Chinese Society of Clinical Oncology (CSCO) diagnosis and treatment guidelines for malignant lymphoma 2021 (English version)

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Lymphomas are a group of heterogeneous diseases, which is divided into two main categories: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). There is an estimated 75,400 incidence cases and 40,500 deaths annually in China, of which NHL accounts for about 90% of lymphoma burden (1,2).

1. General guidelines

Pre-treatment evaluation includes clinical evaluation, physical examination, laboratory examination, imaging examination and histological examination. Clinical evaluation includes age, sex, tumor-related symptoms such as fatigue and pruritus. B symptom (fever to more than 38.3 °C, drenching night sweats, or unexplained weight loss of more than 10% of body mass over 6 months) is recorded. Physical examination includes measurement of palpable lymph nodes and hepatosplenomegaly. Hepatitis B virus (HBV) surface antigen (HBsAg) and anti-hepatitis B core antibody (anti-HBc) are examined, and HBV DNA is examined once HBsAg or anti-HBc is positive. Prophylactic anti-HBV therapy is administered during chemotherapy or anti-CD20 antibody-based immuno-therapy if HBsAg or anti-HBc is positive. Propylactic anti-HBV therapy is administered during chemotherapy or anti-CD20 antibody-based immuno-therapy if HBsAg or HBV DNA is positive. Imaging examination including computed tomography (CT) or positron emission tomography (PET)-CT is employed for staging and response assessment.

Chemotherapy-based mode is preferred for most aggressive lymphomas. Anthracyclines-based regimens are commonly used, of which rituximab is used for CD20-positive lymphomas. Indication-oriented individualized strategies should be considered for most indolent lymphomas. “Watch and wait” approach is used for patients without therapeutic indication, and chemotherapy or target therapy is used for those who are suitable for initialization of therapy.

2. Diagnosis

Pathological types are based on the 2016 revision of the World Health Organization classification of lymphoid neoplasms (3). Pathological diagnosis, based on morphology, immunohistochemistry, flow cytometry and...
cytogenetics, is vitally important for comprehensive diagnosis. Complete or partial resection of lesion is the preferred biopsy method, which provides a basis of accurate pathological diagnosis. Core needle biopsy is an alternative method for those unresectable masses. However, fine needle biopsy is not recommended. Of note is that clinical, laboratory, and imaging data are equally important. Thus, multidisciplinary team (MDT) is emphasized in both diagnosis and treatment procedure.

3. Staging

The staging criteria recommended in the Lugano classification are applicable for nearly all types of lymphoma (Table 1) (4). In addition, chronic lymphocytic leukemia (CLL), primary gastrointestinal tract lymphoma and primary cutaneous lymphoma have their unique staging systems.

4. Treatment

4.1 Diffuse large B-cell lymphoma (DLBCL)

As shown in Table 2, the strategy for newly-diagnosed patients with DLBCL depends on age, tumor size, cardiac function and prognostic scores such as international prognostic index (IPI) and age-adjusted international prognostic index (aaIPI). Both anthracycline and anti-CD20 monoclonal antibody are crucial for the treatment of DLBCL (5). The most common regimen is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone). Radiotherapy is applied for patients who have bulky disease (≥7.5 cm) or extranodal invasion at baseline, and for those who can’t achieve complete remission at the end of induction chemotherapy. Central nervous system (CNS) prophylaxis with intrathecal or intravenous methotrexate is recommended for patients with high risk according to CNS-IPI (6).

Salvage chemotherapy with individualized regimens such as ICE (ifosfamide, carboplatin and etoposide), GDP (gemcitabine, dexamethasone and cisplatin) or DHAP (dexamethasone, high-dose cytarabine and cisplatin) is recommended for relapsed/refractory patients. Autologous stem cell transplantation (ASCT) consolidation is recommended for transplant-eligible patients who achieved remission from salvage therapy (7). Clinical trials including chimeric antigen receptor T-cell immunotherapy (CAR-T) are options, especially for patients who are ineligible for ASCT or resistant to salvage therapy.

4.2 Follicular lymphoma (FL)

The Chinese Society of Clinical Oncology (CSCO) guidelines for FL is applicable for patients with grade FL1–3a. Patients with grade FL3b and histologically-transformed lymphoma should be treated according to clinical practice guidelines for DLBCL.

