BHS guidelines for the treatment of newly diagnosed diffuse large B-cell lymphoma (DLBCL) anno 2020

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SUMMARY

Diffuse large B-cell lymphoma is the most common subtype of non-Hodgkin lymphoma. Prognosis of diffuse large B-cell lymphoma has improved dramatically since the introduction of rituximab and about two thirds of patients can be cured with immunochemotherapy. In the last twenty years, it became clear that diffuse large B-cell lymphoma is a very heterogeneous disease and based on the genetic mutation landscapes numerous efforts have been made to develop novel treatment strategies to improve the prognosis of diffuse large B-cell lymphoma further. This article provides an update of diagnosis, current treatment guidelines and novel treatment strategies for newly diagnosed patients with diffuse large B-cell lymphoma in Belgium. It will also focus on treatment of elderly patients and high-grade B-cell lymphoma.

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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL) accounting for approximately 30% of all NHL cases worldwide.[1] The incidence is three to five cases per 100.000 inhabitants and increases with age, with a median age of 60-65 years.[2] Chemoimmunotherapy (CIT) with rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) is the standard front-line treatment in DLBCL and can cure approximately 60% of patients. However, 10-15% of the patients have primary refractory disease and 20-30% of the patients will eventually relapse and have a poor prognosis.[3] Advances in molecular-genetic studies have shown that DLBCL is a biologically very heterogeneous disease and comprises at least two distinct molecular subtypes (the activated B-cell-like (ABC) and the germinal center B-cell-like (GCB) subtype) with varied natural history and response to therapy. These findings have led to improved insights in molecular and genetic pathogenesis of these subtypes and to the development of targeted therapies.[4]

DIAGNOSIS

DLBCL can develop de novo or as a transformation of a less aggressive lymphoma such as chronic lymphocytic leukaemia (CLL), follicular lymphoma (FL), marginal zone lymphoma or nodular lymphocyte predominant Hodgkin lymphoma with the latter one being a rare phenomenon only mentioned in case reports. Underlying immunodeficiency is a known risk factor.[5] Diagnosis is made on a surgical excision biopsy providing sufficient material for assessment of the nodal architecture and material for phenotypic and molecular studies. Core needle biopsy should be discouraged and is reserved for patients for whom a surgical approach is impossible or carries a high-risk. The diagnosis is based on morphology and immunophenotypic investigations (immunohistochemistry (IHC) or flow cytometry).[6] The pathological report should report the diagnosis according to the WHO 2016 classification, subdividing DLBCL according to morphological variants, molecular subtypes and distinct disease entities.[1] Most cases however do not belong to a specific diagnostic category, and will be classified as DLBCL, not

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TABLE 1. Lugano classification.

Stage	Involvement	Extranodal (E) status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesion without nodal involvement
II	Two or more nodal groups on either side of the diaphragm	Stage I or II with limited contiguous extranodal involvement
II bulky	II as above with bulky disease	
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional non-contiguous extralymphatic involvement	Not applicable

otherwise specified (NOS). In contrast to the WHO 2008 classification, the WHO 2016 classification defines two principal DLBCL, NOS molecular subtypes according to the "cell of origin" (COO) principle, the GCB and the ABC subtype, both defined by a different genetic landscape, and with the first one having a better prognosis when treated with standard CIT.[1,7] In 2000, gene expression profiling (GEP) was used to define these two subtypes.[8] GEP is considered the gold standard but it is not routinely available and difficult to use in clinical practice because this method relies on fresh frozen tissue (FFT) and microarray technology. Several studies have attempted to recapitulate the COO by using IHC algorithms. The most widely used is the Hans algorithm which uses CD10, BCL6, and MUM1 to distinguish GCB and non-GCB DLBCL.[9] This algorithm correlates with prognosis in DLBCL but it is not as accurate as GEP and cannot be used to make clinical decisions. Over the last decade, several new technologies have been developed to determine COO using formalin-fixed paraffin-embedded tissue. One of the most promising methods currently being investigated is the Nanostring platform, which uses a 20-gene panel.[10]

STAGING AND RISK ASSESSMENT

Patient history including B-symptoms and a complete clinical examination with assessment of the performance status (PS) should be obtained. A complete blood count, lactate dehydrogenase (LDH), liver and kidney function, uric acid, as well as screening tests for HIV, hepatitis B virus and hepatitis C virus are required. Although not incorporated in

TABLE 2. International prognostic index (IPI): 5-year overall survival (OS) before and 3-year OS after the introduction of rituximab (R).

IPI: Risk factors: elevated LDH, age >60 years, ECOG PS ≥ 2, >1 extranodal site, Ann Arbor stage III/IV			
Score	Risk group	5-year OS without R (%)[20]	3-year OS with R (%)[21]
0-1	Low	73	91
2	Low-intermediate	51	81
3	High-intermediate	43	65
4-5	High	26	59

TABLE 3. Age-adjusted international prognostic index (aa-IPI): 5-year overall survival (OS) in patients ≤60 years old vs >60 years old before the introduction of rituximab.

aa-IPI: Risk factors: elevated LDH, ECOG PS ≥ 2, Ann Arbor stage III/IV			
Score	Risk group	5-year OS age ≤ 60 (%)[20]	5-year OS age > 60 (%)[20]
0	Low	86	56
1	Low-intermediate	66	44
2	High-intermediate	53	37
3	High	58	21

the prognostic scoring systems, beta-2-microglobulin testing can be valuable, since elevated levels are associated with unfavourable prognosis.[11] Left ventricular function needs to be assessed before anthracycline treatment. Fertility preservation should be considered in eligible patients.

