



SEOM–GOTEL clinical guidelines on diffuse large B-cell lymphoma (update 2025)

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Abstract

Diffuse large B-cell lymphoma (DLBCL) is the most frequent histological subtype of non-Hodgkin lymphoma and the paradigm for the management of aggressive lymphoma. An excisional or incisional lymph node biopsy evaluated by an experienced hematopathologist is recommended to establish the diagnosis. Twenty years following its introduction, the combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) remains the standard first-line treatment. No modification of this scheme (increased chemotherapy dose intensity, new monoclonal antibodies, or the addition of immunomodulators or anti-target agents) has significantly improved the clinical outcomes, whereas therapy for recurrence or progression is evolving rapidly. The introduction of chimeric antigen receptor T cells, polatuzumab vedotin, tafasitamab, and cluster of differentiation (CD)20/CD3 bispecific antibodies is changing the natural history of patients with relapsed DLBCL and will challenge R-CHOP as the benchmark for newly diagnosed patients. These updated guidelines (2025) summarize current evidence and available therapies for the medical management of DLBCL.

Keywords Diagnosis · Diffuse large B-cell lymphoma · Guideline · Treatment

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Introduction

This article presents the 2025 update to the clinical practice guidelines for the management of diffuse large B-cell lymphoma (DLBCL), developed jointly by the Spanish Society of Medical Oncology (Sociedad Española de Oncología Médica; SEOM) and the Oncology Group for the Treatment and Study of Lymphomas (Grupo Oncológico para el Tratamiento y Estudio de los Linfomas; GOTEL). The previous edition was published in 2022 [1]. Since then, new clinical trial data and regulatory developments have emerged, prompting a review and revision of selected recommendations (Table 1). The current update incorporates these changes, refines the wording of prior guidance where needed, and maintains alignment with evolving international standards. It is intended as a practical reference for oncologists managing patients with DLBCL in Spain and reflects expert consensus on evidence-based strategies across the diagnostic, therapeutic, and post-treatment continuum.

Methodology

This guideline is based on relevant published studies and the consensus of ten GOTEL and SEOM oncologists with expertise in lymphoma treatment. The updated recommendations in these guidelines reflect the results of clinical trials released since the publication of the previous version in 2022, as well as minor corrections to the wording of the original text. The updated version has been reviewed and

approved by all the authors. The Infectious Diseases Society of America–United States (US) Public Health Service Grading System for Ranking Recommendations in Clinical Guidelines [2] has been used to assign levels of evidence and grades of recommendation (Supplementary Table).

Incidence and epidemiology

In Spain, non-Hodgkin lymphoma (NHL) is the seventh most common tumor in men and the eighth most common in women [3]. As in other Westernized countries, its incidence increased by 6% per year between 1975 and 1995 for unknown reasons and, since then, has remained stable [4].

DLBCL is the most common histological subtype of NHL (35%) in Spain, followed by follicular lymphoma (27%) and marginal cell lymphoma (13%), and is the paradigm of aggressive lymphoma [1]. The estimated number of cases of DLBCL diagnosed in Spain in 2024 was 4473, with a crude incidence rate of 9.3 cases/100,000 inhabitants/year [5]. The median age at diagnosis was 64 years and, as with most hematological neoplasms, it was more frequent in men (sex ratio 1.1) [6, 7]. During the 2002–2013 period, the 5-year relative survival of DLBCL in Spain was 55.6% [8].

Diagnosis, pathology, and molecular biology

The diagnosis of lymphoma is based on a comprehensive evaluation of histologic, immunophenotypic, cytogenetic, and molecular studies, interpreted in the context of the

Table 1 Summary of changes to recommendations compared with 2022 SEOM–GOTEL guidelines

Section	Recommendation	Change type	Details
Diagnosis, pathology, and molecular biology	Use of NGS in diagnosis	Substantive revision	Previous recommendation was a clear non-recommendation. The revised recommendation now adds that NGS may be used for improved classification. Level of evidence changed from IVC to IIIA
Treatment of relapsed/refractory DLBCL	CAR-T in first recurrence	Upgraded recommendation	Previous recommendation stated CAR-T cells “not yet justified” in first recurrence [IIC]. The revised recommendation is to use CAR-T in early relapse or refractory disease [IA]
Treatment of relapsed/refractory DLBCL	Anti-CD20/CD3 bispecific mAbs after relapse following second-line treatment	New recommendation	New recommendation added recognizing bispecific antibodies as promising for patients who relapse after second-line treatment, including CAR-T [IIA]

CAR-T chimeric antigen receptor T-cell therapy, *CD* cluster of differentiation, *DLBCL* diffuse large B-cell lymphoma, *GOTEL* Oncology Group for the Treatment and Study of Lymphomas (Grupo Oncológico para el Tratamiento y Estudio de los Linfomas), *mAbs* monoclonal antibodies, *NGS* next-generation sequencing, *SEOM* Spanish Society of Medical Oncology (Sociedad Española de Oncología Médica)

clinical presentation (Table 2). The differential diagnosis of DLBCL includes other entities that can result in lymphadenopathy and similar pathologic features. Patients usually present with a growing mass in a lymph node area or with symptoms of infiltration of extralymphatic organs. One-third have systemic B symptoms (i.e., fever, weight loss, sweats), and 40% have extranodal disease.