As shown in Table 3, involved-site radiotherapy (ISRT) is appropriate for patients with stage I or contiguous stage II disease, while anti-CD20 monoclonal antibody-based immunotherapy with or without chemotherapy and ISRT is preferred for those with non-contiguous stage II disease. For stage III–IV disease, “watch and wait” approach is applicable for patients without treatment indication, while chemotherapy with or without immunotherapy is an option for those with treatment indication (8). The common front-line chemotherapy regimens include R-CHOP, R-CVP (rituximab, cyclophosphamide, vincristine and prednisone), BR (bendamustine and rituximab) and R2 (lenalidomide and rituximab). Rituximab maintenance can be chosen for those responders for rituximab-based therapy who have high tumor burden at baseline (9,10).

The choice of salvage treatment depends on age, physical condition, pathological type and previous treatment efficacy. Original or alternative front-line regimens can be used for patients with long-term remission (>12 months) after front-line treatment, while non-cross-resistance regimens can be used for those who had early relapse (<12 months) or refractory diseases. ASCT can be used for those

| Stage | Involvement |
|-------|-------------|
| I     | One node, or a group of adjacent nodes, or single extranodal lesions without nodal involvement |
| II    | Two or more nodal groups on the same side of the diaphragm, or stage I or II by nodal extent with limited contiguous extra-nodal involvement |
| II bulky | II as above with “bulky” disease |
| III   | Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement |
| IV    | Additional noncontiguous extra-lymphatic involvement |
transplant-eligible patients who are sensitive to salvage chemotherapy.

4.3 Mantle cell lymphoma (MCL)

For newly-diagnosed MCL, treatment selection is based on age and fitness. Intensive therapies are preferred for young and fit patients, and non-intensive approaches are appropriate for elderly or frail patients (Table 4). Immunotherapy is required for stage I–II disease with large tumor burden or adverse prognostic features and stage III–IV disease. The regimens based on rituximab and

Table 2 Treatment strategies for newly-diagnosed diffuse large B-cell lymphoma

| Age (year) | Risk stratification | Category I recommendations | Category II recommendations |
|------------|---------------------|----------------------------|----------------------------|
| <60        | IPI low risk (aaIPI=0) and no bulk | R-CHOP21×3 cycles + radiotherapy or R-CHOP21×6 cycles ± radiotherapy or R-CHOP21×4 cycles + R×2 cycles ± radiotherapy (Level 1A evidence) | |
|            | IPI low risk (aaIPI=0) with bulk or IPI low-intermediate risk (aaIPI=1) | R-CHOP21×6 cycles + radiotherapy (Level 2A evidence) | |
|            | IPI intermediate-high risk or IPI high risk (aaIPI≥2) | Clinical trials R×8 cycles + CHOP21×(6–8) cycles ± radiotherapy or R×8 cycles + CHOP14×6 cycles ± radiotherapy (Level 1A evidence) | R-CHOEP14×6 cycles (ASCT for aaIPI=3) (Level 2A evidence) |
| 60–80      | Non-cardiac insufficiency | R×8 cycles + CHOP21×(6–8) cycles (R×8 cycles + CHOP21×6 cycles for IPI low risk); R×8 cycles + CHOP14×6 cycles ± radiotherapy (Level 1A evidence) | |
|            | With cardiac insufficiency | Doxorubicin substitution with liposomal doxorubicin, etoposide, or gemcitabine (Level 2A evidence) | |
| >80        | Non-cardiac insufficiency | R-miniCHOP21×6 cycles (Level 2A evidence) | |
|            | With cardiac insufficiency | Doxorubicin substitution with liposomal doxorubicin, etoposide, or gemcitabine (Level 2A evidence) | |

aaIPI, age-adjusted international prognostic index; ASCT, autologous stem cell transplantation; CHOP, cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone; IPI, international prognostic index; R, rituximab; R-CHOEP, rituximab, cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone.

Table 3 Treatment strategies for newly-diagnosed follicular lymphoma

| Stage stratification | Category I recommendations | Category II recommendations |
|----------------------|---------------------------|-----------------------------|
| I–II Stage I or contiguous stage II | ISRT (Level 2A evidence) | Observation or ISRT + rituximab/obinutuzumab ± chemotherapy or rituximab/obinutuzumab ± chemotherapy + ISRT (ISRT is considered for selected patients) (Level 2A evidence) |
| Non-contiguous stage II | Rituximab/obinutuzumab ± chemotherapy + ISRT (Level 2A evidence) | Observation (Level 2A evidence) |
| III–IV Without indication* | Observation (Level 1A evidence) | Clinical trial (Level 2A evidence) |
| With indication* | Chemotherapy + rituximab/obinutuzumab (Level 2A evidence) | Clinical trial Palliative ISRT (Level 2A evidence) |