Evaluation of the PS is of great importance and not at least in the elderly. There is no clear definition to identify 'frail' elderly patients. The Comprehensive Geriatric Assessment (CGA) can detect functional, psychological, social and environmental problems not otherwise identified but is time-consuming. Alternative screening tools have been developed to separate fit from frail patients for example the Flemish version of the Triage Risk Screening Tool (fTRST) or the G8 questionnaire. These easy-to-use geriatric screening tools appear to have a strong prognostic value for overall survival (OS) in older patients with DLBCL.[12]

The optimal imaging method for staging DLBCL is fluorodeoxyglucose (FDG) positron emission tomography (PET)-computed tomography (CT).[13] PET-CT with Contrast-enhanced CT (ceCT) is more accurate in the detection of abdominal and pelvic disease than low-dose CT (without contrast). Baseline findings can determine whether cePET-CT or low dose PET/CT are sufficient for further imaging examinations.[14]

Since 2014, the Lugano modification of the Ann Arbor staging system is recommended for staging DLBCL at diagnosis (*Table 1*). It defines limited disease (stage I, II and non-bulky) and extensive disease (stage III, IV). Stage II bulky disease is defined as limited or extensive disease depending on histology and a number of prognostic factors. Cut-off ranges from five to ten cm in literature. The addition of "E" defines extranodal disease and is only relevant for stage I disease in the absence of nodal involvement (IE) and stage II disease (IIE). Systemic "B" symptoms are no longer incorporated into the staging system for DLBCL because they are not integrated in the prognostic scoring systems.[15]

Bone marrow involvement in DLBCL is seen in up to one third of the cases. Bone marrow biopsy has long been considered the gold standard to confirm bone marrow involvement but several studies show that PET-CT has a better sensitivity and specificity to detect bone marrow involvement than bone marrow biopsy. However, involvement of the bone marrow by indolent NHL may be missed by only using PET-CT. Thus, bone marrow biopsy can be omitted when bone marrow involvement is detected on staging PET-CT. When there is no bone marrow involvement on PET-CT, a bone marrow biopsy is still advised.[16,17] Magnetic resonance imaging (MRI) of the brain, conventional cytology and flow cytometry on cerebrospinal fluid (CSF) should be incorporated in the initial work-up of patients with neurological symptoms.[18,19] Central nervous system (CNS) prophylaxis is recommended in high risk groups as defined later in this section.

The International Prognostic Index (IPI) was developed before the introduction of R but still remains the most widely used prognostic tool for DLBCL. The five factors of the IPI are elevated LDH, age >60 years, Eastern Cooperative Oncology Group (ECOG) PS ≥2, involvement of more than one extranodal site and stage III/IV disease (*Table 2*). The age-adjusted IPI (aa-IPI) is a simplified index that includes only three of the IPI risk factors (stage, LDH and PS) and can be used when comparing patients within an age group (≤ 60 years old versus >60 years old) (*Table 3*).[20]

Although the IPI remains predictive it distinguishes only two risk groups in the R era (the two lower risk groups and the two higher risk groups have overlapping outcomes) rather than the four groups originally described (*Table 2*).[20,21] Redistribution of the IPI risk factors into the revised IPI (r-IPI) provides a more clinically relevant prediction of outcome with three prognostic subgroups with significantly

TABLE 4. Revised international prognostic index (r-IPI): 4-year overall survival (OS) in the rituximab era.

r-IPI: Risk factors: elevated LDH, age > 60 years, ECOG PS ≥ 2, > 1 extranodal site, Ann Arbor stage III/IV		
Score	Risk group	4-year OS (%)[22]
0	Very good	94
1, 2	Good	79
3, 4, 5	Poor	55

different outcome: very good risk, good risk and poor risk (*Table 4*).[22]

Another prognostic scoring system is the enhanced National Comprehensive Cancer Network IPI (NCCN-IPI) which appears better to discriminate low and high risk groups. It uses the same risk factors of the IPI but assigns varying weights to the different categories (*Table 5*).[23]

These four prognostic tools predict clinical outcome with high accuracy.[24] Tumour bulk is not integrated in these scoring systems but several studies have demonstrated a worse clinical outcome in patients with high tumour mass. An analysis of the phase III GOYA trial showed that PET derived total metabolic tumour volume (TMTV) is an independent prognostic factor for primary refractoriness in previously untreated patients with DLBCL.[25]

The incidence of CNS relapse in DLBCL is low in unselected cohorts (±5%) but there are certain high-risk groups. Most studies have found a slight decrease in the incidence of CNS relapse since the introduction of R but the impact is not significant.[26] The CNS-IPI is a prognostic model based on data from 2.164 patients in the German High-Grade NHL Study Group (DSHNHL) and estimates the risk of CNS relapse. It is composed of the IPI risk factors in addition to involvement of the kidneys and/or adrenal glands. Patients are divided in three risk groups: low-risk, intermediate-risk and high-risk (*Table 6*).[27] Certain extranodal sites are also associated with an increased risk of CNS relapse of which testicular involvement is the most well-established, even in stage I disease. Other sites include the bone marrow, paranasal sinus, orbit, pericardium, ovary, uterus, and breast but data are not consistent. Kidney and adrenal involvement are well-known high-risk locations and they are now included in the CNS-IPI. Adverse biological risk factors for CNS relapse include translocations of MYC proto-oncogene (*MYC*), B-cell lymphoma 2 (*BCL2*) and/or B-cell lymphoma 6 (*BCL6*) and detectable co-expression of MYC and BCL2 in the absence of translocations, particularly in the ABC subtypes of DLBCL.[28]

