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Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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clinical practice guidelines

incidence and epidemiology

Diffuse large B-cell lymphoma (DLBCL) constitutes 30%–58% of non-Hodgkin's lymphoma series. The crude incidence in Europe is 3.8/100 000/year [1]. The incidence increases with age and varies considerably across Europe. A family history of lymphoma, autoimmune disease, human immunodeficiency virus (HIV) infection, hepatitis C virus (HCV) seropositivity, a high body mass as a young adult and some occupational exposures have been identified as risk factors of DLBCL [2]. In recent years, there have been important survival improvements for DLBCL in all European regions [3].

diagnosis and pathology/molecular biology

The diagnosis of DLBCL should be carried out in a reference haematopathology laboratory with expertise in morphological interpretation and the facilities to carry out the full range of phenotypic and molecular investigations [V, A].

A surgical excision biopsy remains the optimal method of diagnosis [V, A]. This allows assessment of nodal architecture and provides adequate material for phenotypic and molecular studies. Ideally, the biopsy should be sent unfixed to the laboratory to allow flow cytometric studies to be carried out and high-quality DNA and RNA to be extracted. Needle-core and endoscopic biopsies should be reserved for patients for whom a surgical approach is impractical or would entail excessive risk [IV, B]. A fine-needle aspirate should not be used as the sole basis for a diagnosis of DLBCL [V, E].

A morphological diagnosis of DLBCL should be confirmed in all cases by immunophenotypic investigations, either immunohistochemistry (IHC) or flow cytometry or a combination of both techniques [V, A]. Panels used must be designed to confirm B-cell lineage, and must be comprehensive enough to highlight possible variant forms such as immunoblastic lymphoma [4], primary mediastinal B cell lymphoma (PMBCL), T-cell/histiocyte rich large B-cell lymphoma, primary cutaneous DLBCL leg-type or EBV-positive DLBCL of the elderly. They must also distinguish alternative diagnoses that may be difficult to make on the basis of morphology alone, and which have important clinical consequences as plasmablastic lymphoma or soft tissue involvement by myeloma, Burkitt lymphoma, unclassifiable B-cell lymphoma with features intermediate between diffuse large cell lymphoma and Burkitt lymphoma, blastic mantle cell lymphoma and some cases of Hodgkin's lymphoma. A suggested immunohistochemical panel would include CD20, CD79a, BCL6, CD10, MYC, BCL2, Ki67, IRF4, CyclinD1, CD5 and CD23. EBER-1 staining may be used to identify the Epstein–Barr virus-positive DLBCL subtype of the elderly population. The histological report should give the diagnosis according to the current World Health Organization classification [5].

Where the level of confidence in the diagnosis is reduced, for example, because only a small biopsy specimen is available or where the putatively neoplastic population has a normal phenotype by IHC, demonstration of B-cell monoclonality by a polymerase chain reaction-based method should be considered [IV, C] [6].

The cell of origin phenotype determined by gene expression profiling is also a major prognostic factor in DLBCL [7–9]. Tumours with a germinal centre phenotype have a significantly better clinical outcome that those with an activated B-cell phenotype. The nature of type 3 or unclassified subgroups requires further clarification. Newer methods, based on evaluation of a limited set of genes, have been validated in comparison with standard gene expression, and are now used in the setting of clinical trials [9, 10]. Cell of origin can also be determined by IHC but published data on the prognostic effect of immunohistochemical techniques are contradictory, and it is not recommended to routinely base clinical decisions on these results [11, 12]. General

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issues of reproducibility may also limit the value of IHC as a prognostic biomarker [13].

The presence of an MYC rearrangement in combination with BCL2 rearrangement, and possibly other genetic abnormalities, has been described as a special entity ('double-hit' or 'triple-hit' lymphoma). However, the prognostic significance of these rearrangements remains controversial and optimal clinical management is not established [14–16]. This assessment is recommended, wherever technically possible, in newly diagnosed and relapsed patients being treated with curative intent, using interphase fluorescence *in situ* hybridisation [IV, B]. The immunohistochemical expression of MYC and/or BCL2 or both (double expressors) is only partly correlated with genetic abnormalities, but the concurrent expression of MYC and BCL2 is usually associated with a poor outcome [17–19].

staging and risk assessment

Physical examination, performance status (PS) and assessment of B symptoms are necessary [V, A]. A complete blood count, routine blood chemistry including lactate dehydrogenase (LDH) and uric acid, as well as screening tests for HIV, hepatitis B virus (HBV) (HBs antigen, anti-HBs and anti-HBc antibodies) and HCV are required [V, A]. Protein electrophoresis is recommended [IV, B].

