

## REVIEW ARTICLE

# Updated overview of first-line treatment for diffuse large B-cell non-Hodgkin lymphoma

## Resumen actualizado del tratamiento de primera línea para el Linfoma no Hodgkin de células B grandes

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### ABSTRACT

The therapeutic approach to Diffuse Large B-Cell Lymphoma (DLBCL) is based on the curative intent of the treatment regardless of its clinical stage and the presence of poor prognostic factors. Chemoimmunotherapy remains the standard treatment, with or without radiation therapy. Monoclonal antibodies have shown significant improvement in survival and are currently being incorporated into first-line treatment at the onset of the disease. Novel therapies have shown encouraging results for the first line, however data still immature and not yet better than the standard of care. Remarkably, first-line treatment involves certain considerations that we should take into account in clinical situations such as older age, pregnancy, HIV infection, resected and extranodal disease.

#### Keywords

*Lymphoma; Lymphoma, Large B-Cell, Diffuse; Standard of Care; Prognosis (source: MeSH-NLM).*

### RESUMEN

El abordaje terapéutico del linfoma difuso de células B grandes (LDCBG) está basado en su intención curativa independientemente de su estadio clínico y de la presencia de factores de mal pronóstico. La quimioinmunoterapia sigue siendo el tratamiento estándar, con o sin radioterapia. Los anticuerpos monoclonales han mostrado una mejora significativa en la supervivencia y actualmente están incorporados al tratamiento de primera línea al inicio de la enfermedad. Hoy en día, terapias novedosas han mostrado resultados alentadores en primera línea; sin embargo, los datos aún son inmaduros y aún no son mejores que el tratamiento estándar. Cabe destacar que en el tratamiento de primera línea, implica tener consideraciones en situaciones clínicas como; edad avanzada, embarazo, infección por VIH, enfermedad reseca y enfermedad extranglionar.

#### Palabras clave

*Linfoma; Linfoma de Células B Grandes Difuso; Nivel de Atención; Pronóstico (fuente: DeCS-BIREME).*



## INTRODUCTION

Diffuse Large B-Cell Lymphoma (DLBCL) is the most common lymphoid neoplasm in adults. It is the most common histological subtype of non-Hodgkin lymphoma (NHL), accounting for approximately 25-35% of NHL<sup>(1)</sup>. In Peru, it ranks sixth in both incidence and mortality among all cancers<sup>(2)</sup>. The initial treatment of DLBCL is determined by the clinical stage (CS), whether it is limited disease (CS I or II) or advanced disease (CS III or IV). Currently, the standard treatment for DLBCL is chemoimmunotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). The addition of rituximab to CHOP has improved event-free survival (EFS), progression-free survival (PFS), and overall survival (OS)<sup>(3)</sup>. However, despite great efforts to improve results in the first line, 45 to 50% of patients still experience relapse after this treatment, especially if they belong to the high-risk population based on IPI<sup>(4)</sup>. Currently, no new drugs have surpassed rituximab in terms of overall survival. Advances in understanding the genomic and transcriptomic spectrum of DLBCL will enable the identification of subgroups with poor prognoses and reveal new therapeutic targets that may improve outcomes in the future. In this article, we provide an updated short review of different approaches and recommendations to the first-line management of the heterogeneous spectrum of DLBCL, along with updated aspects of special considerations that we should take into account in our daily clinical practice.

### 1. Management of localized disease

DLBCL with localized disease includes stages I and II of Ann Arbor, and its mainstay of treatment is chemoimmunotherapy with R-CHOP, which can be administered alone or with radiotherapy (RT) as combined modality therapy (CMT)<sup>(5,6)</sup>. It is defined based on the presence of adverse prognostic features:

#### 1.1 Without adverse features

For patients with normal serum lactate dehydrogenase (LDH), Eastern Cooperative Oncology Group- Performance Status (ECOG-PS) 0 to 1, and no bulky disease, 4 cycles of R-CHOP are suggested instead of 6 or more cycles, CMT, or RT alone. This recommendation is based on findings from a phase 3 non-inferiority trial (FLYER) and the results of a phase 2/3 trial conducted by the Lymphoma Study Association/French Acute Leukemia and Blood Diseases West-East Group (LYSA/GOELAMS)<sup>(7,8)</sup>.

