^2 for patients who have used ADM; THP as 950 mg/m^2; DNR as 550 mg/m^2; MIT as 160 mg/m^2, less than 120 mg/m^2 for patients who have used ADM.
HD-MTX (MTX ≥500 mg/m^2)	Increasing of level of serum ALT and renal insufficiency	Damaging normal cell metabolisms, with folinic acid as a treatment	Transfusion, diuresis, alkalization of urine should be conducted before and after treatment; After HD-MTX transfusion, folinic acid treatment for 2–3 d to reduce toxic effect of MTX.

Appendix 5 Prognostic scoring system for lymphoma

Appendix 5.1 Prognostic score for HL

Table A11 Adverse prognostic factors of early HL

Study group	Adverse prognostic factors of early HL
NCCN	Erythrocyte sedimentation rate >50 mm/h or with B symptoms; the maximum diameter of mass/chest cavity >0.33 or diameter >10 cm; involved lymph nodes >3
GHSG	Erythrocyte sedimentation rate >50 mm/h without B symptoms; erythrocyte sedimentation rate >30 mm/h with B symptoms; the maximum diameter of mass/chest cavity >0.33; the lymph node area >2 with extranodal lesions
EORTC	Age ≥50 years old, erythrocyte sedimentation rate >50 mm/h without B symptoms, erythrocyte sedimentation rate >30 mm/h with B symptoms, the maximum diameter of mass/horizontal transverse diameter of thoracic T5/6 >0.35, and involved lymph nodes >3
NCIC	Age ≥40 years old, mixed cell type or lymphocyte subtractive type; erythrocyte sedimentation rate >50 mm/h or with B symptoms; the maximum diameter of mass/chest cavity >0.33 or diameter >10 cm, involved lymph nodes >3

HL, Hodgkin's lymphoma; NCCN, National Comprehensive Cancer Network; GHSG, German Hodgkin Study Group; EORTC, European Organization for Research and Treatment of Cancer; NCIC, National Cancer Institute, Canada.

Table A12 IPS of advanced HK

Item	0	1
Albumin (g/L)	≥40	<40
Hemoglobin (g/L)	≥10^5	<10^5
Male	No	Yes
IV stage	No	Yes
Hemameba	<15×10^9/L	≥15×10^9/L
Lymphocyte	Proportion of hemameba <8% and/or count <0.6×10^9/L	Proportion of hemameba ≥8% and/or count ≥0.6×10^9/L

IPS, international prognostic score; HK, Hodgkin's lymphoma.

Table A13 IPS and survival rate of advanced HK

Score	5-year PFS rate (%)	5-year OS rate (%)
0	84	89
1	77	90
2	67	81
3	60	78
4	51	61
≥5	42	56

IPS, international prognostic score; HK, Hodgkin's lymphoma; PFS, progression-free survival; OS, overall survival.

Appendix 5.2 Prognostic score of diffuse large B-cell lymphoma

Table A14 IPI

Item	Score	
	0	1
Age (year)	≤60	>60
ECOG score	0 or 1	2–4
Clinical stage	I or II	III or IV
Number of sites of extranodal invasion	<2	≥2
LDH	Normal	Rise

IPI, International prognostic index; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase.

Table A15 Prognosis of DLBCL patients accoding to IPI score

Risk group	Number of risks	5-year DFS (%)	5-year OS (%)
Low risk	0 or 1	70	73
Low-medium risk	2	50	51
High-medium risk	3	49	43
High risk	4 or 5	40	26

DLBCL, diffuse large B cell lymphoma; IPI, international prognostic index; DFS, disease-free survival; OS, overall survival.

Table A16 Revised IPI

Item	Score	
	0	1
Age (year)	≤60	>60
ECOG score	0 or 1	2–4
Clinical stages	I or II	III or IV
Number of sites of extranodal invasion	<2	≥2
LDH	Normal	Rise

IPI, international prognostic index; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase.

Table A17 Prognosis of DLBCL patients accoding to revised IPI score

Risk group	Number of risks	4-year PFS (%)	4-year OS (%)
Prognosis is very good	0	94	92
Prognosis is good	1–2	82	82
Prognosis is poor	3–5	45	58

DLBCL, diffuse large B cell lymphoma; IPI, international prognostic index; PFS, progression-free survival; OS, overall survival.

Table A18 Age adjusted IPI

Item	Score	
	0	1
ECOG score	0 or 1	2–4
Clinical stages	I or II	III or IV
LDH	Normal	Rise

IPI, international prognostic index; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase.

Table A19 Prognosis of DLBCL patients accoding to age adjusted IPI score

Risk group	Number of risks	5-year DFS (%)	5-year OS (%)
Low risk	0	56	83
Low-medium risk	1	44	69
High-medium risk	2	37	46
High risk	3	21	32

DLBCL, diffuse large B cell lymphoma; IPI, international prognostic index; DFS, disease-free survival; OS, overall survival.