When available, a lymph node is generally the preferred tissue for diagnosis. Biopsy specimens should include both fresh and formalin-fixed material and should be evaluated by an experienced hematopathologist. If nodal involvement is not identified, diagnosis can be made using extranodal tissue. The tissue sample should be obtained urgently if aggressive NHL is suspected and, ideally, prior to steroid treatment.

An excisional or incisional lymph node biopsy is recommended to establish the diagnosis of DLBCL. A core needle biopsy is not optimal but can be used in certain clinical circumstances. Importantly, fine-needle aspiration alone is not an acceptable substitute for an initial diagnosis of lymphoma, although it may suffice to diagnose recurrence [9].

In addition to morphological classification, pathology assessment must necessarily include immunohistochemistry (IHC), flow cytometry, fluorescent in situ hybridization (FISH), and molecular tests. Three main morphologic subtypes of DLBCL (centroblastic, immunoblastic, and anaplastic) have been recognized, albeit with poor reproducibility among pathologists and scant clinical relevance. The IHC core panel for DLBCL diagnosis includes cluster of differentiation (CD)20, CD3, CD5, CD10, CD45, B-cell lymphoma (BCL)2, BCL6, Ki-67, interferon regulatory factor 4 (IRF4)/multiple myeloma oncogene 1 (MUM1), and MYC. CD30, human herpesvirus (HHV)-8, and Epstein–Barr virus (EBV) may be needed for classification.

Gene expression profiling (GEP) classifies DLBCL into three biological subtypes that arise from the developmental stages of normal B cells or their so-called ‘cell of origin’ (COO): germinal center B-cell-like (GCB, 56%), activated B-cell-like (ABC, 32%), and type 3 (11%). Retrospective studies have revealed significantly better outcomes for GCB compared with ABC [10–12]. However, prospective studies have failed to detect significant differences in terms of survival. Furthermore, COO alone does not explain the clinical heterogeneity across patients, and up to 20% of DLBCL cannot be classified using this genetic signature [13].

Hans’ immunohistochemical algorithm based on CD10, BCL6, and IRF4/MUM1 differentiates the COO more quickly and cost-effectively, but does not identify the entire ABC subgroup, and there is insufficient scientific evidence to be of use for treatment decisions [14].

Genomic sequencing platforms classify DLBCL into groups with different genetic signatures that are related to treatment outcomes. However, a significant proportion of

cases remain unclassified by these genetic models, and they are not currently available in routine clinical practice [15].

FISH analysis of aggressive B-cell lymphomas is needed to detect MYC and BCL2/BCL6 translocations, as they define a new entity in the latest World Health Organization (WHO) classification (“High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements”), which more often than not belongs to the GCB. These patients have particularly poor outcomes with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), making them good candidates for inclusion in clinical trials. DLBCL overexpressing MYC and BCL2 (double expressors) tend to be included in the ABC group and should not be confused with double-hit or triple-hit, high-grade lymphomas that carry genetic translocations [16].

Staging and risk assessment

The staging process should include a complete medical history, physical examination, laboratory tests, and imaging studies according to the recommendations for initial evaluation, staging, and response assessment of Hodgkin lymphoma and NHL of the Lugano classification (Table 2) [17]:

- Anamnesis with special attention to the presence of B symptoms (fever, profuse night sweats, and loss of more than 10% of body weight the last 6 months) and signs suggestive of extralymphatic involvement, in addition to Eastern Cooperative Oncology Group performance status (ECOG PS).
- Complete physical examination should be performed, focusing on peripheral lymph node regions, Waldeyer’s ring, and skin.
- Routine laboratory studies including complete blood count, electrolytes, kidney and liver function tests, those necessary to determine prognostic indices (serum lactate dehydrogenase [LDH] and β_2 -microglobulin), as well as serologies for hepatitis B and C, and human immunodeficiency virus (HIV).
- Positron emission tomography (PET) and computed tomography (CT) with iodinated contrast medium is the imaging test *par excellence* for staging aggressive lymphomas and will serve as a baseline reference for treatment response.
- Since PET-CT can detect bone marrow involvement in DLBCL, bone marrow biopsy is not routinely recommended [18].
- Cerebrospinal fluid cytology for patients at risk of central nervous system (CNS) involvement (high-risk International Prognostic Index [IPI], kidney or adrenal involvement, or primary testicular or breast DLBCL).