The FLYER trial randomized 592 patients aged ≤60 years with stage I-II DLBCL and no adverse risk factors. This trial reported that four cycles of R-CHOP (followed by two additional treatments of rituximab alone) were

not inferior to six cycles of R-CHOP and were associated with less toxicity. After a median follow-up of 66 months, 4 cycles of R-CHOP were associated with 96% (95% CI 94-99) 3-year PFS, which was 3% better than six cycles of R-CHOP, and was associated with less hematological and non-hematological toxicity. Estimated 5-year OS, PFS, and EFS did not differ between the trial arms. Although the FLYER trial only included patients under 60 years old, the authors believe that the conclusions can be interpreted as applicable to older patients as well<sup>(7)</sup>.

The LYSA/GOELAMS trial randomized 334 adults to receive either 40 Gy of RT versus no RT for patients with stage I/II DLBCL and low tumor burden (<7cm in diameter) who achieved complete response (CR) by PET after 4 cycles of R-CHOP-14 (14-day treatment cycles). The majority of these patients had non-adverse factors, and 66% were younger than 60 years old. Patients were stratified to receive either 4 or 6 cycles of R-CHOP-14 based on the initial IPI. When comparing R-CHOP alone versus CMT, the 5-year EFS was 92% versus 89%, respectively, and 5-year OS was 96% and 92%, with no significant differences observed. Hematologic and cardiac toxicity of R-CHOP was modest and comparable between the two arms, but two patients treated with RT had grade 3 mucositis and one patient had mandibular osteonecrosis<sup>(8)</sup>.

#### 1.2 With adverse features, no bulky disease

For patients with elevated LDH and/or ECOG PS ≥2, but no bulky disease, two approaches are shown:

##### 1.2.1 Risk-adapted therapy

It is referred to treatment decisions informed by the results of an interval PET performed between days 18 and 20 after the start of the third cycle of R-CHOP ("PET3") as follows:

*Negative PET3* (Deauville 1 to 3): treatment with an additional cycle of R-CHOP is suggested (i.e., a total of 4 cycles of R-CHOP), instead of more than four cycles of R-CHOP or the addition of RT, based on the excellent long-term results and the desire to avoid additional toxicity from RT or additional chemotherapy, according to the results of the FLYER trial<sup>(7)</sup>.

*Positive PET3* is distinguished as follows<sup>(9)</sup>:

- Partial response: for patients with limited residual fluorodeoxyglucose (FDG) avidity (e.g., a small focus of activity Deauville 4 to 5 and at least ≥1.5 cm of diameter), consideration of 3 additional cycles of R-CHOP (i.e., 6 total cycles of R-CHOP) versus treatment with Involved-site radiation therapy (ISRT) of 30 Gy with an additional boost of 6 to 10 Gy in the FDG-avid area (without further

chemoimmunotherapy; i.e., a total of 3 cycles of R-CHOP) as equally acceptable approaches.

- Refractory disease: for patients with more extensive Deauville 4 to 5 disease, a biopsy of the FDG-avid tissue is suggested.

### 1.2.2 Conventional management

Patients who did not undergo an interim PET evaluation, treatment with 6 cycles of R-CHOP alone or CMT with 3 cycles of R-CHOP plus 30 Gy ISRT is considered equally acceptable <sup>(10)</sup>. The choice of chemoimmunotherapy alone versus CMT is influenced by adverse effects, comorbid conditions, and personal preferences. For example, in patients for whom RT may cause substantial early morbidity (e.g., involvement of the oronasopharynx or pelvis) or late toxicity (young women whose breasts would be in the RT field), we strongly favor treatment with chemoimmunotherapy alone. Conversely, the lower total dose of doxorubicin in a shortened course of chemotherapy associated with CMT may be preferable for a patient with marginal cardiac function <sup>(11)</sup>. The suggested regimens of R-CHOP alone versus CMT described above achieve similar results in this setting. For either approach, 5 and 10-year OS rates are approximately 55% and 55% for chemotherapy alone, and 82% and 64% for CMT ( $p < 0.001$ ) respectively, but outcomes may vary by the International Prognostic Index (IPI) <sup>(12)</sup>.

The number of cycles of R-CHOP varies based on the presentation (e.g., elevated LDH, poor ECOG PS, bulky disease). In SWOG 0014, patients with limited-stage DLBCL and at least one adverse risk factor were treated with 3 cycles of R-CHOP plus RT of the affected field (IFRT) at 40-46 Gy ( $n=60$ ). The 2 and 4-year PFS rates were 93% and 88%, respectively; while the corresponding 4-year OS rate was 92% <sup>(13)</sup>.

### 1.3 Bulky disease

Bulky disease has been defined as a tumor mass  $\geq 10$  cm in diameter <sup>(13)</sup>, but more recent studies defined as  $\geq 7.5$  cm in diameter <sup>(7)</sup>.