Appendix 5.3 Prognostic score of follicular lymphomas

Table A20 FLIPI

Item	Score	
	0	1
Age (year)	<60	≥60
Hemoglobin level (g/L)	≥120	<120
Clinical stages	I or II	III or IV
Number of invaded lymph nodes	<5	≥5
LDH	Normal	Rise

FLIPI, folicullar lymphoma international prognostic index; LDH, lactate dehydrogenase.

Table A21 Risk grouping and survival rate of FLIPI

Risk group	Score	Percentage of patients (%)	5-year OS rate (%)	10-year OS rate (%)
Low risk	0 or 1	36	90.6	70.7
Medium risk	2	37	77.6	50.9
High risk	3–5	27	52.5	35.5

FLIPI, folicullar lymphoma international prognostic index; OS, overall survival.

Table A22 FLIPI2

Item	0	1
Age (year)	<60	≥60
Hemoglobin level (g/L)	≥120	<120
The longest diameter of lymph node (cm)	≤6	>6
β2 microglobulin	Normal	Rise
Bone marrow	Uninvaded	Invaded

FLIPI, folicullar lymphoma international prognostic index.

Table A23 Risk grouping and survival rate of FLIPI2

Risk group	Score	5-year OS rate (%)	5-year PFS (%)
Low risk	0 or 1	98	79
Medium risk	2	88	51
High risk	3–5	77	20

FLIPI, folicullar lymphoma international prognostic index; OS, overall survival; PFS, progression-free survival.

Appendix 5.4 Prognostic score of mantle cell lymphoma

Table A24 MIPI

Score	Age (year)	ECOG	LDH (× upper normal limit)	Hemameba (×10^9/L)
0	<50	0–1	<0.67	<6.7
1	50–59	–	0.67–0.99	6.7–10
2	60–69	2–4	1.0–1.49	10–15
3	≥70	–	≥1.5	≥15

MIPI, mantle cell lymphoma international prognostic index; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase.

Table A25 Simplified IPI and survival of mantle cell lymphoma

Risk group	Score	Median survival (month)
Low risk	0–3	Not reached
Medium risk	4–5	51
High risk	6–11	29

IPI, international prognostic index.

Table A26 MIPIc

MIPIc	MIPI	Ki-67	Percentage of patients (%) GLSG (n=246)	Percentage of patients (%) EMCLN (n=508)	5-year OS (%) EMCLN	Median OS (year) GLSG
Low risk	Low risk	<30%	32	44	85	9.4
Low to medium risk	Low risk	≥30%	5	9	72	4.9
	Medium risk	<30%	25	29		
High to medium risk	Medium risk	≥30%	6	10	43	3.2
	High risk	<30%	10	13		
High risk	High risk	≥30%	5	11	17	1.8

MIPIc, international prognostic index of mantle cells combined with Ki-67; GLSG, German Low-Grade Lymphoma Study Group; EMCLN, European Mantle Cell Lymphoma Network.

Appendix 5.5

Table A27 Prognostic index for T-cell lymphoma (PIT)

Item	Score	
	0	1
Age (year)	≤60	>60
Bone marrow invasion	No	Yes
ECOG score	0 or 1	2–4
LDH	Normal	Rise

ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase.

Table A28 Prognosis of PTCL patients accoding to PIT score

Score	5-year OS rate (%)	10-year OS rate (%)
0	62.3	54.9
1	52.9	38.8
2	32.9	18.0
3–4	18.3	12.6

PTCL, peripheral T-cell lymphoma; PIT, prognostic index for T-cell lymphoma; OS, overall survival.

Appendix 6 World Health Organization (WHO) classification of lymphoid neoplasms (2017 revision)

Prolymphoid tumor

1. B-lymphoblastic leukemia/lymphoma, non-specific type
2. B-lymphoblastic leukemia/lymphoma with abnormal frequency gene
   - B lymphoblastic leukemia/lymphoma with t (9; 22) (q34.1; q11.2); BCR-ABL1
   - B lymphoblastic leukemia/lymphoma with t (v; 11 q23. 3); KMT2A rearrangement
   - B lymphoblastic leukemia/lymphoma with t (12;21) (p13.2; q22.1); ETV6-RUNX1
   - B lymphoblastic leukemia/lymphoma with hyperdiploid
   - B lymphoblastic leukemia/lymphoma with low diploid
   - B lymphoblastic leukemia/lymphoma with t (5;14) (q31.1; q32.3); IL3-IGH
   - B lymphoblastic leukemia/lymphoma with t (1;19) (q23; p13.3); TCF3-PBX1
   - B lymphoblastic leukemia/lymphoma, BCR-ABL1
   - B lymphoblastic leukemia/lymphoma with iAMP21
3. T lymphoblastic leukemia/lymphoma
   - Early T-prolymphoblastic leukemia
4. Natural killer lymphoblastic leukemia/lymphoma