Based on the available data the role, method and timing of CNS prophylaxis remains highly controversial. It should be considered for patients with *MYC* and *BCL2* and/or *BCL6* translocation, patients with a high-risk CNS-IPI score (4-6) and intermediate risk patients who are ABC subtype with dual expression of *MYC* and *BCL2*. It is also recommended

TABLE 5. Enhanced national comprehensive cancer network international prognostic index (NCCN-IPI): 5-year overall survival (OS) in the rituximab era.

NCCN-IPI: Risk factors: age (>40 to ≤60, 1 point; >60 to ≤75, 2 points; >75, 3 points), LDH > upper limit of normal (>1-3, 1 points; ≥3, 2 points), extranodal disease in major organs (bone marrow, CNS, liver/GI tract, or lung), Ann Arbor stage III-IV, and ECOG PS (≥2)		
Score	Risk group	5-year OS (%)[23]
0-1	Low	96
2-3	Low-intermediate	82
4-5	High-intermediate	64
≥6	High	33

TABLE 6. Central nervous system international prognostic index (CNS-IPI) as developed by the German High Grade NHL Study Group (DSHNHL).

CNS-IPI: Risk factors: elevated LDH, age > 60 years, ECOG PS ≥ 2, > 1 extranodal site, Ann Arbor stage III/IV, involvement of kidneys and/or adrenal glands		
Score	Risk group	2 year rates of CNS relapse[26]
0-1	Low	0.6%
2-3	Intermediate	3.4%
4-6	High	10.2%

in patients with primary testicular DLBCL, orbital disease involving the globe or posterior compartment, and disease directly infiltrating spinal neuroforamina. CNS prophylaxis for other extranodal locations remains controversial and the overall clinical and biological risk factors of the patient should be taken into account.[28,29]

TREATMENT GUIDELINES (*FIGURE 1*)

EARLY STAGE DISEASE (AA-IPI 0 WITHOUT/ WITH BULKY DISEASE, AA-IPI 1)

Only few trials have explored the optimal treatment of limited stage DLBCL and most were performed before the introduction of R. Several trials have shown that before the