#### 1.3.1 Risk-adapted therapy

After the 6 cycles of R-CHOP, the management is decided according to the PET results, if:

*Negative PET* (Deauville 1 to 3): according to Tokola et al., RT is not needed after achieving a complete metabolic response. However, this has to be approached with caution as it is based on a retrospective study <sup>(14)</sup>.

*Positive PET* is distinguished as follows <sup>(14)</sup>:

- Partial response: for patients with limited residual disease (a small focus of at least  $\geq 1.5$  cm of diameter,

not progressive disease and activity Deauville 4 to 5), it is an option to treat with ISRT of 30 Gy followed by an additional boost of 6 to 10 Gy in the area with fluorodeoxyglucose (FDG).

- Refractory disease: for patients with more extensive Deauville 4 to 5 disease, a biopsy of the FDG tissue is suggested. In those with persistent disease, second-line or salvage treatment is recommended.

### 1.3.2 Conventional approach

Overall, treatment with 6 cycles of R-CHOP followed by 30 to 40 Gy ISRT is recommended. The prospective study (RICOVER-noRTh) treated patients  $\geq 60$  years old with bulky disease with 6 cycles of R-CHOP-14 (bi-weekly cycles), but without RT <sup>(15)</sup>. The results of RICOVER-noRTh were compared with the same chemoimmunotherapy plus RT from the prospective RICOVER-60 trial <sup>(16)</sup>. Multivariate analysis reported that the elimination of RT was associated with inferior EFS, PFS, and OS, but the interpretation of these findings is limited by the small number of patients and substantial crossover to unplanned RT in the RICOVER-noRTh study <sup>(15)</sup>.

*Conclusion:* The choice of chemoimmunotherapy alone or CMT in DLBCL limited stage depends on the presence of adverse features and/or bulky tumor of the disease, as well as patients' features (poor performance status and comorbidities).

## 2. Management of advanced disease

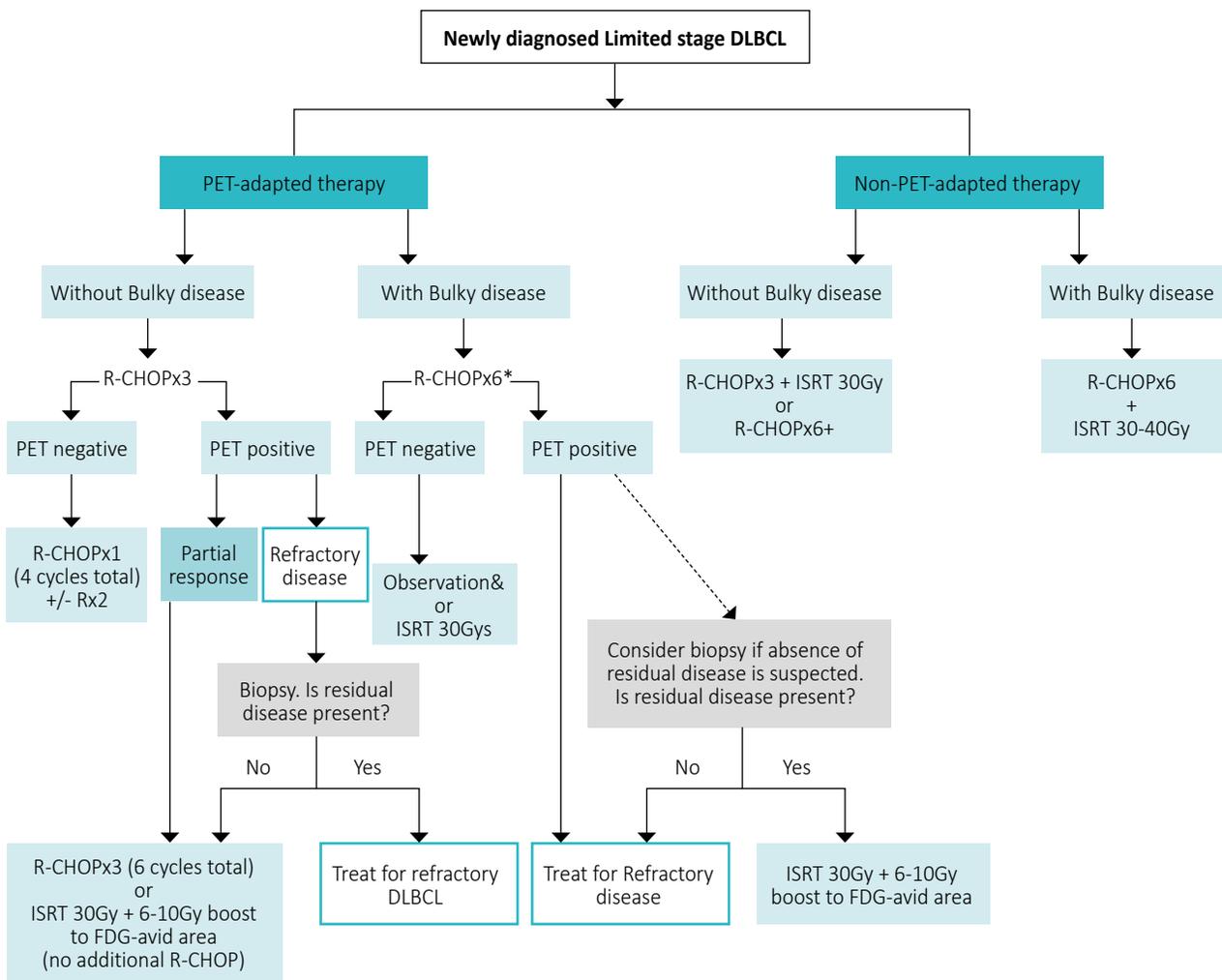
This corresponds to disease in stage III or IV and accounts for approximately two-thirds of patients with DLBCL.