Mature B-cell neoplasms

5. Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)
   - Onoclonal B-cell lymphocytosis (MBL)
6. B-cell prolymphocytic leukemia
7. Splenic marginal zone lymphoma
8. Hairy cell leukemia
9. Splenic B-cell lymphoma/leukemia, unclassifiable
   - Splenic diffuse red pulp small B-cell lymphoma
   - Hairy cell leukemia-variant
10. Lymphoplasmacytic lymphoma
11. Monoclonal gammopathy of undetermined significance (MGUS), IgM
12. Heavy-chain disease
    - μ heavy-chain disease
    - γ heavy-chain disease
    - α heavy-chain disease
13. Plasma cell myeloma
    - MGUS, Non-IgM
    - Plasma cell myeloma
      - Variant
        - Asymptomatic plasma cell myeloma
        - Non-secretory myeloma
        - Plasma leukemia
      - Plasma cell tumors
        - Solitary plasmacytoma of bone
        - Extraosseous plasmacytoma
      - Monoclonal immunoglobulin deposition diseases
        - Primary amyloidosis

Light chain and heavy chain deposition disease
Plasma cell tumor with accessory tumor syndrome
POEMS syndrome
TEMPI syndrome
14. Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) lymphoma
15. Nodal marginal zone lymphoma
Pediatric nodal marginal zone lymphoma
16. Follicular lymphoma
In situ follicular neoplasia
Duodenal-type follicular lymphoma
Testicular follicular lymphoma
17. Pediatric-type follicular lymphoma
18. Large B-cell lymphoma with IRF4 rearrangement
19. Primary cutaneous follicle center lymphoma
20. Mantle cell lymphoma
Leukemic non-mantle cell lymphoma
In situ mantle cell neoplasia
21. Diffuse large B-cell lymphoma (DLBCL), NOS
Germinal center B-cell type
Activated B-cell type
22. T-cell/histiocyte-rich large B-cell lymphoma
23. Primary DLBCL of CNS
24. Primary cutaneous DLBCL, leg type
25. EBV+ DLBCL, NOS
26. EBV+ mucocutaneous ulcer
27. DLBCL associated with chronic inflammation
Diffuse large B cell lymphoma with fibrin exudation
28. Lymphomatoid granulomatosis
29. Primary mediastinal (thymic) large B-cell lymphoma
30. Intravascular large B-cell lymphoma
31. ALK+ large B-cell lymphoma
32. Plasmablastic lymphoma
33. Primary effusion lymphoma
34. Lymphoproliferative diseases related to HHV8
Multicentric Castleman disease
HHV8+ DLBCL, NOS
HHV8+ biological center lymphoproliferative disease
35. Burkitt lymphoma
36. Burkitt-like lymphoma with 11q aberration
37. High-grade B-cell lymphoma
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements
High-grade B-cell lymphoma, NOS
38. B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

Mature T and NK neoplasms

1. T-cell prolymphocytic leukemia

2. T-cell large granular lymphocytic leukemia
3. Chronic lymphoproliferative disorder of NK cells
4. Aggressive NK-cell leukemia
5. EBV+ T cells and NK cell proliferative diseases in children
    - Systemic EBV+ T-cell lymphoma of childhood
    - Chronic active EBV infection (T cell and NK cell type), systemic
    - Hydroa vacciniforme–like lymphoproliferative disorder
        - Severe allergy to mosquito bites
6. Adult T-cell leukemia/lymphoma
7. Extranodal NK-/T-cell lymphoma, nasal type
8. Intestinal T-cell lymphoma
    - Enteropathy-associated T-cell lymphoma
    - Monomorphic epitheliotropic intestinal T-cell lymphoma
    - Intestinal T-cell lymphoma, NOS
    - Indolent T-cell lymphoproliferative disorder of the GI tract
9. Hepatosplenic T-cell lymphoma
10. Subcutaneous panniculitis-like T-cell lymphoma
11. Mycosis fungoides
12. Sézary syndrome
13. Primary cutaneous CD30+ T-cell lymphoproliferative disorders
    - Lymphomatoid papulosis
    - Primary cutaneous anaplastic large cell lymphoma
14. Primary cutaneous peripheral T-cell lymphoma, rare subtype
    - Primary cutaneous $\gamma\delta$ T-cell lymphoma
    - Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma
    - Primary cutaneous acral CD8+ T-cell lymphoma
    - Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder
15. Peripheral T-cell lymphoma, NOS
16. Angioimmunoblastic T-cell, Follicular and other lymphomas with TFH phenotype
    - Angioimmunoblastic T-cell lymphoma
    - Follicular T-cell lymphoma
    - Nodal peripheral T-cell lymphoma with TFH phenotype
17. Anaplastic large-cell lymphoma, ALK+
18. Anaplastic large-cell lymphoma, ALK–
19. Breast implant-associated anaplastic large-cell lymphoma

Hodgkin lymphoma

1. Nodular lymphocyte predominant Hodgkin lymphoma
2. Classical Hodgkin lymphoma
    - Nodular sclerosis classical Hodgkin lymphoma
    - Lymphocyte-rich classical Hodgkin lymphoma
    - Mixed cellularity classical Hodgkin lymphoma
    - Lymphocyte-depleted classical Hodgkin lymphoma