Based on recent consensus recommendations for staging and restaging of lymphoma developed by the clinical and imaging working groups of the international conference of malignant lymphomas (Lugano classification), fluorodeoxyglucose positron emission tomography (FDG-PET)/computed tomography (CT) scan is now recommended as the gold standard for staging DLBCL patients [V, A] [20, 21]. PET/CT is more accurate than contrast-enhanced CT (CeCT), with increased sensitivity for nodal and extranodal sites; in practice, CeCT is often carried out before PET/CT. Should this not be the case, a full diagnostic high-dose CeCT should be carried out when necessary, in combination with PET/CT and after the PET scan [V, B]. Indeed, CeCT may be necessary for a better delineation of lymphadenopathy from the bowel; the detection of compression/thrombosis of central/mediastinal vessels, radiation planning or a more accurate measurement of nodal sites in the context of a trial. The findings of CeCT when carried out at baseline determine whether the low-dose non-enhanced CT part of the PET/CT scan will be sufficient for restaging.

Focal bone marrow FDG uptake with or without increased diffuse uptake is more sensitive than bone marrow biopsy (BMB) for infiltration in DLBCL and is highly specific [22]. Low-volume involvement (<10%–20%) and discordant lymphoma may be missed by PET/CT imaging but these positive BMB/negative PET/CT findings are <10% [23]. Thus, biopsy is no longer required when a PET/CT scan demonstrates bone or marrow involvement indicating advanced-stage disease but is appropriate in case of negative PET, when its results would change prognosis and treatment, especially when a shortened number of immunochemotherapy cycles is proposed [V, C].

For suspected central nervous system (CNS) lymphoma, magnetic resonance imaging is the modality of choice [III, A].

A diagnostic lumbar puncture should be considered in high-risk patients as described above [V, A]. Flow cytometry, when available, enhances the detection of lymphoma cells in the cerebrospinal fluid [24].

Cardiac function (left ventricular ejection fraction) should be assessed before treatment [V, A]. The risks of infertility and possibilities of fertility preservation should be discussed, depending on the type of treatment being proposed.

The staging is established according to the Ann Arbor classification system [I, A] (Table 1). A new staging system that has not been prospectively validated has been recently proposed [20]. For prognostic purposes, the International Prognostic Index (IPI) and age-adjusted IPI (aaIPI) should be calculated [I, A] [25] (Table 2). Other factors that may affect prognosis and treatment strategies, including the maximum bulk of the disease, should be assessed [30].

Table 1. Ann Arbor staging classification

Stage	
I	Involvement of a single lymphatic region (I) or localized involvement of single extralymphatic organ or site (IE)
II	Involvement of two or more lymphatic regions on the same side of the diaphragm (II) or localized involvement of a single extralymphatic organ or site and of one or more lymphatic regions on the same side of the diaphragm (IIE)
III	Involvement of lymphatic regions on both sides of the diaphragm
IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without lymphatic involvement

Table 2. International prognostic index (IPI)

International prognostic index (IPI)			Estimated 3-year overall survival [26–29] (95% CI)
Risk factors	Age >60 years Serum LDH > normal Stage III–IV Performance status 2–4 Extranodal sites >1		
Risk categories	Low	0–1	91 (89–94)
	Low intermediate	2	81 (73–86)
	High intermediate	3	65 (58–73)
	High	4–5	59 (49–69)
Age-adjusted international prognostic index (aaIPI) in patients ≤60 years			
Risk factors	Serum LDH > normal Stage III–IV Performance status 2–4		
Risk categories	Low	0	98 (96–100)
	Low intermediate	1	92 (87–95)
	High intermediate	2	75 (66–82)
	High	3	

LDH, lactate dehydrogenase; CI, confidence interval.