### 2.1 The rituximab era

Nowadays, R-CHOP every 21 days is considered the standard first-line treatment in patients with advanced-stage DLBCL. This is based on the results of the phase III study by the GELA group in 2002, which evaluated 8 cycles of R-CHOP versus CHOP in older patients (age 60 to 80 years,  $n = 399$ ). The 2 year EFS was 57% vs. 37% for R-CHOP and CHOP alone, respectively; the 2 year OS was 70 % vs. 57%, for R-CHOP and CHOP alone, respectively. At a median follow-up of 10 years, the 10-year PFS (37% vs. 20%), EFS (64% vs. 43%), and OS rates (44% vs. 28%) were significantly higher for R-CHOP <sup>(17)</sup>. The MInT study (6 cycles of R-CHOP vs. CHOP) extended these findings to younger patients with 0 or 1 risk factors according to the IPI <sup>(18)</sup>.

### 2.2 Regimen choice

It is recommended for first line of treatment 6 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) or 6 cycles of R-pola-CHP



\*If partial response or complete response was obtained in interim evaluation.  
 & This recommendation is based on a retrospective study.  
 +According to interim evaluation.

**Figure 1.** Shows the proposed treatment algorithm for limited stage (Stage I-II) DLBCL.

(rituximab, polatuzumab vedotin, cyclophosphamide, doxorubicin, prednisone) in patients with unfavorable risk factors: >60 years-old, activated B-cell-like (ABC) subtype or high risk IPI score (3-5). R-CHOP cures approximately 60% of patients with DLBCL, is associated with acceptable AEs, and has long been the standard initial treatment for DLBCL (19). R-pola-CHP compared with R-CHOP, achieved better PFS, but no OS with similar toxicity in a phase 3 trial POLARIX (20).

The evidence supporting the treatment suggestions includes:

- *R-pola-CHP vs. R-CHOP*: an international phase 3, double-blind, placebo-controlled trial (POLARIX)

reported that R-pola-CHP achieved superior outcomes compared to R-CHOP for newly diagnosed intermediate- or high-risk DLBCL adults; one-third of the 879 patients had ABC DLBCL and nearly two-thirds had an initial International Prognostic Index (IPI) score of 3-5. OS was 89% for both groups, but compared to R-CHOP, R-pola-CHP achieved superior PFS and EFS. R-pola-CHP was associated with a 77% PFS at 2 years, compared to 70% with R-CHOP (HR 0.73 [95% CI: 0.57-0.95]); the HR for EFS was 0.75 (95% CI: 0.58-0.96); however, this benefit did not translate to OS. Severe AEs were reported in 30 to 34% of patients (mainly neutropenia and anemia), and peripheral neuropathy of grade ≥2 occurred in 14 to 17%. On the other hand, subgroups that did

not benefit from R-pola-CHP were young patients, germinal-center B-cell–like subtype, low IPI (IPI 2), and bulky disease <sup>(20)</sup>.