Table 2 SEOM–GOTEL recommendations for diffuse large B-cell lymphoma

	LoE; GoR
Diagnosis, pathology, and molecular biology	
Excisional/incisional biopsy of the adenopathy or affected extranodal tissue is the method of choice for the diagnosis of DLBCL	IA
The combination of clinical data with histopathological, IHC, and cytogenetic/molecular studies enables DLBCL to be categorized according to the standard WHO system. The basic panel for IHC in DLBCL includes CD20, CD3, CD5, CD10, CD45, BCL2, BCL6, Ki-67, IRF4/MUM1, and MYC	IA
An immunophenotyping algorithm is required to establish the COO [14], albeit, outside of a clinical trial, there is currently insufficient clinical evidence upon which to base a therapeutic decision. GEP studies are not deemed standard when diagnosing DLBCL in clinical practice	IIB
Tissue that is IHC-positive for MYC, BCL2, or BCL6 expression should undergo FISH to detect MYC, BCL2, and BCL6 gene rearrangements	IIA
In the absence of prospective studies demonstrating a more effective targeted therapy, NGS cannot be recommended in routine clinical practice to decide the treatment strategy, however, if available, it is recommended for better classification of DLBCL	IIIA
Staging and risk assessment	
The initial evaluation and staging should be performed according to the Lugano classification, which establishes PET-CT as the recommended imaging test for staging and response assessment	IA
Bone marrow biopsy is not routinely recommended	IIA
The original IPI should be used to appraise the risk of treatment failure	IA
Treatment of early-stage DLBCL	
mIPI of 0–1 with adverse prognostic factors: R-CHOP×4	IIA
mIPI of ≥2 with adverse prognostic factors:	
Conventional treatment: R-CHOP×3 + ISRT or R-CHOP×6	IIA
Risk-adapted therapy:	IIC
• R-CHOP×4 if PET3-negative	
• R-CHOP×6 or R-CHOP×3 + ISRT if PET3-positive	
Bulky disease (≥7.5–10 cm): R-CHOP×6 + ISRT	IIA
Treatment of advanced-stage DLBCL	
Six cycles of R-CHOP-21 remain the standard of care for advanced-stage DLBCL. Its replacement by polatuzumab-CHP is a possibility that should be considered in the future if this combination is approved by the Spanish regulatory authorities	IA
The value of consolidative radiation therapy after immunochemotherapy has not been proven	IVC
Treatment of relapsed or refractory DLBCL	
Fit patients with first relapse or refractory DLBCL should be treated with second-line chemotherapy, followed by HDC in those who demonstrate chemosensitivity	IIA
Patients with first relapse or refractory DLBCL who are not candidates for HDC should be treated with conventional second-line chemotherapy	IIIA
In patients refractory to first-line chemotherapy or who relapse within the first year of completion, CAR-T has shown superior efficacy compared with salvage chemotherapy followed by autologous stem cell transplantation and should be considered in eligible patients	IA
Patients who do not respond or who relapse after HDC could be candidates for CAR-T	IIIA
Patients with recurrences after HDC and CAR-T or patients who are not candidates for CAR-T could be treated with combinations of bendamustine, rituximab, and polatuzumab, tafasitamab, lenalidomide, and pixantrone, or low-dose, conventional palliative chemotherapy. Treatment with bispecific antibodies or other novel drugs in a clinical trial setting is highly recommended	IIIA
Anti-CD20/CD3 bispecific mAbs display promising efficacy and a favorable safety profile in patients who relapse after second-line chemotherapy and beyond, including those who have received prior CAR-T	IIA
Follow-up	
Anamnesis and clinical examination should be performed every 3 months in the first year, every 6 months the second and third years, and once a year thereafter	IVA
Blood tests, including complete blood count, LDH, and erythrocyte sedimentation rate assessments, should be performed every 6 months for the first 2 years and annually thereafter	IVA
Routine imaging tests are not recommended in the absence of clinical suspicion of recurrence	IIB
Yearly breast MRI scans should be considered in women who received treatment with thoracic radiotherapy starting at 8 years post-treatment	IVB
Smoking cessation counseling should be provided to all patients	IVA

BCL B-cell lymphoma, *CAR-T* chimeric antigen receptor T-cell therapy, *CD* cluster of differentiation, *CHP* cyclophosphamide, doxorubicin, and prednisone, *COO* cell of origin, *DLBCL* diffuse large B-cell lymphoma, *FISH* fluorescent in situ hybridization, *GEP* gene expression profiling, *GoR* grade of recommendation, *GOTEL* Oncology Group for the Treatment and Study of Lymphomas (Grupo Oncológico para el Tratamiento y Estudio de los Linfomas), *HDC* high-dose chemotherapy, *IHC* immunohistochemistry, *IPI* International Prognostic Index, *IRF4* interferon regulatory factor 4, *ISRT* involved-site radiation therapy, *LDH* lactate dehydrogenase, *LoE* level of evidence, *mAbs* monoclonal antibodies, *mIPI* modified International Prognostic Index, *MRI* magnetic resonance imaging, *MUM1* multiple myeloma oncogene 1, *NGS* next-generation sequencing, *PET3* positron emission tomography after 3 cycles of therapy, *PET-CT* positron emission tomography–computed tomography, *R-CHOP* rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, *SEOM* Spanish Society of Medical Oncology (Sociedad Española de Oncología Médica), *WHO* World Health Organization

- Echocardiogram or radionuclide ventriculogram in individuals at risk for heart failure if anthracyclines or mediastinal radiotherapy are indicated.
- Inform the patient about possible fertility preservation techniques before the start of chemotherapy.