ISRT, involved-site radiotherapy; *, indications for treatment: 1) candidate for clinical trial; 2) symptoms; 3) threatened end-organ function; 4) cytopenia secondary to lymphoma; 5) bulky disease; 6) steady or rapid progression.
high-dose cytarabine, including R-CHOP alternating with R-DHAP (rituximab, dexamethasone, high-dose cytarabine and cisplatin), dose-intensified R-CHOP alternating with high-dose cytarabine, R-hyper-CVAD/MA (rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate and cytarabine) are preferred. For patients with stage I–II disease, ISRT can be chosen for limited non-bulky diseases, and consolidation radiotherapy after systemic chemotherapy may be considered for diseases with large tumor burden. For transplant-eligible patients, consolidation ASCT followed by rituximab maintenance is preferred (11). For elderly or frail patients, rituximab combined with less aggressive regimens such as CHOP or bendamustine can be used as induction chemotherapy, and rituximab maintenance may be used for those responders.

Non-cross-resistant approaches such as bendamustine-containing regimens are preferred as salvage treatment. Lenalidomide and venetoclax, Bruton tyrosine kinase (BTK) inhibitors such as ibrutinib, zanubrutinib, and orelabrutinib, can be considered, especially for patients with early relapsed or refractory diseases (12). ASCT or allogeneic stem cell transplantation (allo-SCT) should be a consolidation option for transplant-eligible patients.

4.4 Marginal zone lymphoma (MZL)

The front-line therapy of MZL refers to the primary site and disease stage (Table 5). For primary gastric disease, Helicobacter pylori (H. pylori) eradication is preferred for H. pylori-positive stage I disease, and radiotherapy is chosen for primary gastric stage II disease, bulky tumor, translocation with t(11;18) and no-responders for anti-H. pylori therapy. For non-gastric stage I–II disease, radiotherapy is an option for most patients while rituximab can be applied to radiotherapy-ineligible patients. Splenectomy is the diagnostic and therapeutic approach for spleen MZL, and anti-HCV therapy is considered when HCV is positive. For stage III–IV disease, “watch and wait” approach is used for patients without treatment indication, and rituximab combined with cytotoxic drugs such as chlorambucil, bendamustine, CHOP and CVP regimens is the common therapeutic approach for those who need initiation of treatment (13,14).

For salvage treatment, prior regimens can be re-used if the duration of response exceeded 2 years. BTK inhibitors including ibrutinib or zanubrutinib are reasonable choices, especially for early relapsed or refractory diseases (15). In addition, the clinical trial is a reasonable option.

4.5 Burkitt lymphoma (BL)

As shown in Table 6, dose-intensive multi-agent chemotherapy with CNS prophylaxis is preferred for newly-diagnosed BL. Dose-intensive regimens including CODOX-M-R (cyclophosphamide, vincristine, doxorubicin, methotrexate and rituximab), CODOX-M/IVAC-R (CODOX-M/IVAC-R, cyclophosphamide, vincristine, doxorubicin, methotrexate and rituximab), VR-CVP, bortezomib, rituximab, cyclophosphamide,
vincristine, doxorubicin, methotrexate and rituximab), R-hyper-CVAD/MA, Rituximab (Level 2A)

CODOX-M-R, cyclophosphamide, vincristine, doxorubicin, methotrexate and rituximab; CODOX-M/IVAC-R, cyclophosphamide, vinvincible, doxorubicin, methotrexate, ifosfamide, etoposide, cytarabine and rituximab; R-hyper-CVAD/MA, rituximab, cyclophosphamide, vinvincible, doxorubicin, dexamethasone, methotrexate and cytarabine; DA-EPOCH-R, dose-adjusted etoposide, prednisone, vinvincible, cyclophosphamide, doxorubicin and rituximab.