- *Full-dose vs. reduced-dose*: full-dose planned therapy is associated with better clinical outcomes in patients, while reduced-dose R-CHOP in those patients was associated with lower survival outcomes. This is supported by a systematic review that found that patients aged 70-79, who received a dose  $\geq$  80%, had significantly higher PFS and OS ( $p < 0.001$ ), whereas in patients aged  $\geq$  80 years there was no significant difference in either PFS ( $p = 0.88$ ) or OS ( $p = 0.75$ ). This data support full-dose in patients with DLBCL aged  $<$  80 years-old, but not in patients  $\geq$  80 years old where dose-reduced R-CHOP does not appear to compromise survival <sup>(21)</sup>.
- *Number of cycles*: We suggest 6 cycles of initial therapy, instead of eight cycles, based on comparable results with less toxicity. The preference for 6 cycles is based on the desire to avoid unnecessary toxicity and favorable results with 6 cycles of R-CHOP in the MInT trial <sup>(22)</sup>. No randomized trial has directly addressed the optimal number of cycles of R-CHOP-21 (21-day treatment cycles) or R-pola-CHP. However, the RICOVER-60 trial did not report differences in OS at three years for patients treated with 6 versus 8 cycles of R-CHOP-14 (14-day cycles; 78% and 73%, respectively) in 1222 patients (61-80 years) with aggressive non-Hodgkin lymphoma (80% DLBCL). In this trial, older patients (aged 61-80) were randomized to receive CHOP-14 (6 or 8 cycles) with or without 8 cycles of rituximab <sup>(23)</sup>. With a median follow-up of 82 months, R-CHOP-14 was associated with significantly improved EFS and OS compared to CHOP-14 ( $p < 0.001$ ). While there was no difference in clinical benefit, increased toxicity was observed with 8 cycles compared to 6 cycles of therapy.
- *Bulky disease in advanced stage*: according to a recent study, for patients with an advanced stage and a bulky tumor at the onset of the disease, if they test PET negative at the end of treatment, consolidative radiotherapy may be omitted and still result in excellent outcomes. Key indicators, such as time to progression (TTP) and a 3-year overall survival (OS) rate, are 83% and 87%, respectively <sup>(24)</sup>.

### 2.3 Alternative regimens

In comparison to R-pola-CHP and R-CHOP, no alternative regimen or variation in the administration of R-CHOP has achieved superior outcomes, but some alternative regimens were more toxic. Informative studies include:

- *Standard dose vs. intensification dose*: R-CHOP-14 is not superior to R-CHOP-21 chemotherapy for first

line in DLBCL. Two randomized trials reported that R-CHOP-21 and R-CHOP-14 achieved similar results, but R-CHOP-14 was associated with more toxicity. One trial compared 8 cycles of R-CHOP-21 vs. 6 cycles of R-CHOP-14 plus 2 additional doses of rituximab in patients with DLBCL. With a median follow-up of 46 months, there were no significant differences in OS or PFS between the two treatment groups <sup>(25)</sup>. Another trial found that eight cycles of R-CHOP-14 vs. eight cycles of R-CHOP-21 reported similar rates of OS and ORR for the two treatment regimens. CHOP-14 has been associated with increased toxicity, including an increased risk of *Pneumocystis jirovecii* pneumonia <sup>(26)</sup>. A recent phase 3 trial showed that 2-year OS was 82.7% versus 80.8% in the R-CHOP14 and R-CHOP 21, respectively (HR 0.90, 95% CI 0.70-1.15;  $p = 0.37$ ). No significant improvement was noted in 2-year PFS with 75.4% versus 74.8% in the R-CHOP14 and R-CHOP 21, respectively (HR: 0.94, 0.76-1.17;  $p = 0.59$ ) <sup>(27)</sup>.

- *Adjusted dose (da)-R-EPOCH vs. R-CHOP*: A multicenter trial reported no differences in 2-year OS, 2-year PFS, or ORR among 491 patients who were randomly assigned to (da)-R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) vs. R-CHOP <sup>(28)</sup>. Grade  $\geq$  3 AEs were more frequent with (da)-R-EPOCH, including infections (17 vs. 11%), febrile neutropenia (35 vs. 18%), mucositis (8 vs. 2%), and neuropathy (19 vs. 3%). A phase 3 trial (CALGB 50303), presented in abstract form, comparing (da)-R-EPOCH vs. R-CHOP, reported no significant differences in OS (76 vs. 80 percent, respectively), EFS (66 vs. 69 percent), or ORR (89 percent for both arms); however, (da)-R-EPOCH was associated with more cytopenias and neuropathy <sup>(28)</sup>. Other regimens that have been examined for DLBCL include R-CHOP plus lenalidomide <sup>(29)</sup>, R-CHOP plus ibritinib <sup>(30)</sup>, and R-CHOP plus bortezomib <sup>(31)</sup>, but none have been associated with a more favorable balance of outcomes and toxicity.