Table 3. Recommended treatment strategies in diffuse large B-cell lymphoma

Patients ≤60 years		
IPI low risk (aaIPI = 0) and no bulk	IPI low risk (aaIPI = 0) with bulk or IPI low-intermediate risk (aaIPI = 1)	IPI intermediate-high risk or IPI high risk (aaIPI = 2, 3)
R-CHOP21 × 6 Consider CNS prophylaxis in patients at risk for CNS progression	R-ACVBP and sequential consolidation or R-CHOP21 × 6 + IF-RT on bulk	R-CHOP21 × 6–8 or R-CHOP14 × 6 with 8 R Consider more intensive regimens in selected patients: R-CHOEP14 × 6 or R-CHOP or R-ACVBP plus HDCT with ASCT
Elderly >60 years		
Fit, 60–80 years	>80 years without cardiac dysfunction	Unfit or frail or >60 years with cardiac dysfunction
R-CHOP21 × 6–8 (R-CHOP21 × 6 for IPI low risk) or R-CHOP14 × 6 with 8 R Consider CNS prophylaxis in patients at risk	Attenuated regimens: R-miniCHOP21 × 6	Doxorubicin substitution with gemcitabine, etoposide or liposomal doxorubicin or others: R-C(X)OP21 × 6 or palliative care
First relapse/progress		
Eligible for transplant	Not eligible for transplant	
Platinum-based chemotherapy regimens (i.e. R-DHAP, R-ICE, R-GDP) as salvage treatment For chemosensitive patients: R-HDCT with ASCT as remission consolidation Consider allogeneic transplantation in patients relapsed after R-HDCT with ASCT or in patients with poor-risk factors at relapse	Platinum- and/or gemcitabine-based regimens Clinical trials with novel drugs	
>2 relapse/progress		
Eligible for transplant	Not eligible for transplant	
Allogeneic transplantation Clinical trials with novel drugs	Clinical trials with novel drugs Palliative care	

IPI, International Prognostic Index; aaIPI, age-adjusted IPI; R, rituximab; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; ACVBP, doxorubicin, vindesine, cyclophosphamide, bleomycin and prednisolone; IF-RT, involved-field radiotherapy; HDCT, high-dose chemotherapy; ASCT, autologous stem-cell transplantation; DHAP, cisplatin, cytarabine, dexamethasone; ICE, ifosfamide, carboplatin, etoposide; GDP, cisplatin, gemcitabine, dexamethasone; CNS, central nervous system; CHOEP, cyclophosphamide, doxorubicin, vincristine, etoposide, prednisolone; R-C(X)OP, R-CHOP with substitution of doxorubicin.

treatment

Treatment strategies should be stratified according to age, IPI and feasibility of dose-intensified approaches (Table 3). Whenever available, the inclusion in a clinical trial is recommended.

In cases with high tumour load, precautions such as the administration of prednisone (p.o.) several days as 'prephase' treatment are advised to avoid tumour lysis syndrome [I, A]. Dose reductions due to haematological toxicity should be avoided [I, A]. Febrile neutropaenia justifies prophylactic use of haematopoietic growth factors in patients treated with curative intent and in patients older than 60 years of age [I, A].

young low-risk patients (aa-IPI = 0) without bulky disease

Six cycles of combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) treatment combined with six doses of rituximab given every 21 days is the current standard [I, A] [31]. Consolidation by radiotherapy to initial non-bulky sites has no proven benefit in patients treated with rituximab or not [I, A] [32, 33].

young low-intermediate-risk patients (aa-IPI = 1) or IPI low risk (aa-IPI = 0) with bulky disease

Rituximab (R)-CHOP 21 × 6 with radiotherapy to the sites of previous bulky disease was shown to be effective in this group of patients, based on the results of the MINT study [II, B] [31]. Alternatively, an intensification of chemotherapy with R-ACVBP (rituximab, doxorubicin, vindesine, cyclophosphamide, bleomycin and prednisolone), given every 2 weeks followed by sequential consolidation, has been shown to improve survival compared with eight cycles of R-CHOP in this category, but radiotherapy was omitted in both arms of this trial [I, A] [26]. In this group of patients, either R-CHOP21 × 6 with radiotherapy to the sites of previous bulky disease or the intensified regimen R-ACVBP is recommended [II, B].

young high- and high-intermediate-risk patients (aa-IPI ≥ 2)