For staging, the Lugano modification of the Ann Arbor classification system is used (Table 3). Note that the suffixes A and B are no longer applied in this staging system. There is no consensus regarding the cut-off point to define bulky disease, with thresholds ranging from 7.5 to 10 cm.

The IPI, with five variables (including stage), improves prognostic accuracy over stage alone (Table 4). Despite the original IPI [19] being conceived in the pre-rituximab era, more recent studies have validated this score for patients treated with chemotherapy plus rituximab. For those treated with CHOP or CHOP-like chemotherapy plus rituximab, 3-year overall survival (OS) for low, low-intermediate, high-intermediate, and high-risk groups was 91%, 81%, 65%, and 59%, respectively [20].

Patients with limited-stage DLBCL have a markedly better prognosis, and the IPI has been modified for this subgroup (see below) [21, 22].

Treatment of early-stage DLBCL

Limited-stage DLBCL is commonly defined as Ann Arbor stages I and II, usually anatomically located in a potential radiation field. Standard treatment consists of chemoimmunotherapy with R-CHOP, alone or in combination with involved-site radiation therapy (ISRT; Table 2, Fig. 1).

Radiotherapy alone is not an acceptable treatment for limited-stage DLBCL, with the exception of a selected group of patients with stage I disease and comorbidities, in whom the use of chemotherapy may be contraindicated.

To select the most appropriate treatment, patients with limited-stage DLBCL can be stratified based on the presence of adverse prognostic factors according to the

Table 4 International Prognostic Index

Adverse prognostic factors	Risk group: number of adverse prognostic factors
Age > 60 years	Low: 0–1
Serum LDH > ULN	Low-intermediate: 2
ECOG PS ≥ 2	High-intermediate: 3
Stage III–IV	High: 4–5
Extranodal involvement > 1 site	

ECOG PS Eastern Cooperative Oncology Group performance status, *LDH* lactate dehydrogenase, *ULN* upper limit of normal

stage-modified version of IPI (mIPI) [22]. This version includes the same prognostic factors described by Shipp and colleagues [19], except that for limited-stage disease, stage II is considered an adverse risk factor instead of stages III and IV (Table 5):

- Stage II.
- Serum LDH above normal limits.
- Age > 60 years.
- ECOG PS ≥ 2.

Moreover, the presence or absence of bulky disease (defined as a tumor >7.5–10 cm) must be taken into account.

Patients with stage I DLBCL without any adverse prognostic factors have a 5-year median OS of >90%, and those with stages I and II and some adverse prognostic factors have a 5-year OS of 70% [22]. However, in bulky disease, OS decreases to 50% at 5 years (similar to advanced stages) [22].

For practical purposes, early stages of DLBCL can be divided into three groups:

- Group I: 0–1 adverse prognostic factors, non-bulky.
- Group II: ≥2 adverse prognostic factors, non-bulky.

Table 3 Revised staging system for primary nodal lymphomas (Lugano classification) [17]

Stage	Involvement	Extranodal status
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky ^a	II as above with “bulky” disease	Not applicable
III	Nodes on both sides of the diaphragm; nodes above the diaphragm	Not applicable
IV	Additional noncontiguous extranodal involvement	Not applicable

Extent of disease is determined by positron emission tomography–computed tomography. Tonsils, Waldeyer’s ring, and spleen are considered nodal tissue