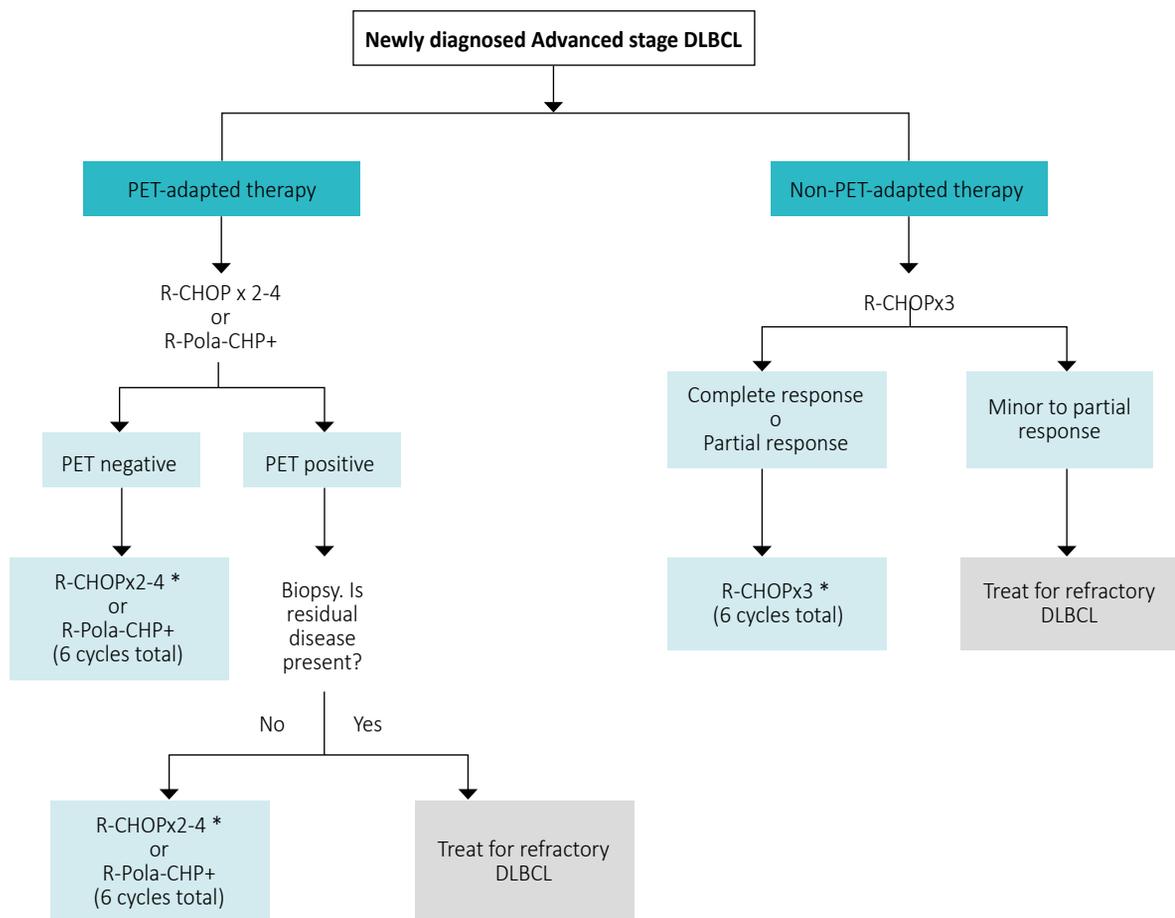
*Conclusion*: The first line in advanced DLBCL remains the backbone R-CHOP for six cycles; however, Polatuzumab can be added in the presence of certain adverse patients features such ABC phenotype and as high IPI score and.

### 3. Treatment considerations before starting treatment

#### 3.1 Prophylaxis of tumor lysis syndrome (TLS)

Prophylaxis for TLS should be considered for patients with a high tumor burden (e.g., large tumor masses or markedly elevated LDH). It most often occurs within the first 12 to 72 hours of treatment <sup>(32)</sup>.





\* There is insufficient evidence to recommend consolidative radiotherapy in advanced bulky disease.  
 + ABC subtype, IPI 3-5 and without voluminose disease (if it is available) and treat according to study protocol.

**Figure 2.** Proposed algorithm for the treatment of Advanced Disease.

### 3.2 Prophylaxis of hepatitis B virus (HBV) reactivation

Treatment with rituximab can increase the risk of hepatitis B reactivation<sup>(33)</sup>. The *Chronic Hepatitis B Guidelines* define reactivation of hepatitis B as the reappearance of active necroinflammatory disease of the liver in a person known to have an inactive hepatitis B surface antigen (HBsAg) carrier state or resolved hepatitis B<sup>(34)</sup>. It is recommended to start with a daily dose of entecavir beginning one week before initiation of chemoimmunotherapy to 6 months after completion of chemotherapy. This suggestion is supported by a RCT phase 3 that showed that the addition of entecavir compared with lamivudine resulted in a lower incidence of HBV-related hepatitis and HBV reactivation<sup>(35)</sup>.