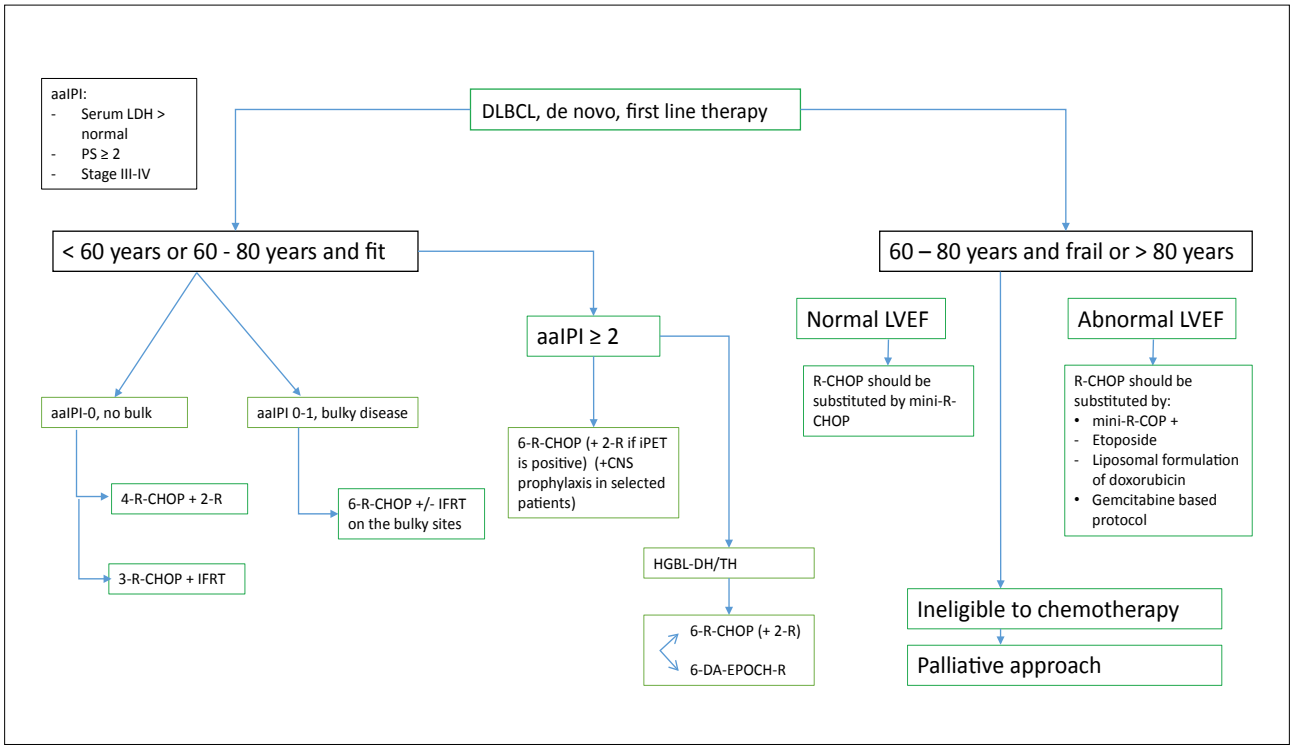

FIGURE 1. Approach to the treatment of newly diagnosed DLBCL.
LDH (lactate dehydrogenase); PS (Performance status); DLBCL (diffuse large B-cell lymphoma); aaIPI (age-adjusted international prognostic index); R (rituximab); CHOP (cyclophosphamide, doxoruibicin, vincristine and prednisolone); IFRT (involved field radiotherapy); iPET (interim PET); CNS (central nervous system); HGBL-DH/TH (high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 translocation – double or triple hit lymphoma); DA-EPOCH (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin); LVEF (Left Ventricular Ejection Fraction). The definition of bulky disease ranges from 5 – 10 cm in different studies. CHOP = CHOP-21 (CHOP given every 21 days).

introduction of R, OS was not different for patient groups treated with eight courses of CHOP versus 3-4 courses of CHOP followed by involved field radiotherapy (IFRT).[30-33]
Prognosis of DLBCL dramatically changed with the introduction of R. The Southwest Oncology Group (SWOG) 0014 study reported a 4-year progression free survival (PFS) of 88% and OS of 92% in patients with limited stage nonbulky disease and at least one adverse risk factor as defined by the stage-modified IPI (nonbulky stage II disease, age >60 years, ECOG PS of two, or elevated serum LDH) when treated with three cycles of R-CHOP given every 21 days (3-R-CHOP-21) followed by IFRT (40-46 Gy for patients achieving complete response (CR) with a small boost volume to a maximum of 50-55 Gy for patients failing to achieve CR).[34] The phase III randomised MabThera International Trial (MInt) compared 6-R-CHOP-21 with 6-CHOP-21 in young patients (<60 years) with aaIPI 0 or 1. Additional IFRT (30 - 40 Gy) was included for patients with extranodal or bulky disease (>7.5cm). The trial showed a benefit in six year OS (90.1% *vs.* 80%) and six year event free survival (EFS) (74.3% *vs.* 55.8%) in favour of R-CHOP. After treatment with CIT a favourable subgroup (IPI=0, no bulk) could be defined from a less favourable subgroup (IPI=1 or bulk, or both; 6-year EFS 84,3% *vs.* 71%) despite additional IFRT in patients with bulky disease.[35] In a 2 x 2 unfolded randomised trial of the DSHNHL/German Lymphoma Alliance (GLA) group young patients (18–60 years) with aaIPI 0 and bulky disease or aaIPI 1 were randomised to 6 x R-CHOP-14 or 6 x R-CHOP-21 followed by IFRT (39.6 Gy) or observation. Three-year EFS was worse in patients not assigned to radiotherapy (68% vs. 84%) due to a higher rate of partial response (PR).[36] Results from the RICOVER without radiotherapy trial (RICOVER-noRTh), an amendment of the R with CHOP over age 60 years (RICOVER-60) trial discussed later) also showed a significant improvement in EFS and trends for better PFS and OS in patients receiving additional IFRT to initial sites of bulky disease.[37]
The recent FLYER trial of the DSHNHL/GLA group showed that PFS, EFS and OS after 4-R-CHOP + 2-R were as good as after 6-R-CHOP in young patients with favourable prognosis DLBCL (18-60 year-old patients, aaIPI 0 without bulky disease).[38] IFRT was not planned to be given except for prophylactic radiotherapy of the contralateral testis in patients with testicular lymphoma.
In 2005, the Lymphoma Study Association/Groupe Ouest-Est des Leucemies et des Autres Maladies du Sang (LYSA/GOELAMS group) initiated a RCT comparing four to six cycles of R-CHOP alone to four to six cycles of R-CHOP plus IFRT (40 Gy) in patients with early-stage non-bulky disease. This trial showed no significant difference in 5-year EFS and OS between the two treatment groups.[39] There are no RCTs that compare abbreviated R-CHOP (three cycles) plus IFRT versus treatment with R-CHOP alone. Uncontrolled prospective and retrospective trials suggest that both treatment options are possible and choice of treatment is mainly based on the toxicity profile.
The LNH03-2B phase III RCT showed that for young patients (<60 years old) with stage I-IV disease and aaIPI 1 4-R-ACVBP (rituximab - doxorubicine – cyclofosfamide – vindesine – bleomycine – prednisone) and subsequent consolidation containing different treatment sequences (two cycles intravenous methotrexate, four cycles rituximab plus ifosfamide plus etoposide and two cycles cytarabine) significantly improves 3-year PFS, 3-year EFS and OS in comparison to 8-R-CHOP although hematological toxicity is more frequent.[40] This approach is not anymore used in Belgium.
In patients with primary testicular DLBCL contralateral testis irradiation is recommended besides CNS prophylaxis.[41]

We recommend a treatment with 4-R-CHOP-21 + 2-R or 3-R-CHOP-21 followed by IFRT in young, low risk patients (aaIPI 0) without bulky disease.