^aWhether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors

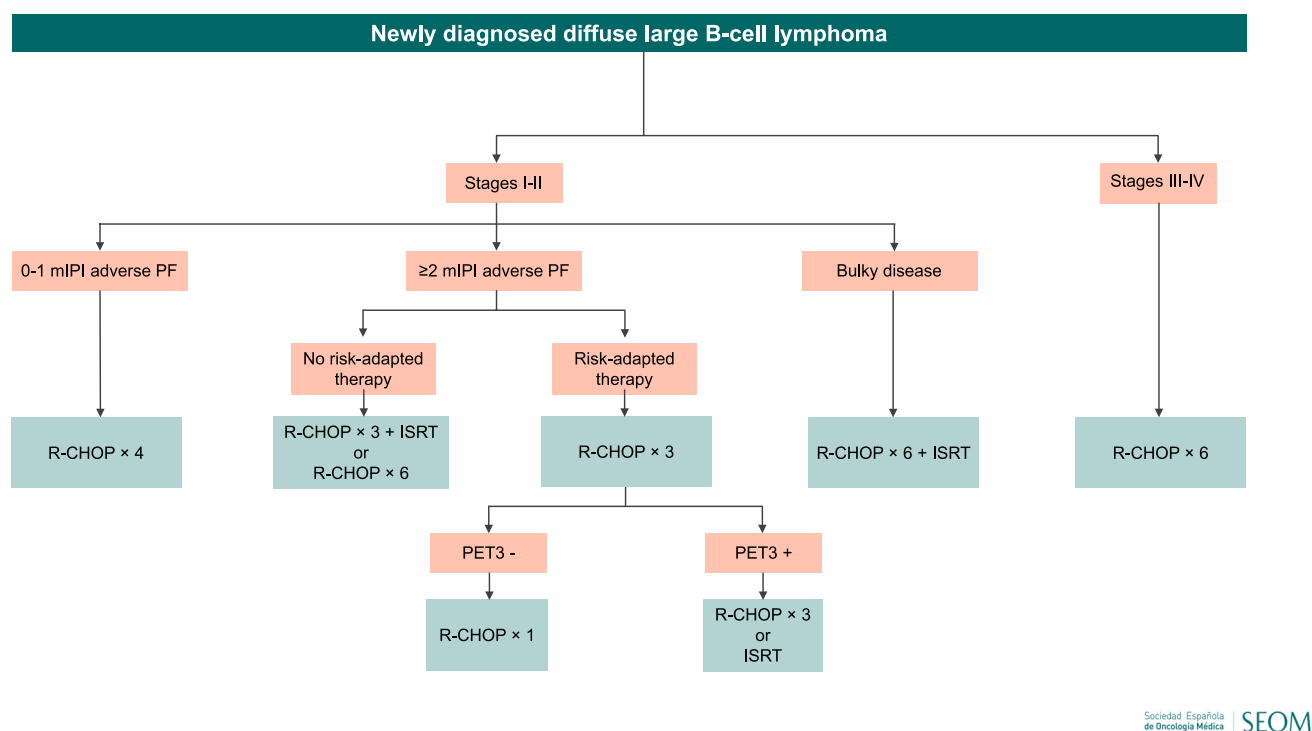


Fig. 1 Treatment algorithm for newly diagnosed diffuse large B-cell lymphoma. *ISRT* involved-site radiation therapy, *mIPI* modified International Prognostic Index, *PF* prognostic factor, *PET3* positron emission

tomography after 3 cycles of therapy, *R-CHOP* rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone

Table 5 Stage-modified International Prognostic Index [22]

Adverse prognostic factors	Risk group: number of adverse prognostic factors
Stage II	Low: 0–1
Serum LDH > ULN	Low: 0–1
Age > 60 years	High-intermediate: 3
ECOG PS ≥ 2	High: 4–5

ECOG PS Eastern Cooperative Oncology Group performance status, *LDH* lactate dehydrogenase, *ULN* upper limit of normal

- Group III: bulky disease.

For group I patients, treatment with 4 cycles of R-CHOP is usually enough. There are two trials that endorse this strategy. The phase III, non-inferiority FLYER trial included 592 patients aged ≤60 years with stage I–II DLBCL without adverse prognostic factors. Four cycles of R-CHOP followed by 2 doses of rituximab alone were compared with 6 cycles of R-CHOP. No differences were found in terms of 5-year OS, progression-free survival (PFS), or event-free survival (EFS); toxicity was lower with 4 cycles of R-CHOP [23]. In the LYSA trial, 334 patients without bulky disease received 4 cycles of R-CHOP every 14 days (R-CHOP-14) if they had mIPI of 0 and 6 cycles if they had mIPI of ≥1, with or

without 40 Gy ISRT. No differences were detected in EFS or OS and, similarly, no benefit was derived from the addition of radiotherapy [24].

In group II, two options are considered acceptable, depending on whether a risk-adapted therapeutic approach based on interim PET imaging is used. If such an approach is not used, both 3 cycles of R-CHOP followed by radiation therapy (30 Gy ISRT) and 6 cycles of R-CHOP are suitable treatment alternatives [21, 25]. Although no head-to-head studies have compared risk-adapted therapy versus conventional treatment in any stage of DLBCL [26], some authors have proposed the following recommendations:

- If PET-negative after 3 cycles of R-CHOP, complete treatment with one additional cycle of the same chemotherapy.
- If PET-positive after 3 cycles of R-CHOP, complete treatment with either 3 additional cycles of the same chemotherapy or 36–40 Gy of ISRT [27].

Prioritization of more cycles of chemotherapy over radiotherapy or vice versa should be based on the individual's comorbidities and the probability of long-term toxicities.

The therapeutic approach for cases of bulky disease (group III) should be the same as in advanced disease, although in this scenario, radiotherapy can play a more

prominent role. Administration of 6 cycles of R-CHOP followed by 30–40 Gy ISRT is generally recommended [28, 29].

Treatment of advanced-stage DLBCL

Approximately 70% of patients have advanced-stage disease at diagnosis. The standard of care in first-line therapy of advanced-stage DLBCL remains R-CHOP every 21 days (R-CHOP-21; Table 2). This is based on the results of the phase III study by the GELA group, in which 8 cycles of R-CHOP in patients >60 years of age significantly improved survival compared with 8 cycles of CHOP [30]. This survival benefit has been upheld in subsequent trial updates: 5-year OS for patients treated with CHOP and R-CHOP was 45% and 58%, respectively ($p=0.0073$) [31]. In the MiNT trial, individuals aged <60 years were randomized to receive either 6 cycles of CHOP-like therapy or 6 cycles of R-CHOP-like therapy; 6-year EFS was 55.8% versus 74.3% ($p<0.0001$) [28].