### 3.3 Prophylaxis of central nervous system (CNS)

While CNS involvement is uncommon at the debut of DLBCL, occurring in approximately 5% of patients, it is

crucial to assess all patients at the time of diagnosis due to its association with poor prognosis.

CNS prophylaxis is generally recommended for patients with renal/adrenal, primary testicular lymphoma (PTL), or breast involvement; ≥2 extranodal sites; or high-risk CNS-IPI score (4- 6 points). The optimal approach to CNS prophylaxis for patients at high risk of CNS involvement is controversial and varies between institutions<sup>(36)</sup>.

We favor and recommend high-dose systemic methotrexate (HD-MTX) but consider intrathecal (IT) MTX an acceptable option. Some experts favor treatment with both IT and systemic MTX, especially in PTL. Either approach should be integrated with chemoimmunotherapy, as follows:

- *High-dose intravenous MTX* (3 to 3.5 g/m<sup>2</sup>) is administered with leucovorin rescue. The optimal

number of high-dose MTX treatments is uncertain, but it is typically administered for two or three cycles following the completion of the initial six cycles of R-CHOP. It is not recommended to administer high-dose MTX in between cycles due to its associated toxicity and to prevent delays in the backbone treatment, R-CHOP<sup>(37,38)</sup>.

- *IT MTX*, 4-8 doses, at least once per chemoimmunotherapy cycle<sup>(39)</sup>.

*Primary testicular DLBCL (PTL)*: This presentation has higher risk of CNS and contralateral scrotal recurrence, even when presenting with stage I disease. Therefore, the inclusion of methotrexate for CNS prophylaxis (HD-MTX and IT) is recommended, as well as scrotal radiotherapy (25-30 Gy) after completing chemoimmunotherapy<sup>(38)</sup>.

## 4. Special considerations

### 4.1 Elderly patients

Elderly patients ( $\geq 65$  years old) tend to have poorer outcomes, and many may not be fit to receive the full doses of R-CHOP. Managing these patients should involve collaboration between geriatrics and cardio-oncology<sup>(40)</sup>.

#### *Evaluation of patient fitness*

Several geriatric assessment tools are available to assess fitness of patients; however, most of them are time consuming. A simplified comprehensive geriatric assessment (sCGA) is the simplest and widely used tool, and stratifies patients as follows: fit, unfit and frail patients<sup>(41)</sup>.

#### *Pretreatment considerations*

- Five days of prephase steroids (prednisone 100mg per day) along with allopurinol and sufficient fluid intake before starting first line with R-CHOP is suggested. After the prephase, it is encouraged to assess performance status (PS) to see if there has been an improvement in the general condition of the patient. If the patient has a good PS and non-bulky disease at the onset, it may not be necessary to start with this consideration.

#### *Management according to geriatric assessment, age and cardiotoxicity risk*

- Fit patients, < 80 years-old and non-contraindication to anthracyclines: Full dose of R-CHOP is safely recommended for these patients.
- Unfit patients, < 80 years-old and non-contraindication to anthracyclines: Dose reduction of 25-50% to R-CHOP is suggested. It is encouraged

to escalate to at least 70% of the treatment if the GA is improved and PS is 0-1.

- Fit, unfit with  $\geq 80$  years-old or frail patients and non-contraindication to anthracyclines: R-mini CHOP is recommended.
- Contraindication to anthracyclines irrespective of GA and age: R-CEOP or R-GCVP is recommended.

Real-world data demonstrated that patients aged 80 years or older had comparable outcomes whether they received R-mini CHOP or R-CHOP, with a 3-year OS rate of 54% for both regimens in this age group<sup>(42)</sup>. In a more recent Latin American study involving patients aged 80 years and above, the 5-year OS was 49% regardless of the chemotherapy regimens containing rituximab. However, the outcomes differed significantly based on treatment completion, with a median OS of 80 months for completed therapy compared to 5 months for incomplete therapy<sup>(43)</sup>.

### 4.2 HIV-associated DLBCL

Nowadays, life expectancy has improved after the introduction of highly active antiretroviral therapy (HAART)<sup>(44,45)</sup>. A recent European trial indicated that DLBCL patients under 65 years old, treated with RCHOP/RCHOP-like regimens, have similar long-term survival independent of HIV status<sup>(46)</sup>. Hence, HIV-associated DLBCL has seen an improvement in its survival rates from 40% to 70-80% following the introduction of HAART<sup>(44)</sup>. Clinically, HIV-associated DLBCL can manifest as nodal or extranodal compromise, with the gastrointestinal tract being the most common site<sup>(45)</sup>.