For young patients with low-intermediate risk (aaIPI 1) or low risk (aaIPI 0) with bulky disease we recommend a treatment with 6-R-CHOP-21 with or without additional IFRT on the bulky sites.

When there is rapid and confirmed complete metabolic remission additional IFRT can probably be omitted in patients with bulky disease. There is an ongoing LYSA study (LNH09-1B) comparing four to six cycles R-CHOP with or without IFRT in these patients.

ADVANCED STAGE DISEASE (AAIPI 2 AND 3)

In advanced stage disease, the benefit of adding R to CHOP has also clearly been demonstrated. Four RCTs showed a significant improvement in OS in patients treated with R-CHOP versus CHOP alone.[42-45]
The optimal number of treatment cycles has been investigated in The RICOVER-60 trial, which showed no benefit of 8-R-CHOP-14 compared to 6-R-CHOP-14 (and 2 additional courses of R) in elderly patients. Mortality rate was higher in the treatment group receiving 8-R-CHOP.[43] The Nordic Lymphoma Group published a population based study in

1.200 patients (18–90 years old) and concluded that there was no difference in outcome in patients treated with 6-R-CHOP-21 and patients treated with 8-R-CHOP-21.[46]

Two additional courses of R monotherapy could be considered, but the recent published results of the Positron Emission Tomography-Guided Therapy of Aggressive Non-Hodgkin Lymphomas (PETAL) trial showed no improved outcome when increasing the number of R administrations if interim PET-CT is negative.[47]

Whether we have to give R-CHOP every 21 days or every fourteen days has been investigated in two RCTs. One of the trials was conducted by the UK National Cancer Research Institute (NCRI) and showed no difference in OS or PFS between the group where R-CHOP was given every fourteen days in comparison with R-CHOP every 21 days in patients >18 years old.[48] The LNH03-6B trial from the Groupe d'Etude des Lymphomes de l'Adulte (GELA) confirmed these results in patients aged 60-80 years.[49]

More intensive treatment regimens with R-ACVBP or R-CHOEP (rituximab plus cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone) are frequently used but they were never compared with R-CHOP in this patient group.[40,50] There is also no evidence to intensify to dose adjusted EPOCH (etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin) with R (DA-EPOCH-R). This was shown by the Cancer and leukaemia group B (CALGB) 50303 study, a RCT comparing treatment with 6-DA-EPOCH-R with 6-R-CHOP in newly diagnosed DLBCL patients. There was no difference in 2-year EFS and 2-year OS in both groups and there was more toxicity in the group treated with DA-EPOCH-R.[51]

In conclusion we can say that 6-R-CHOP given every 21 days is at the moment the standard treatment regimen for young patients (<60 years or 60 to 80 years and fit) with newly diagnosed DLBCL in advanced stage (aaIPI 2 and 3). CNS prophylaxis is recommended for selected patients according to the CNS-IPI.

Consolidation IFRT may be beneficial in advanced stage disease especially in patients with initially bulky disease, bone involvement or in the setting of partial response to systemic therapy but evidence is mainly based on institutional experiences.[52]

Autologous stem cell transplantation (ASCT) does not seem to improve outcomes for high-risk (IPI 4-5) patients in first remission. There are four RCTs in the R era that compared CIT alone versus CIT followed by high-dose chemotherapy (HDC) and ASCT. Two trials showed a PFS benefit in the group treated with HDC and ASCT but no impact on OS.[53,54] The two other trials failed to show any improvement for the HDC arm.[50,55]

At present, there is no evidence for HDC followed by ASCT consolidation for patients with high risk DLBCL in first remission.

R administered subcutaneously is as effective as intravenous administration with comparable clinical efficacy and safety with the advantage of a reduced treatment burden for patients (shortened drug administration) as well as improved health-care resource utilisation.[56]

HIGH GRADE B-CELL LYMPHOMA WITH *MYC* AND *BCL2* AND/OR *BCL6* TRANSLOCATION

High grade B-cell lymphoma (HGBL) with *MYC* and *BCL2* and/or *BCL6* translocation, so-called double or triple hit lymphomas (HGBL-DH/TH), form a separate entity in the 2016 revised WHO classification.[1] Only 5-10% of all DLBCL cases fall into this subgroup.[57] They have a poor prognosis regardless of the IPI when treated with standard CIT with high relapse rates and a high risk of CNS involvement. The HGBL-DH with *BCL2* translocation are mainly of GCB phenotype. The dual expressor DLBCL (DE-DLBCL), marked by the co-expression of *MYC* and *BCL2* without *MYC* or *BCL2* rearrangement, also have an inferior prognosis but the outcome is better than the HGBL-DH/TH. In the WHO 2016 classification they fall into the category of DLBCL not otherwise specified (DLBCL-NOS) and are mainly of ABC phenotype.[1,58]

Accurate diagnosis of HGBL-DH/TH can be made by using fluorescence in situ hybridisation (FISH). Immunohistochemistry to detect *MYC* overexpression can be useful for screening patients who require FISH testing. However not all patients with *MYC* rearrangement overexpress the protein and some cases can be missed using this selective approach. Furthermore, the cut-off value for *MYC* expression is not standardised. The most used approach is to perform *MYC* FISH when *MYC* staining is positive in >40% of tumour cell nuclei. If *MYC* rearrangement is detected, further testing should be performed for *BCL2* and *BCL6* rearrangements.[57,58]