There is no current standard in this subgroup, and in this group especially, enrolment in clinical trials should be a priority. Six to eight cycles of chemotherapy with CHOP combined with eight doses of rituximab given every 21 days are most frequently applied [III, B]. Dose dense treatment with R-CHOP given every 14 days has not demonstrated a survival advantage over standard R-CHOP given every 21 days [I, C] [34]. In this trial, R-CHOP 14 failed to show a better outcome in any DLBCL subset, including young poor-risk patients, although the trial was not powered to compare multiple clinical subgroups. Intensive treatment with R-ACVBP or R-CHOEP (rituximab, cyclophosphamide, doxorubicin, vincristine, etoposide and prednisolone) is frequently used but these regimens have not been directly compared with R-CHOP in this category [II, B] [27, 35].

Four randomised trials comparing rituximab chemotherapy (R-chemotherapy) followed by high-dose chemotherapy (HDC) and autologous stem-cell transplantation (ASCT) versus R-chemotherapy alone have been presented. Two trials showed a progression-free survival (PFS) benefit for HDC with ASCT but no impact, at present, on overall survival (OS) [36, 37], while two trials failed to demonstrate an improvement for the HDC arm [35, 38]. Therefore, HDC with ASCT in first line remains experimental or may be proposed for selected high-risk patients [II, C]. The role of consolidation by radiotherapy to initial sites of bulky disease is unknown. The role of interim PET to select patients who could benefit from consolidative ASCT [39] or from radiotherapy [40] is under evaluation [I, C].

patients aged 60–80 years

Six to eight cycles of combination chemotherapy with CHOP plus eight doses of rituximab given every 21 days is the current standard [I, A] [41]. R-CHOP given every 14 days did not demonstrate a survival advantage over R-CHOP 21 [I, C] [34, 42]. If R-CHOP is given every 14 days, six cycles of CHOP with eight cycles of rituximab are sufficient [I, A] [43]. In patients with localised disease (IPI = 0), no benefit of consolidation by radiotherapy was shown in patients treated before the introduction of rituximab [I, A] [44], but a recent study indicated that irradiation could improve the outcome of elderly patients with bulky disease [II, C] [45]. In a phase II study, extended rituximab exposure has been shown to improve outcome of elderly poor-prognosis patients without increasing toxicity [III, C] [46]. A comprehensive geriatric assessment in order to ascertain co-morbidities and functional decline is recommended to guide the choice of treatment in these patients [III, A] [47, 48]. R-CHOP treatment can usually be used up to 80 years of age in fit patients [I, A] but modulation of treatment according to geriatric assessment is recommended [III, C] [49].

patients aged >80 years

The combination of rituximab with attenuated chemotherapy, such as R-miniCHOP, can induce complete remission and long survival in fit patients older than 80 years [III, B] [50]. Substitution of doxorubicin by gemcitabine, etoposide or liposomal doxorubicin, or even its omission, can be considered from the beginning or after a few cycles in patients with cardiac dysfunction or who are frail or unfit [III, C] [51].

central nervous system (CNS) prophylaxis

Patients with high-intermediate and high-risk IPI, especially those with more than one extranodal site or elevated LDH, are at higher risk of CNS relapse [52]. Testicular, renal and adrenal involvements have been validated as additional risk factors [53]. CNS prophylaxis should be recommended in these populations [II, A]. MYC gene rearrangement is associated with a high risk of CNS relapse [43]. Although widely used, intrathecal injections of methotrexate may not be an optimal method. Intravenous high-dose methotrexate has been shown to be associated with efficient disease control [IV, C] [54–56]. Prospective trials are ongoing to evaluate this alternative approach.

some DLBCLs require special consideration

- Extranodal DLBCLs and PMBCLs are considered in other guidelines.
- Patients with HIV infection should usually receive the same treatment as HIV-negative patients in association with antiviral therapy [II, A] [57].
- Patients previously exposed to HBV (HBs antigen-negative, anti-HBc-positive) are at risk of reactivation during treatment with R-CHOP. Antiviral prophylaxis or periodic HBV DNA monitoring and antiviral treatment in the case of reactivation are recommended [III, A] [58].

response evaluation

post-treatment evaluation

FDG-PET/CT is now the recommended standard for post-treatment assessment in DLBCL [I, A] [59]. The recent Lugano classification based on the visual Deauville criteria (5-point scale, Table 4)