Table 6 Treatment strategies for newly-diagnosed Burkitt lymphoma

| Stratification | Category I recommendations | Category II recommendations |
|---------------|---------------------------|-----------------------------|
| Low risk (normal LDH; stage I with complete resection of abdomen lesion, or single lesion outside abdomen <10 cm) | CODOX-M-RHyperCVAD/MA-R (Level 2A evidence) | DA-EPOCH-R (Level 2A evidence) |
| High risk (stage I with bulky abdomen lesion, or single lesion outside abdomen >10 cm, or stage II–IV) | CODOX-M/IVAC-R HyperCVAD/MA-R (Level 2A evidence) | DA-EPOCH-R (Level 2A evidence) |

Rai (19) and Binet (20) staging system are applied for CLL while Lugano staging system is applied for SLL. For newly-diagnosed CLL/SLL, “watch and wait” approach is applied when a patient has no treatment indications including progressive marrow failure, massive or progressive or symptomatic splenomegaly, massive or progressive or symptomatic lymphadenopathy, progressive lymphocytosis, autoimmune complications, symptomatic or functional extranodal involvement, and disease-related symptoms. As shown in Table 7, front-line therapy choice is based on TP53 status and comorbidities when treatment
indications are present. For patients without del(17p)/TP53 mutation, BTK inhibitors, venetoclax, bendamustine and FCR (fludarabine, cyclophosphamide and rituximab) regimens can be used. For patients with del(17p)/TP53 mutation, BTK inhibitors are preferred (21-23).

For patients who have a relapse within 3 years, refractory disease, del(17p)/TP53 mutation, individualized strategy including BTK inhibitors (i.e. ibrutinib, zanbrutinib, orelabrutinib), venetoclax, lenalidomide and high-dose methylprednisolone with rituximab can be applied. For patients who relapse 3 years after induction therapy and have no del(17p)/TP53 mutation, repeat of first-line regimen can be considered. The clinical trial is a treatment option.

4.7 Extra-nodal natural killer/T-cell lymphoma (ENKTCL), nasal type

For newly-diagnosed ENKTCL, treatment models are based on stage and risk stratification (24). As shown in Table 8, combined radio-chemotherapy is preferred for stage I–II disease, and chemotherapy with asparaginase-containing regimens is often used for stage III–IV disease (25-27). Risk stratification is recommended for the treatment of early-stage ENKTCL, in which radiotherapy alone with an optimal dose of 50 Gy can be chosen as primary therapy for low-risk patients, while sequential chemotherapy and radiotherapy are mostly used for intermediate- and high-risk patients. Asparaginase-based or pegasparagase-based chemotherapy with SMILE

| Stratification 1 | Stratification 2 | Category I recommendations | Category II recommendations |
|-----------------|-----------------|-----------------------------|----------------------------|
| Without del(17p)/TP53 mutation | Frail patients with significant comorbidities (not able to tolerate purine analogs) | Ibrutinib Venetoclax + obinutuzumab (Level 1 evidence) | Chlorambucil + obinutuzumab (Level 2A evidence) |
| ≥65 years or <65 years with significant comorbidities | Ibrutinib (Level 1 evidence) Venetoclax + obinutuzumab (Level 1 evidence) Bendamustine (70 mg/m² cycle1, escalate to 90 mg/m² if tolerated) + anti-CD20 monoclonal antibody | Ibrutinib + obinutuzumab (Level 2B evidence) Obintuzumab (Level 2B evidence) High-dose methylprednisolone + rituximab (Level 2B evidence) | Chlorambucil + obinutuzumab (Level 2A evidence) Zanubrutinib (Level 2B evidence) Ibrutinib + obinutuzumab (Level 2B evidence) Obintuzumab (Level 2B evidence) High dose methylprednisolone + rituximab (Level 2B evidence) |
| <65 years without significant comorbidities | FCR (preferred for patients with mutated IGHV) (Level 1 evidence) Ibrutinib (Level 1 evidence) | Fludarabine + rituximab (Level 2A evidence) Ibrutinib (Level 2B evidence) | Bendamustine ± anti-CD20 monoclonal antibody (Level 2A evidence) Fludarabine + rituximab (Level 2A evidence) Zanubrutinib (Level 2B evidence) Venetoclax + obinutuzumab, (Level 2B evidence) High-dose methylprednisolone + rituximab (category 2B) |
| With del(17p)/TP53 mutation | Ibrutinib (Level 2A evidence) Zanbrutinib (Level 2B evidence) Clinical trial | Venetoclax + obinutuzumab (Level 2A evidence) High dose methylprednisolone + rituximab (Level 2B evidence) Obintuzumab (Level 2B evidence) |

del(17p), deletion of chromosome 17p; FCR, fludarabine, cyclophosphamide and rituximab.
Table 8 Treatment strategies for newly-diagnosed extra-nodal natural killer/T-cell lymphoma, nasal type