Because of the rarity of HGBL/DH-TH and high median age

in this patient group (6th-7th decade), an optimal treatment strategy has not yet been established. Currently, conclusions can only be drawn on retrospective data or subset analysis of prospective trials. Data available at the moment suggest that more intensive treatment regimens may improve response rates and outcome for HGBL-DH with a preference for the DA-EPOCH-R regimen.[59,60,61] There is no scientific evidence for consolidation with ASCT.[62] Because of the high risk of CNS involvement in HGBL-DH (4-7%) all patients should have a diagnostic lumbar puncture as part of the initial staging and prophylactic CNS therapy is recommended.[59-61]

When possible patients should be enrolled in clinical trials. Novel promising agents may include small molecule inhibitors of *BCL-2* such as venetoclax and bromodomain inhibitors.

ELDERLY PATIENTS

The incidence of lymphoma in older patients has increased over time. They appear to have unfavourable features such as the ABC subtype, a high *BCL2* expression or high genomic complexity, and treatment is more challenging because of decreased fitness and comorbidities. As mentioned before a CGA should be performed in frail patients with special attention to the prognostic value of the functional and nutritional state. In fully fit patients <80 years old the aim of treatment should be curative and R-CHOP can usually be used. For fully fit patients who are >80 years old without comorbidities, dose-attenuated R-CHOP may be appropriate (mini-R-CHOP) with encouraging results and a 2-year OS rate of 59%.[63]

In the group of vulnerable older patients with comorbidities, especially cardiac, doxorubicin can be substituted by drugs such as etoposide or a liposomal formulation of doxorubicin (not available in Belgium for lymphoma). Also a gemcitabine based protocol can be used.[64] Radiotherapy to sites of bulky disease can be considered. For terminally ill patients the goal is to achieve control of symptoms in a palliative approach and to maintain quality of life as much as possible.

NOVEL TREATMENT STRATEGIES

NOVEL ANTIBODIES

Obinutuzumab (G) is a glycoengineered, type II anti-CD20 monoclonal antibody with greater direct cell death induction and antibody-dependent cellular cytotoxicity and phagocytosis than R. G appeared to be more effective than R in previously untreated patients with CLL or FL.[65,66] The GOYA phase III RCT compared treatment with G-CHOP *vs* R-CHOP in patients with previously untreated advanced-stage DLBCL. There was no difference in 3-year PFS (67% for R-CHOP, 70% for G-CHOP) and toxicity was greater in the G-CHOP arm. After this study, R-CHOP was maintained as the standard of care.[67]

Polatuzumab vedotin (PoV) is an antibody-drug conjugate that targets the *CD79b* component of the B-cell receptor. It has demonstrated activity in relapsed or refractory (R/R) DLBCL. An open-label, non-randomised phase 1b dose escalation and phase II dose expansion study evaluated the safety and preliminary activity of PoV in combination with R-CHP or G-CHP in patients with previously untreated DLBCL. The safety profile appears to be similar to that or R-CHOP and G-CHOP with promising activity.[68] The phase III POLARIX RCT comparing the efficacy and safety of PoV in combination with R-CHP versus R-CHOP in previously untreated patients with DLBCL has been initiated in November 2017 and is still ongoing.

ADDITION OF TARGETED AGENTS

Vascular endothelial growth factor (VEGF) is involved in lymphoma growth, suggesting a potential role for anti-VEGF therapies in DLBCL. The addition of the anti-VEGF monoclonal antibody bevacizumab (RA-CHOP) did not appear successful in the MAIN study (median PFS of 42.9 months for R-CHOP and 40.2 months for RA-CHOP) with a higher occurrence of cardiac events.[69]

As already mentioned DLBCL is a very heterogeneous disease and two important subtypes can be distinguished: the ABC and the GCB subtype with the first one having the worst prognosis. A major hallmark of ABC-DLBCL is the constitutive activation of nuclear factor-kappa B (*NF-KB*). This can result from activating mutations in the myeloid differentiation primary response 88 gene (*MYD88*) and caspase recruitment domain-containing protein 11 (*CARD11*) or from inactivating mutations such as A20/TNF Alpha Induced Protein 3 (*TNFAIP3*). In addition, constitutive B-cell receptor (BCR) activation, often due to mutations in *CD79A* and *CD79B*, is another upstream activator of NF-KB signalling associated with ABC-DLBCL. The GCB-DLBCL subtype is characterised by recurrent mutations in the epigenetic regulator enhancer of zeste homolog 2 (*EZH2*).[4]

Addition of a proteasome inhibitor such as bortezomib could be interesting because it can prevent degradation of IkB kinase, maintaining *NF-kB* in its inactive state. The phase II PYRAMID trial compared R-CHOP with bortezomib *vs* R-CHOP alone in patients > 18 years old with untreated DLBCL of the non-GCB subtype as defined by the Hans algorithm. There was no significant difference in 2-year PFS (82% *vs*. 77.6%) and 2-year OS (93% *vs*. 88.4%).[70]

In the phase III randomised evaluation of molecular guided therapy for DLBCL with bortezomib (ReMoDL-B) study

patients initiated treatment with R-CHOP and COO was simultaneously analysed with GEP. Patients were then randomly assigned to R-CHOP or R-CHOP plus bortezomib for five cycles. There was no significant difference in PFS in patients treated with R-CHOP versus R-CHOP plus bortezomib (30 month PFS 70.1% and 74.3%) in all of the COO subgroups.[71]