Table 4. PET 5-point scale (Deauville criteria)

1	No uptake
2	Uptake ≤mediastinum
3	Uptake >mediastinum but ≤liver
4	Moderately increased uptake compared with liver
5	Markedly increased uptake to liver and/or new lesions

has proposed different response categories, termed 'metabolic response categories' [20, 21]:

- Complete metabolic response (CMR) is defined when no residual uptake exists or if the residual uptake is lower to or equal to the liver activity (Deauville score 1–3), with or without evidence of residual mass on the CT part of the examination, and without FDG-avid lesions in the bone marrow. Since most patients with score 3 (uptake greater than mediastinal activity) have a good prognosis with standard treatment, score 3 has been included in the CMR category but a careful evaluation of these patients is recommended.
- Deauville scores 4 and 5 indicate residual disease in most cases. Three categories of response are defined by comparing the residual uptake with the tumour uptake in baseline scan: partial metabolic response when the uptake has decreased, no metabolic response when it has not changed or progressive metabolic disease (PMD) when it has increased. A new site of FDG uptake consistent with lymphoma is graded score 5 and indicates a PMD but should be biopsied or followed by interval scans in case of aetiological uncertainties. In the presence of residual metabolically active tissue, where salvage treatment is being considered, a biopsy is recommended [III, A].

interim evaluation

Mid-treatment imaging after three to four cycles may be used to rule out progression in clinical practice [V, B]. It is usually carried out with CT but PET/CT can also be used when available [20]. Changing treatment solely on the basis of interim PET/CT is discouraged [II, E], unless there is clear evidence of progression.

Early PET evaluation carried out after one to two cycles of treatment has been shown to be predictive of outcome, but should be reserved for clinical trials at the present time [II, D].

follow-up

Patients with DLBCL who are event-free at 2 years have an identical OS to that of the general population, emphasising the need to only specifically monitor the disease in this early period [60].

Careful history and physical examination every 3 months for 1 year, every 6 months for 2 more years and then once a year with attention to development of secondary tumours or other long-term side-effects of chemotherapy is recommended [V, D]. Blood count should be carried out at 3, 6, 12 and 24 months, then only as needed for evaluation of suspicious symptoms or clinical findings in those patients suitable for further therapy [V, C].

Minimal radiological examinations at 6, 12 and 24 months after end of treatment by CT scan are common practice, but there is no definitive evidence that routine imaging in patients in complete remission provides any outcome advantage, and it may increase the incidence of secondary malignancies [V, D] [61, 62]. Routine surveillance with PET scan is not recommended [V, E]. High-risk patients with curative options may potentially mandate more frequent evaluation.

relapsed and refractory DLBCL

incidence. Overall, more than 30% of DLBCL will ultimately relapse. The incidence in the European Union is therefore estimated to be around 1/100 000/year. In addition to initial prognostic factors, the nature of previous treatments and time from initial treatment are of utmost importance [63].

diagnosis. In patients who are suspected of having relapsed on the basis of imaging studies, the diagnosis should be confirmed by biopsy before proceeding to second-line therapy. In these circumstances, a needle-core biopsy is acceptable as primary investigation.

staging and risk assessment. Patients still amenable to curative therapy should have the same examinations as at first diagnosis.

treatment. The following recommendations apply to patients who received adequate rituximab and anthracycline-containing first-line therapy.

In patients aged <65–70 years with good PS and no major organ dysfunction, salvage regimens with rituximab and chemotherapy followed, in responsive patients, by HDC and ASCT, are recommended [II, A] [63–65] Salvage regimens such as R-DHAP (rituximab, cisplatin, cytarabine, dexamethasone) or R-ICE (rituximab, ifosfamide, carboplatin, etoposide) appear to have similar outcomes [I, A] [63]. However, R-GDP (rituximab, cisplatin, gemcitabine, dexamethasone) has been shown to have similar efficacy but less toxicity than R-DHAP [I, A] [66]. One study suggested a possible advantage of R-DHAP in the germinal centre B-cell subtype, but this needs confirmation [IV, C] [67]. BEAM (carmustine, etoposide, cytarabine and melphalan) is the most commonly used high-dose regimen [III, B]. Additional involved-field radiation or iceberg radiation may be used, especially in the few cases with limited stage disease, but this has never been evaluated in controlled trials [IV, C]. Maintenance with rituximab is not recommended [I, E] [68]. Allogeneic transplantation with a sibling or matched unrelated donor may be considered in patients with refractory disease, early relapse or relapse after ASCT [III, B] [69].