| Stage | Stratification 1 | Stratification 2 | Category I recommendations                              | Category II recommendations                  |
|-------|------------------|------------------|--------------------------------------------------------|---------------------------------------------|
| I     | Low risk: without risk factors* |          | Extended field radiation therapy (Level 2B evidence) | Extended field radiation therapy+L-asparaginase-containing chemotherapy (Level 3 evidence) |
| I–II  | Intermediate and high risk: with at least one risk factors* | Fit for chemotherapy | Extended field radiation therapy followed by L-asparaginase-containing regimens (Level 2A evidence) | Sandwich chemoradiation (SMILE regimens) (Level 2A evidence) |
|       |                  |                  | Chemotherapy of L-asparaginase-containing regimens followed by extended field radiation therapy (Level 2A evidence) | Concurrent chemoradiation (L-asparaginase-containing regimens) (Level 2B evidence) |
|       |                  |                  | Sandwicb chemoradiation (L-asparaginase-containing regimens, no SMILE regimens) (Level 2A evidence) | Clinical trial |
|       |                  | Unfit for chemotherapy | Extended field radiation therapy (Level 2B evidence) | Clinical trial |
| III–IV|                  |                  | Chemotherapy (SMILE, P-GemOx, DDGP, COEP-L, AspaMetDex) followed by ASCT (Level 2A evidence) | Clinical trial |

* Risk factors according to nomogram-revised risk index: >60 years, elevated lactate dehydrogenase (LDH) level, primary tumor invasion (PTI), Eastern Cooperative Oncology Group (ECOG) performance status (PS)>2, stage II ENKTL. ASCT, autologous stem cell transplantation; AspaMetDex, L-asparaginase, methotrexate and dexamethasone; COEP-L, cyclophosphamide, vincristine, etoposide, prednisone and L-asparaginase; DDGP, dexamethasone, cisplatin, gemcitabine, and pegaspargase; P-GemOx, pegaspargase, gemcitabine and oxaliplatin; SMILE, dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide.

(dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide), P-GemOx (pegaspargase, gemcitabine and oxaliplatin), DDGP (dexamethasone, cisplatin, gemcitabine, and pegaspargase), COEP-L (cyclophosphamide, vincristine, etoposide, prednisone and L-asparaginase), AspaMetDex (L-asparaginase, methotrexate and dexamethasone) regimens are used for stage III/IV disease. ASCT is used for transplant-eligible patients.

For relapsed or refractory diseases, clinical trials such as anti-PD-1 antibody and chidamide are treatment options. In absence of suitable clinical trials, salvage chemotherapy with non-cross-resistance regimens can be used. Although it is controversial, ASCT can be considered for patients who achieved a complete remission after salvage treatment (28).

4.8 Peripheral T-cell lymphoma (PTCL)

For newly-diagnosed PTCL, there are limited data to support a specific treatment model. As shown in Table 9, CHOEP regimen is commonly used for ALK-positive anaplastic large cell lymphoma (ALCL, ALK+), while clinical trials are optimal for other PTCL subtypes including PTCL-not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL) and ALK-negative anaplastic large cell lymphoma (ALCL, ALK−). Consolidation ASCT is applied for transplant-eligible patients achieving remission (29-31).

For relapsed or refractory diseases, participation in a clinical trial is preferred. In the absence of suitable clinical trials, salvage therapy with single agents such as pralatrexate (32), chidamide (33), and bendamustine or with multiagent regimens such as ICE, DHAP, GDP, ESHAP (etoposide, methylprednisolone, cytarabine and cisplatinum), and GemOx (gemcitabine and oxaliplatin) are considered. Brentuximab vedotin can be used for systemic ALCL. Crizotinib can be used for ALCL, ALK+. ASCT or allo-SCT is applied for transplant-eligible patients.

4.9 HL

For newly-diagnosed classic Hodgkin lymphoma (CHL), treatment strategy is based on stage and prognosis risk stratification. PET-guided adjustment strategy is preferred. As shown in Table 10, the combined chemoradiotherapy with ABVD (doxorubicin, bleomycin, vinblastine and
dacarbazine) or BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) regimen is preferred for stage I–II disease, while chemotherapy with or without radiotherapy is commonly applied to stage III–IV disease. For nodular lymphocyte-predominant HL, stage IA disease without unfavorable factors can be treated with radiotherapy alone, other conditions refer to the treatment principles of CHL.

For relapsed or refractory disease, salvage chemotherapy followed by ASCT is preferred (34,35). Immune checkpoint inhibitors (i.e. sintilimab, tislelizumab, camrelizumab, nivolumab, pembrolizumab, and zimberelimab) and brentuximab vedotin can be considered to integrate into salvage regimens (36-38).