The RICOVER-60 trial demonstrated that increasing dose density, by administering R-CHOP-14, significantly improved survival compared with CHOP-14 [32]. Subsequently, the two large, randomized trials comparing R-CHOP-21 with R-CHOP-14 revealed no survival benefit [33, 34].

Several studies have evaluated whether increasing the dose intensity of chemotherapy can improve outcomes with R-CHOP, and results have been mixed. In a randomized study conducted in France in patients aged 18–59 years with untreated DLBCL and an age-adjusted IPI score (aaIPI) of 1, a dose-intensive regimen of rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (R-ACVBP), with subsequent consolidation using methotrexate, rituximab–ifosfamide–etoposide, and cytarabine, significantly improved survival outcomes compared with those who received R-CHOP. The 3-year OS rate was 92% in the R-ACVBP group versus 84% in the R-CHOP group ($p=0.0071$), but this benefit came at the expense of much greater toxicity [35]. In a phase II study, patients with high-risk large B-cell lymphoma (IPI 3–5, aaIPI 2–3) were treated with dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R), achieving 10-year EFS and OS rates of 47.8% and 63.6%, respectively [36]. However, in the randomized ALLIANCE/CALGB50303 trial that compared R-CHOP with DA-EPOCH-R, the latter was associated with greater toxic effects and no benefit in PFS or OS [37].

Another strategy in first-line treatment of advanced-stage DLBCL is to change the type of monoclonal antibody (mAb) associated with CHOP. The randomized, phase III GOYA study compared R-CHOP with obinutuzumab-CHOP and

detected no differences in PFS [38]. Polatuzumab is an anti-CD79b antibody conjugated to monomethyl auristatin, an anti-tubulin agent. In the randomized, phase III POLARIX clinical trial, 879 treatment-naïve patients with intermediate-risk or high-risk DLBCL were randomized to receive 6 cycles of either R-CHOP or polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) [39]. Two-year PFS was 76.7% in the experimental arm and 70.2% in the control arm (hazard ratio [HR] 0.73; 95% confidence interval [CI] 0.57–0.95; $p=0.02$). OS was similar in both arms, although more patients in the control arm required salvage treatment. Toxicity was similar, and a potential benefit in the activated B-cell-like subtype was suggested in the subgroup analysis (HR 0.4), although these results must be viewed with caution as patients were not stratified by this characteristic.

Various randomized trials have evaluated the addition of new agents to R-CHOP, including bortezomib [40], ibrutinib [41], venetoclax [42], and lenalidomide [43]. However, none demonstrated statistically significant differences. Similarly, several phase III trials have failed to demonstrate a survival benefit of post-R-CHOP maintenance therapy, with agents such as rituximab [44], enzastaurin [45], everolimus [46], or lenalidomide [47].

Treatment of relapsed or refractory DLBCL

Unfortunately, 10–15% of patients do not respond to initial treatment (primary refractory disease) and 20–30% will relapse after achieving a complete response (CR).

Salvage regimens are recommended with rituximab and chemotherapy, to be followed by high-dose chemotherapy (HDC) and autologous hematopoietic cell transplantation (HCT) in patients who respond (Table 2, Fig. 2). The use of rituximab, dexamethasone, cytarabine, and cisplatin (R-DHAP) or rituximab, ifosfamide, carboplatin, and etoposide (R-ICE) combinations as salvage regimens appears to result in similar outcomes [48]. However, in the LY.12 trial, the combination of rituximab, cisplatin, gemcitabine, and dexamethasone (R-GDP) demonstrated similar efficacy, but lower toxicity compared with R-DHAP [49]. For selected cases with documented CNS involvement, high-dose cytarabine-based salvage regimens (rituximab, etoposide, methylprednisolone, cytarabine, cisplatin [R-ESHAP], R-DHAP) can be considered, but no studies have directly compared high-dose cytarabine-based salvage therapy with other intensive regimens for relapsed/refractory DLBCL. Carmustine, etoposide, cytarabine, and melphalan (BEAM) are the most commonly used high-dose regimen, although no randomized studies have demonstrated its superiority over other conditioning regimens. Response should be evaluated by fluoro-deoxyglucose PET (FDG-PET) scan after 3–4 cycles of the