Patients not suitable for high-dose therapy may be treated with the same or other salvage regimens as R-GEMOX (rituximab, gemcitabine, oxaliplatin) [III, B] [70]. Pixantrone, a new anthracycline-like drug with reduced cardiotoxicity, demonstrated some efficacy in heavily treated patients [II, C] [71]. However, these patients should be preferably enrolled in clinical trials testing the activity of other novel drugs.

response evaluation. Response criteria are identical to those of first-line treatment evaluation. An evaluation should be carried out after three to four cycles of the salvage regimen (before high-dose treatment) and after the end of all therapy. Results of PET before high-dose treatment are correlated to clinical outcome [72].

follow-up. Follow-up of patients in second response is the same as for first response.

personalised medicine

Progress in the knowledge of pathological and molecular heterogeneity of DLBCL has led to the study of new agents that have distinct activity in molecular subtypes, or have specific efficacy on molecular targets involved in disease pathogenesis. At the

Table 5. Summary of recommendations

Diagnosis and pathology/molecular biology

- Diagnosis should be carried out in a reference haematopathology laboratory with expertise in morphological interpretation and the facilities to carry out the full range of phenotypic and molecular investigations [V, A].
- Surgical biopsy is the optimal method of diagnosis. [V, A].
- Needle-core and endoscopic biopsies should be reserved for patients for whom a surgical approach is impractical or would entail excessive risk [IV, B].
- A fine-needle aspirate should not be used as the sole basis for a diagnosis of DLBCL [V, E].
- A morphological diagnosis of DLBCL should be confirmed in all cases by immunophenotypic investigations [V, A].
- If there is doubt in the diagnosis, demonstration of B-cell monoclonality by a PCR-based method should be considered [IV, C].
- Assessment of MYC and BCL2 rearrangement is recommended (whenever technically possible) in newly diagnosed and relapsed patients treated with curative intent, using interphase FISH [IV, B].

Staging and risk assessment

- Physical exam, performance status and assessment of B symptoms are necessary [V, A].
- A complete blood count, routine blood chemistry including LDH and uric acid, as well as screening tests for HIV, HBV and HCV are required [V, A].
- Protein electrophoresis is recommended [IV, B].
- FDG-PET/CT scan is recommended as the gold standard for staging DLBCL patients [V, A].
- If CeCT is not carried out before PET/CT, a full diagnostic high-dose CeCT should be carried out when necessary, in combination with PET/CT [V, B]. Biopsy may be avoided when PET/CT scans demonstrate bone or marrow involvement indicating advanced-stage disease but is appropriate in the case of negative PET, when its results would change prognosis and treatment, especially when a shortened number of immunochemotherapy cycles is proposed [V, C].
- For suspected CNS lymphoma, MRI is the modality of choice [III, A].
- A diagnostic lumbar puncture should be considered in high-risk patients [V, A].
- Cardiac function (LVEF) should be assessed before treatment [V, A].
- The staging is established according to the Ann Arbor classification system [I, A].
- For prognostic purposes, the IPI and aa-IPI should be calculated [I, A].