4.10 Primary central nervous system lymphoma

For newly-diagnosed patients with primary central nervous system lymphoma, high-dose methotrexate-based chemotherapy is preferred (Table 11). Whole brain radiotherapy (WBRT) with a dose of 45 Gy can be utilized for patients who could not tolerate systemic chemotherapy. Both ASCT and WBRT are considered as consolidation therapy, but the long-term neurotoxicity of WBRT should be paid attention (39,40).

For relapsed or refractory diseases, clinical trials are preferred. In the absence of suitable clinical trials, high-dose methotrexate can be reused for patients who achieve >1 year of duration of remission, while non-cross-resistance chemotherapy and WBRT can be used for other conditions. BTK inhibitors including ibrutinib, zanbrutinib and orelabrutinib can be considered. ASCT can be conducted as consolidation strategy for patients who achieved complete remission after salvage therapy.

5. Prognosis

Pathological type plays a crucial role in the prognosis of lymphoma (41-43). Moreover, multiple clinical and laboratory data further determined prognosis. Of note is iteration of prognosis model over time. For example, IPI is widely used for most aggressive lymphomas in the pre-target therapy era, and the revised IPI (R-IPI) and the National Comprehensive Cancer Network IPI (NCCN-IPI) are developed for DLBCL in the target therapy era (44). In addition, some pathological types such as FL and MCL have unique prognosis assessing systems (45,46).
Table 10 Treatment strategies for newly-diagnosed classic Hodgkin lymphoma

| Stage | Stratification | Category I recommendations | Category II recommendations |
|-------|----------------|-----------------------------|-----------------------------|
| I–II  | Favorable      | ABVD × (2–4) cycles + ISRT (20 Gy) (Level 1A evidence) | Dose-escalated BEACOPP × 2 cycles + ABVD × 2 cycles + ISRT (30 Gy) (Level 1B evidence) |
|       |                | ABVD × 2 cycles + dose-escalated BEACOPP × 2 cycles + ISRT (30 Gy) (Level 1A evidence) | |
|       | Unfavorable    | ABVD × 4 cycles + ISRT (30 Gy) (Level 1A evidence) | |
|       |                | ABVD × 2 cycles + dose-escalated BEACOPP × 2 cycles + ISRT (30 Gy) (Level 1A evidence) | |
| III–IV|                | ABVD × 6 cycles ± ISRT (Level 1A evidence) | ABVD × 2 cycles + dose-escalated BEACOPP × 4 cycles ± ISRT (Level 2B evidence) |
|       |                | Dose-escalated BEACOPP × (4–6) cycles ± ISRT (Level 1A evidence) | Brentuximab vedotin + AVD × 6 cycles ± ISRT (Level 1B evidence) |
|       |                | ABVD × 2 cycles + AVD × 4 cycles ± ISRT (Level 1A evidence) | |

ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; AVD, doxorubicin, vinblastine and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone; ISRT, involved-site radiotherapy.

Table 11 Treatment strategies for newly-diagnosed primary central nervous system lymphoma

| Stratification | Therapy section | Category I recommendations | Category II recommendations |
|----------------|----------------|-----------------------------|-----------------------------|
| Fit patients who can tolerate systemic chemotherapy | Induction | High-dose methotrexate-based regimen (Level 1 evidence)* | If CSF positive or spinal MRI positive, consider intra-CSF chemotherapy** consider clinical trials |
|                | Consolidation  | For patients achieved complete remission: High-dose chemotherapy (thiotepa-based regimen) with stem cell rescue (Level 1 evidence) | |
|                |               | High-dose cytarabine ± Etoposide (Level 2A evidence) | |
|                |               | Low-dose WBRT (Level 2A evidence) | |
|                | Maintenance   | Low-dose lenalidomide or temozolomide (Level 2B evidence) | |
| Unfit patients who cannot tolerate systemic chemotherapy | Induction | WBRT (Level 1 evidence) | |
|                | Maintenance   | Methotrexate + temozolomide | Lenalidomide or temozolomide (Level 2B evidence) |

*, high-dose methotrexate should be infused with 4–6 h; **, intra-CSF chemotherapy agents include: methotrexate, cytarabine and dexamethasone; ***, long-term neurotoxicity of WBRT should be paid attention, especially in patients elder than 60 years. CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; WBRT, whole brain radiotherapy.

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