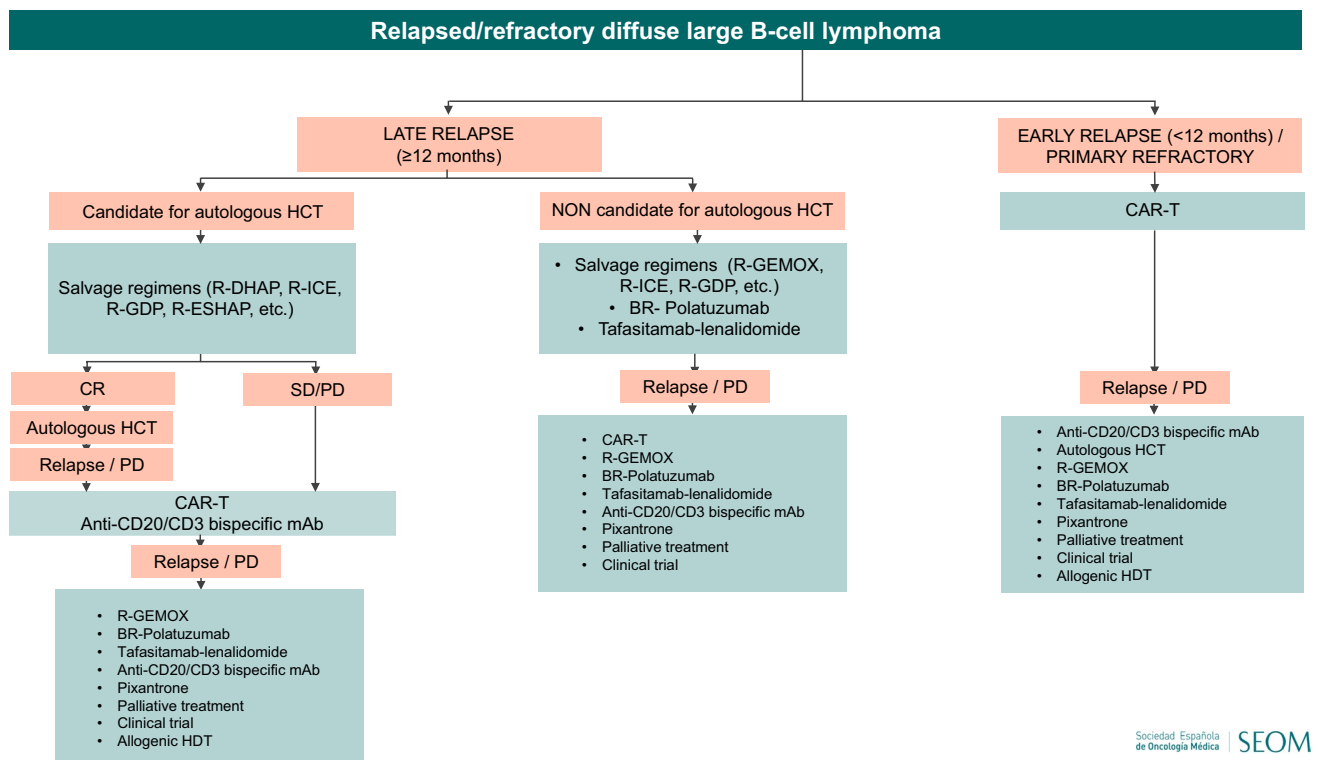


Fig. 2 Treatment algorithm for relapsed or refractory diffuse large B-cell lymphoma. *BR* bendamustine and rituximab, *CAR-T* chimeric antigen receptor T-cell therapy, *CR* complete response; *DLBCL* diffuse large B-cell lymphoma, *HCT* hematopoietic cell transplantation, *HDT* high-dose therapy, *mAb* monoclonal antibody, *PD* progressive

disease, *R-DHAP* rituximab, dexamethasone, cytarabine, and cisplatin, *R-ESHAP* rituximab, etoposide, methylprednisolone, cytarabine, and cisplatin, *R-GDP* rituximab, gemcitabine, dexamethasone, and cisplatin, *R-GEMOX* rituximab, gemcitabine, and oxaliplatin, *R-ICE* rituximab, ifosfamide, carboplatin, and etoposide, *SD* stable disease

salvage regimen (before HDC) and after completion of all therapy.

Results have varied when chimeric antigen receptor T-cell (CAR-T) therapy was used as a second-line treatment in relapsed/refractory DLBCL and compared with standard treatment with salvage chemotherapy followed by HDC. In three published phase III studies conducted in patients with primary refractory DLBCL or DLBCL progressing within 12 months of first-line therapy [50–52], axicabtagene ciloleucel (ZUMA-7 trial) and lisocabtagene maraleucel (TRANSFORM trial) demonstrated superior outcomes compared with HDC, whereas no such benefit was observed with tisagenlecleucel (BELINDA trial). These results may be due to differences in time to CAR-T infusion (29 days with axicabtagene ciloleucel vs. 52 days with tisagenlecleucel). In addition, the fact that bridging therapy was permitted in the trial of tisagenlecleucel may have led to the inclusion of patients with clinically more aggressive disease and worse prognosis.

Long-term follow-up of the ZUMA-7 and TRANSFORM trials has since confirmed the durability of CAR-T responses with axicabtagene ciloleucel and lisocabtagene maraleucel [53, 54]. In addition, real-world studies have validated the

efficacy of CAR-T in early relapse outside of clinical trial settings [55, 56]. In recognition of these findings, both the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) have extended approval of CAR-T therapies to the second-line setting for patients who relapse within 12 months of initial therapy [57, 58]. Accordingly, these updated guidelines recommend CAR-T therapy as a second-line option for eligible patients with early relapsed or refractory DLBCL.