Treatment

- Treatment strategies should be stratified according to age, IPI and feasibility of dose-intensified approaches.
- Whenever available, inclusion in a clinical trial is recommended.
- In cases with high tumour load, precautions are advised to avoid tumour lysis syndrome [I, A].
- Dose reductions due to haematological toxicity should be avoided whenever possible [I, A].
- The risk of febrile neutropenia justifies prophylactic use of haematopoietic growth factors in patients treatment with curative intent and in patients >60 years of age [I, A].
- For young, low-risk patients (aa-IPI = 0) without bulky disease:
  - six cycles of combination chemotherapy with CHOP treatment combined with six doses of rituximab given every 21 days is the current standard [I, A];
  - consolidation by radiotherapy to initial non-bulky sites has no proven benefit in patients treated with rituximab or not [I, A].
- For young low-intermediate-risk patients (aa-IPI = 1) or IPI low risk (aa-IPI = 0) with bulky disease:
  - either R-CHOP21 × 6 with radiotherapy to the sites of previous bulky disease or the intensified regimen R-ACVBP is recommended [II, B].
- For young high- and high-intermediate-risk patients (aa-IPI ≥ 2):
  - enrolment in clinical trials should be a priority;
  - six to eight cycles of chemotherapy with CHOP combined with eight doses of rituximab given every 21 days are most frequently applied [III, B];
  - dose dense treatment with R-CHOP given every 14 days has not demonstrated a survival advantage over standard R-CHOP given every 21 days [I, C];
  - intensive treatment with R-ACVBP or R-CHOEP is frequently used but these regimens have not been directly compared with R-CHOP in this category [II, B];
  - HDC with ASCT in first line remains experimental or may be proposed for selected high-risk patients [II, C];
  - the role of interim PET to select patients who could benefit from consolidative ASCT or from radiotherapy is under evaluation [I, C].
- For patients aged 60–80 years:
  - six to eight cycles of combination chemotherapy with CHOP plus eight doses of rituximab given every 21 days is the current standard [I, A];
  - if R-CHOP is given every 14 days, six cycles of CHOP with eight cycles of rituximab are sufficient [I, A];
  - a comprehensive geriatric assessment in order to ascertain comorbidities and functional decline is recommended to guide the choice of treatment in elderly poor-prognosis patients [III, A];
  - R-CHOP treatment can usually be used up to 80 years of age in fit patients [I, A], but modulation of treatment according to geriatric assessment is recommended [III, C].
- For patients aged >80 years:
  - the combination of rituximab with attenuated chemotherapy, such as R-miniCHOP, can induce complete remission and long survival in fit patients older than 80 years [III, B];
  - substitution of doxorubicin by gemcitabine, etoposide or liposomal doxorubicin, or even its omission, can be considered from the beginning or after a few cycles in patients with cardiac dysfunction or who are frail or unfit [III, C].

Continued

Table 5. *Continued*

- CNS prophylaxis:
  - should be recommended for patients with high-intermediate-risk and high-risk IPI, especially those with more than one extranodal site or elevated LDH or for patients with testicular, renal or adrenal involvement [II, A];
  - intravenous high-dose methotrexate has been shown to be associated with efficient disease control [IV, C].
- Patients with human immunodeficiency virus (HIV) infection should usually receive the same treatment as HIV-negative patients in association with antiviral therapy [II, A].
- Antiviral prophylaxis or periodic HBV DNA monitoring and antiviral treatment are recommended for patients previously exposed to HBV who experience reactivation of the virus during treatment [III, A].

Response evaluation

- FDG-PET/CT is the recommended standard for post-treatment assessment in DLBCL [I, A].
- In the presence of residual metabolically active tissue, where salvage treatment is being considered, a biopsy is recommended [III, A].
- Interim evaluation:
  - mid-treatment imaging after three to four cycles may be used to rule out progression in clinical practice [V, B];
  - changing treatment solely on the basis of interim PET/CT is discouraged [II, E], unless there is clear evidence of progression;
  - early PET evaluation carried out after one to two cycles of treatment has been shown to be predictive of outcome, but should be reserved for clinical trials at the present time [II, D].

Follow-up

- Careful history and physical examination every 3 months for 1 year, every 6 months for 2 further years and then once a year with attention to development of secondary tumours or other long-term side-effects of chemotherapy is recommended [V, D].
- Blood count should be carried out at 3, 6, 12 and 24 months, then only as needed for evaluation of suspicious symptoms or clinical findings in those patients suitable for further therapy [V, C].
- Minimal radiological examinations at 6, 12 and 24 months after end of treatment, by CT scan, is common practice, but there is no definitive evidence that routine imaging in patients in complete remission provides any outcome advantage and it may increase the incidence of secondary malignancies [V, D]. Routine surveillance with PET scan is not recommended [V, E].

DLBCL, diffuse large B-cell lymphoma; PCR, polymerase chain reaction; FISH, fluorescence *in situ* hybridisation; LDH, lactate dehydrogenase; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; CeCT, contrast-enhanced CT; CNS, central nervous system; MRI, magnetic resonance imaging; LVEF, left ventricular ejection fraction; IPI, International Prognostic Index; aa-IPI, age-adjusted IPI; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; R, rituximab; R-AVCBP, rituximab, doxorubicin, vindesine, cyclophosphamide, bleomycin and prednisolone; R-CHOEP, rituximab, cyclophosphamide, doxorubicin, vincristine, etoposide and prednisolone; HDC, high-dose chemotherapy; ASCT, autologous stem-cell transplantation.