Ibrutinib is an inhibitor of Bruton's tyrosine kinase (*BTK*) which is important in BCR signalling. In the ABC subtype of DLBCL, acquired mutations typically affect the BCR. A phase 1/2 clinical trial involving 80 patients with R/R DLBCL showed CR and PR in 37% of patients with ABC DLBCL, but in only 5% of patients with GCB DLBCL.[72] These promising results formed the basis for the phase III PHOENIX RCT comparing R-CHOP to R-CHOP with ibrutinib in previously untreated non-GCB DLBCL (n=838). The primary end point, EFS, was not different in the two treatment groups. However, in patients younger than 60 years old the combination of ibrutinib and R-CHOP did improve EFS, PFS and OS with manageable toxicity. In patients aged 60 years or older there was an increased toxicity leading to premature R-CHOP discontinuation and worse outcomes. Further investigation is needed.[73]

Lenalidomide is an immunomodulatory drug and shows significant activity in R/R lymphomas in monotherapy and in combination with R. Lenalidomide could have major clinical activity in ABC-subtype by downregulation of BCR-dependent *NF-KB* activity through inhibition of the transcription actor interferon regulatory factor 4 (IRF4) and cerebron. A phase II study showed that lenalidomide can be safely combined with R-CHOP (R2-CHOP) with promising clinical efficacy in patients with newly diagnosed DLBCL.[74] The ECOG-ACRIN1412 phase 2 RCT compared R2-CHOP *vs* R-CHOP in previously untreated DLBCL (>18 years old, DLBCL regardless of COO, stage II bulky – IV disease, IPI ≥2, ECOG PS ≤2 and measurable disease). Although overall and complete response rates were comparable, PFS was significantly improved in the R2-CHOP treatment group.[75] The ROBUST trial is a randomised, double-blind, phase III study in which front-line therapy of ABC-DLBCL with 6-R2-CHOP-21 (lenalidomide 15mg, days 1-14) is compared to 6-R-CHOP-21 plus placebo. Unfortunately, the trial did not meet the primary endpoint of demonstrating superiority in PFS in the R2-CHOP group although a positive trend favouring R2-CHOP has been observed in advanced stage and higher risk patients.[76]

In the Cavalli phase Ib trial (n=56), combination therapy with R/G-CHOP plus venetoclax (a BCL-2 inhibitor which leads to apoptosis) showed promising activity in B-cell NHL (DLBCL and FL) with manageable toxicity. The highest response rates were observed in the population with DE lymphoma. These findings have to be validated in larger patient populations and the phase II portion of the study is currently ongoing.[77]

Very recently, the results of the Smart start single-arm, open-label, phase II study were published. In this study, adult patients (n=60) with non-GCB DLBCL (as determined by the Hans method) were treated with two cycles of R, lenalidomide and ibrutinib (RLI) followed by six additional cycles combined with any chemotherapy. The combination therapy with RLI seems to be highly effective and further studies are required evaluating more cycles of RLI with less chemotherapy as consolidation.[78]

MAINTENANCE THERAPY

Maintenance therapy is another therapeutic strategy, which could prevent relapse following first remission.[79] R maintenance therapy showed no benefit. This was investigated in the NHL13 trial where patients were randomised to R maintenance or observation. Three year EFS was 80.1% and 76.5% respectively, which was not statistically significant. There was no difference in PFS and OS. There was a better outcome in men with low IPI, which warrants further investigation.[80] The more recently published RCT from the HOVON-Nordic Lymphoma Group confirmed these findings in patients with a high intermediate or high aa-IPI score.[81]

Enzastaurin, a protein kinase C beta inhibitor showed no significant benefit when given in maintenance therapy as demonstrated in a randomized phase III trial from *Crump et al*.[82] Adjuvant therapy with everolimus, a mammalian target of rapamycin (*mTOR*) inhibitor, could also not improve disease free survival (DFS).[83]

The REMARC phase III study from the LYSA group demonstrated an improvement in 2-year PFS from 75-80% in the patient group treated with lenalidomide maintenance when compared to placebo when reaching PR or CR after first-line therapy in patients aged between 60 and 80 years old, aaIPI 1, stage II to IV disease and newly diagnosed CD20+ DLBCL. However, no difference in OS was seen.[84]

GENETIC SIGNATURE GUIDED TREATMENT

Until now, results of combining novel agents with CIT have been disappointing but efforts are being made to further subdivide patients into molecular subgroups with Next Generation Sequencing and Whole Exome Sequencing which may have therapeutic consequences. A study from *Schmitz et al* described four genetic subtypes consisting of recurrent genetic aberrations, termed MCD (based on the co-occurrence of *MYD88* and *CD79B* mutations), BN2 (based on *BCL6* fusions and Notch homolog 2, translocation-associated

TABLE 7. 5-point Deauville scale.