It is recommended before the start of first-line treatment to continue with HAART while undergoing chemotherapy and closely monitor any important interactions with other drugs<sup>(45)</sup>. In patients with a low cluster of differentiation (CD4) <50/ml, the use of rituximab should be individualized balancing the infection risks and survival outcomes. Patients with CD4>50/ml, standard regimens such as R-EPOCH or R-CHOP-like should be initiated, being R-EPOCH the preferred since showed higher complete responses, however, studies have not showed clear benefits in survival<sup>(45,47)</sup>. As in the general population, the introduction of the novel monoclonal antibody CD79b, polatuzumab vedotin may be considered in special situations, as mentioned before<sup>(48,49)</sup>.

The prophylaxis for opportunistic infections is less clear, but during immunochemotherapy treatment, cotrimoxazole prophylaxis against *Pneumocystis jirovecii* pneumonia and toxoplasmosis should be given regardless of CD4 cell count. In certain situations, such as a low CD4 count, prolonged and profound neutropenia, or prolonged use of steroids, prophylaxis against other infections is generally recommended<sup>(45)</sup>.

### 4.3 Pregnancy

Lymphoma during pregnancy represents a complex diagnostic and therapeutic challenge, since the standard of care in staging and treatment in the non-pregnant patient such as PET-CT scan and chemotherapeutic regimens might interfere with normal fetal development and survival. Updated guidelines recommend to perform as follows<sup>(50)</sup>:

- First trimester: If urgent treatment is not required (asymptomatic), therapy should be deferred to the second trimester or after week 13. If an aggressive disease is presented and requires intensified therapy during the first trimester (weeks 2-12), or when a highly aggressive lymphoma—requiring intensified therapeutic regimens, termination of pregnancy is indicated.
- Later first trimester and symptomatic disease: a short course of steroids, with or without cyclophosphamide, could be given as a bridge to a full anthracycline regimen on week 12. Cyclophosphamide was studied in the context of autoimmunity and was found to be safe after the completion of organogenesis.
- Second to third trimester: R-CHOP can be safely administered beyond the first trimester; however, with increased risk of preterm birth and low birthweight. CNS prophylaxis with high-dose methotrexate is contraindicated until week 20 and its use is not recommended during pregnancy.

Also, metoclopramide can be safely used to address emesis. G-CSF can be administered without fetotoxicity.

### 4.4 Resected lymphoma

Occasionally, diagnostic excisional biopsy can remove all locally visible disease, or in some exceptional cases of obstruction, in patients with extranodal intestinal lymphoma (e.g small bowel obstruction caused by lymphoma that was resected in a laparotomy). Although patients with resected disease have been included in some studies, the results have not been well described. Historical data suggest that localized treatments such as surgery or radiation therapy cannot prevent systemic recurrence.

There is not standard of treatment for completely resected DLBCL patients. A recent phase II trial evaluated the safety and efficacy of three cycles of R-CHOP in patients with completely resected limited-stage DLBCL and reported favorable survival outcomes, and a long-term follow-up showed 5-year OS and DFS rates were both 95%, suggesting that it is enough to administrate an abbreviated treatment<sup>(51)</sup>.

### 4.5 Extranodal stage I diffuse large B-cell lymphoma

The patients with extranodal involvement have an inferior OS and PFS than nodal patients<sup>(52)</sup>. Notably, patients with extranodal stage I DLBCL may benefit from consolidation RT, particularly those who did not achieve a complete response by PET after immunochemotherapy. The UNFOLDER randomized trial by the *German High-Grade Non-Hodgkin Lymphoma Study Group/German Lymphoma Alliance* reported a longer EFS in extranodal patients who received 6 cycles of R-CHOP-14 or -21 plus RT compared with those who did not receive RT (3-year 84% vs 68%, p=0.001). Conversely, in extranodal patients achieving a PET-negative after immunochemotherapy, RT could potentially be spared<sup>(53)</sup>.

*Conclusions:* DLBCL is the most frequent aggressive lymphoma in adult population. The first-line treatment is primarily based on the extent and tumor burden, and R-CHOP remains the standard treatment. However, we must consider molecular studies to decide on variations from the standard treatment, such as R-pola-CHP in the ABC phenotype. Currently, the assessment of the disease with PET/CT is crucial for management, as it can help avoid both undertreatment and overtreatment, thereby reducing refractoriness and long-term treatment toxicity. Finally, special situations in DLBCL management should be considered, and a multidisciplinary approach becomes necessary.

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