Table 6. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, …), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [86].

present time, pending results of large comparative studies, none of these agents is appropriate for routine therapy in practice.

The activated B-cell (ABC) subtype has been shown to have a worse prognosis when compared with germinal centre B-cell (GCB) in patients treated by R-CHOP [8]. A subgroup analysis suggested that R-ACVBP could have a survival benefit over R-CHOP in the non-GCB population [III, C] [73]. The ABC subtype is characterised by a constitutive activation of the NF-κB pathway, which could be targeted by different agents as bortezomib and lenalidomide. Bortezomib combined with dose-adjusted-EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide and prednisone) (DA-EPOCH) has shown selective activity in a small study of relapsed/refractory ABC-DLBCL [74]. A UK/Swiss phase III trial (REMoDL-B) comparing R-CHOP with R-CHOP-bortezomib in gene expression prolife defined cell of origin subgroups of DLBCL is nearly completed. Lenalidomide, as a single agent, demonstrated selective efficacy in the non-GCB subtype [75, 76]. In two phase II studies, the combination of lenalidomide and R-CHOP showed acceptable toxicity [77, 78]. In one of these studies, the PFS and OS of the patients treated with the combination were identical in non-GCB and GCB subtypes [78], leading to the initiation of a randomised study in the ABC subtype.

Ibrutinib, a novel oral Bruton's tyrosine kinase inhibitor, has shown selective activity in ABC-DLBCL. The combination of ibrutinib with R-CHOP has demonstrated promising responses, leading to the initiation of a phase III trial in the non-GCB population [79].

DLBCL with MYC rearrangement and/or MYC overexpression is usually considered a subgroup with aggressive behaviour. However, many uncertainties remain about the extent of this subgroup concerning translocation partners, additional defects (double or triple hit), combination of genetic abnormalities and MYC protein overexpression and dual overexpression with MYC and BCL2 [80]. Although R-CHOP gives poor outcomes for double-hit lymphomas, only preliminary results have suggested better results with more intensive regimens, and clinical trials are required in this subtype [81, 82].

Whole-genome next-generation sequencing studies have identified frequent and recurrent mutations which may play a crucial role in lymphoma development [83–85]. These molecular defects may prove useful targets in the future treatment and management of DLBCL.

methodology

These clinical practice guidelines were developed in accordance with the ESMO standard operating procedures for clinical practice guidelines development. The relevant literature has been selected by the expert authors. A summary of recommendations is shown in Table 5. Levels of evidence and grades of recommendation have been applied using the system shown in Table 6. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty. This manuscript has been subjected to an anonymous peer review process.

conflict of interest

HT has received honoraria from Celgene, Roche, Janssen-Cilag and Takeda; research contracts from Celgene, Roche/Genentech and Janssen-Cilag. MG has reported advisory boards for Roche, Celgene, Janssen-Cilag, Pfizer and Ferrer. UV has reported advisory boards for Roche; lectures sponsored by Roche, Janssen, Celgene and Mundipharma. AL-G has reported advisory boards for Roche, Celgene, Novartis, Mundipharma, Infinity, Bayer and Gilead. JW has declared advisory boards for Roche, Celgene, Janssen-Cilag and Takeda; research support from Roche, Celgene, Janssen-Cilag, Takeda, GlaxoSmithKline, Gilead and Seattle Genetics. PJ has reported research grants partially funded by Janssen-Cilag and Epizyme; member of data monitoring and safety committee for Boehringer Ingelheim; advisory board member for Roche, Bristol-Myers Squibb, Janssen-Cilag and Takeda. MP has declared advisory boards for Boehringer-Ingelheim, Celgene and Roche; research support from Roche, Amgen and Spectrum. ML has reported honoraria from Celgene, Janssen-Cilag, Roche, Amgen Mundipharma and Teva; research contracts from Celgene, Pfizer, Mundipharma and Roche; funds received from Amgen, Roche and Takeda. MM and MA have reported no potential conflicts of interest. UV has not reported any potential conflicts of interest.

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