Deauville score	Grade of uptake
1	No FDG uptake
2	FDG uptake ≤ mediastinum
3	FDG uptake > mediastinal but ≤ liver
4	FDG uptake > liver at any site
5	FDG uptake > liver and new sites of disease

(Drosophila) (*NOTCH2*) mutations), N1 (based on Notch homolog 1, translocation-associated (Drosophila) (*NOTCH 1*) mutations) and EZB (based on *EZH2* mutations and *BCL2* translocations). These subtypes have a different gene-expression signature and response to CIT with inferior outcome in the MCD and N1 subtypes.[85] Another study from *Chapuy et al*. identified five DLBCL subsets by integrating recurrent mutations, somatic copy number alterations (SCNAs) and structural variants (SVs), defined as clusters one to five (C1 - C5): C1 (favourable risk ABC-DLBCL with genetic features of an extrafollicular, possibly marginal zone origin), C3 (poor risk GCB-DLBCLs with *BCL2* SVs and alterations of *PTEN* and epigenetic enzymes), C4 (good-risk GCB-DLBCLs with distinct alterations in *BCR*/phosphatidylinositol-3-kinase (*PI3K*), janus kinase/signal transducer and activator of transcription (*JAK/STAT*) and proto-oncogene B-Raf (BRAF) pathway components and multiple histones), C2 (a COO independent group of tumours with biallelic inactivation of tumour protein 53 (*TP53*), 9p21.3/cyclin-dependent kinase Inhibitor 2A (*CDKN2A*) and associated genomic instability) and C5 (poor risk ABC DLBCL with frequent *BCL2* gain, concordant *MYD88/CD79B* mutations and additional mutations similar to those described in primary CNS and testicular lymphoma). A small subset of DLBCLs had no defining genetic drivers and was defined as cluster 0 (C0). PFS and OS differed significantly in these subgroups and patients with C3 and C5 tumours had a less favourable outcome.[86] These new genetic signatures are based on complex algorithms with many unclassified subsets and it is unlikely that these data can be repeated broadly in the first coming years. However, in the future it may lead to the development of precision medicine strategies in DLBCL.

FOLLOW-UP

Interim FDG-PET (iPET) during chemotherapy is often performed and there seems to be a correlation with outcome but its prognostic value is uncertain.[87] The results of the GELA/LYSA phase II LNH 2007-3B study formed the base of the GAINED trial (GA in newly Diagnosed DLBCL) which compares G versus R plus chemotherapy (CHOP or ACVBP) for untreated IPI 2-3 DLBCL patients <60 years old and investigates the value of a PET-driven treatment strategy.[88] PETs are performed at diagnosis, after two (iPET-2) and four cycles (iPET-4) of chemotherapy and iPET response is analysed according to the change of the difference of maximum standardised uptake value (ΔSUVmax) method. Early good responders (negative iPET-2/negative iPET-4) received the scheduled CIT according to initial randomization, slow responders (positive iPET-2/negative iPET-4) received two courses of high-dose methotrexate followed by ASCT, whereas nonresponders received a salvage therapy according to local investigators. ΔSUVmax assessment seems to be more predictive than other interpretation tools to identify the small subgroup of early slow responders that could benefit from upfront ASCT. Results are not published yet.[89] Pending the outcome the role and timing of iPET is not clear and it should not be recommended to adapt treatment strategy.

At the end of treatment, FDG-PET/CT should be performed to assess response to treatment. It is recommended to use the 5-point Deauville scale, which is a visual interpretation of the PET-CT that takes the liver as a cut-off for PET positivity (*Table 7*). Scores 1-3 should be interpreted as PET negative. Scores 4 and 5 can be interpreted as partial metabolic response (decreased FDG uptake compared to baseline and absence of structural progression on CT), no metabolic response (no significant change in FDG uptake compared with baseline) or progressive disease (increased FDG uptake compared to baseline and/or any new FDG-avid focus consistent with malignant lymphoma).

KEY MESSAGES FOR CLINICAL PRACTICE

1. **DLBCL is the most common type op NHL. 60% can be cured. 10-15% have primary refractory disease, 20-30% of the patients relapse.**
2. **Immunochemotherapy (R-CHOP-21) remains currently the standard treatment. There is no evidence for consolidation with HDCT and ASCT in first line.**
3. **For HGBL with MYC and BCL2 and/or BCL6 translocation an optimal treatment regimen has not yet been established.**
4. **New molecular insights (ABC vs GCB subtype of DLBCL) have led to investigation of targeted therapeutic approaches but until now results are disappointing.**

In patients who are in remission after treatment the purpose of follow-up during the first 2-3 years is early detection of relapse. In follow-up, we recommend to perform a history, a physical examination, complete blood count and chemistry including LDH. Surveillance imaging is not recommended.[90] Because the relapse rate is highest in the first two years, it is recommended to see patients every three months. Afterwards patients can be seen every six months up to five years. To evaluate late treatment effects, yearly evaluation stays recommended after five years with attention to secondary malignancies.

CONCLUSION

We have to conclude that R-CHOP-21 currently stays the standard therapeutic regimen in for newly diagnosed DLBCL. New molecular insights have led to the development of novel therapeutic strategies but until now results are disappointing. Another challenge is the increasing age of the patients developing DLBCL in which treatment strategies must be adapted taking into account age, comorbidities and geriatric assessment. In patients with high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* translocation, an optimal treatment strategy has not yet been established. Whenever possible patients should be enrolled in clinical trials. In the future, more efforts will be made to develop targeted therapies based on the broad genetic landscape seen in DLBCL.

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For the complete list of references, we refer to the electronic version of this article, which can be downloaded from *www.ariez.com*.

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