Patients who are not candidates for high-dose therapy and autologous HCT may be treated with the aforementioned salvage regimens or others, such as rituximab, gemcitabine, and oxaliplatin (R-GEMOX). Nevertheless, they should preferably be enrolled in clinical trials. Newer treatment options include combinations of anti-CD20 and anti-CD79b mAbs, such as polatumuzumab vedotin, rituximab, and bendamustine, as well as combinations of anti-CD19 mAbs, such as tafasitamab plus lenalidomide. These therapies have shown promising activity, even in patients whose disease was refractory to previous CD20-targeted immunochemotherapies [59, 60].

Individuals who relapse or do not respond to second-line chemotherapy and autologous HCT are candidates for treatment with CAR-T if they maintain a good performance

status. Third-line CAR-T therapy in relapsed/refractory DLBCL achieves objective response in 50–80% of patients, with long-term survival of around 40%. However, neurological toxicity and cytokine release syndrome are potentially life-threatening adverse effects that must be considered [61–63]. Axicabtagene ciloleucel and tisagenlecleucel are the two anti-CD19 CAR-T products that are commercially available for this indication in Spain.

Unfortunately, at least 50% of patients who relapse or are refractory to ≥ 2 lines of therapy are also refractory or relapse following CAR-T therapy. In these cases, there is no optimal standard of care; therefore, it is advisable that they be enrolled in clinical trials. Preliminary data from ongoing, early-phase clinical trials with bispecific anti-CD20/CD3 mAb (mosunetuzumab, glofitamab, epcoritamab, and odronextamab) have shown promising efficacy and a favorable safety profile in patients with heavily pretreated relapsed/refractory DLBCL, including those who have received prior CAR-T therapy. These findings have since been confirmed in pivotal phase II trials. Epcoritamab has demonstrated durable remissions in a substantial proportion of patients with poor prognostic features, with many responses maintained at 2 years [64]. Mosunetuzumab has shown consistent activity across multiple studies, with durable responses in patients previously treated with CAR-T therapy [65–67]. Odronextamab has also demonstrated sustained clinical benefit and minimal residual disease clearance in a significant subset of patients, with a generally manageable toxicity profile [68]. Glofitamab, evaluated in a fixed-duration regimen following obinutuzumab pre-treatment, has shown high CR rates with durable remissions and an acceptable safety profile, including among patients with prior CAR-T therapy [69]. At present, and in view of the activity of new drugs (e.g., bispecific antibodies, polatuzumab vedotin, tafasitamab), allogeneic transplant is only an experimental alternative for selected cases after multiple relapses. Individuals who are not candidates for combined treatment can be treated with monotherapy agents (pixantrone, rituximab, gemcitabine, oxaliplatin, etc.) with poor response rates ($<20\%$), albeit with some symptomatic benefit, or with palliative radiotherapy.

Follow-up, long-term implications, and survivorship

Patients who achieve CR after first-line treatment should undergo follow-up based primarily on history and clinical examination (Table 2). Periodic blood tests are also recommended and may be helpful when recurrence is suspected and to detect possible late treatment toxicities. In asymptomatic cases, routine imaging techniques, such as CT, have not been shown to be useful in terms of improving survival

[70, 71], although many oncological and hematological teams perform them for the first 2–3 years.

In women who have received mediastinal radiotherapy, especially before the age of 25, a breast magnetic resonance imaging (MRI) scan can be considered from 8 to 10 years after treatment. Modern radiotherapy techniques using small fields (such as ISRT) appear to reduce the risk of radiation-induced breast cancer. Smoking cessation counseling is important for all patients, especially those who have received radiation therapy to the head, neck, and chest.

Conclusions

These updated guidelines provide evidence-based recommendations for the diagnosis, staging, treatment, and follow-up of patients with DLBCL, incorporating the most recent clinical data and expert consensus available as of June 2025. While the standard of care remains largely unchanged in many areas, emerging therapies, including CAR-T treatments, bispecific antibodies, and novel antibody–drug conjugates, are beginning to reshape the therapeutic landscape, particularly in relapsed or refractory settings. Continued integration of new evidence into clinical practice and access to innovative treatments through clinical trials remain critical to improving outcomes for patients with DLBCL.

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Data availability Data sharing is not applicable to this article as no datasets were generated or analyzed.

Declarations

Conflict of interest JG has attended an advisory board for Incyte Biosciences and Kite-Gilead and has received other fees from Roche. ARD has received speaker fees and has attended an advisory board for Roche, BMS, MSD, Takeda, Merck, and Gilead. VC has attended an advisory board for Roche, BMS, AstraZeneca, and Boehringer Ingelheim; has received personal fees from Roche, BMS, MSD, AstraZeneca, Takeda, Lilly, and Boehringer Ingelheim; and has received speaker fees from BMS, MSD, AstraZeneca, Takeda, Pfizer, and Boehringer

Ingelheim. ML has attended an advisory board for Incyte and has received speaker fees from Roche. MP has received speaker fees and has attended an advisory board for Roche and Takeda, and has attended an advisory board for Incyte. NPC, SS, RGA, JGC, and NMB declare that they have no conflicts of interest.

Ethics approval and informed consent Not applicable. The manuscript does not contain clinical studies or patient data.

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