

Guidelines for newly diagnosed diffuse large B-cell lymphoma (DLBCL) and relapsed DLBCL

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The guidelines for adult patients in this article are based on 2011 ESMO and NCCN version 4.2011 guidelines and amended for the particular Belgian context of label prescription and reimbursement. Levels of evidence for the use of treatment recommendations are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts of the BHS-lymphoma working party.

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Incidence

DLBCL is the most common type of lymphoma with an incidence of three to five cases per 100.000 inhabitants and is increasing with age.¹ This brings the incidence in Belgium to 600 new cases per year.

Diagnosis

Pathological diagnosis should be made on surgical lymph node biopsy or extranodal tissue providing sufficient material for histologic samples including immunohistochemistry. In patients >50 year an EBV stain is recommended. Core needle biopsy is discouraged. It is recommended to collect fresh frozen material for molecular characterisation. Gene expression profiling is at the time investigational.

Incorporation of this information into treatment guidelines awaits further investigation. The pathological report should give the diagnosis according to the WHO 2008 criteria.

Staging and risk factors

The staging workup should include patient history and complete physical examination, performance status and systemic complaints (B-symptoms), complete blood count, blood chemistry including LDH, screening for hepatitis B and C, HIV, protein electrophoresis, bone marrow aspirate and biopsy. Computed tomography of the chest, abdomen and pelvis is mandatory. Combination of CT/18F deoxyglucose positron emission tomography is

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highly recommended in order to better delineate the extent of the disease and for response evaluation after treatment according to the revised Cheson criteria. In patients with one or more of the following sites of involvement (paranasal sinus, testicular, epidural, breast, bone marrow involvement, presence of two or more extranodal sites), or HIV a diagnostic spinal tap is indicated.

Staging is defined according to the Ann Arbor system. The International Prognostic Index (IPI) and age-adjusted is used for prognostic purposes.²

Table 1. International Prognostic Index

International prognostic Index	
Score	Risk group
0-1	Low risk
2	Low-intermediate
3	High-intermediate
4-5	High-risk

Risk factors: Age >60, serum LDH>normal range, ECOG performance status≥2, Ann Arbor stage III or IV, number of extranodal sites >1.

Age adjusted International prognostic Index	
Score	Risk group
0	Low risk
1	Low-intermediate
2	High-intermediate
3	High-risk

Risk factors: serum LDH>normal range, ECOG performance status ≥2, Ann Arbor stage III or IV.

A study of cardiac ejection fraction is highly recommended for elderly patients or young patients with risk factors (history of cardiac disease).

Reproductive counseling should be offered to young patients of both genders prior to treatment.

Treatment

Treatment options for patients with DLBCL should be stratified according to stage (Ann Arbor stage I-II versus stage III-IV) and risk factors. Patients should be enrolled in clinical trials. Patients with high tumour burden should be treated to avoid tumour lysis syndrome.

Limited stage disease (Ann Arbor stage I or IIA (30-40% of patients))

A number of randomised studies have been published in the pre-rituximab era. In the SWOG 8736 study, patients were randomised between 3-CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) followed by involved field radiation (IFRT) and 8-CHOP chemotherapy only: progression-free survival (PFS) 77% versus 64%, overall survival (OS) 82% versus 72%.³ However, the difference disappeared with further follow up. Patients <60 years with no adverse risk factor and treated with CHOP x 3 and IFRT had excellent five year survival of 95%. These data with brief chemotherapy plus radiotherapy in young, low risk patients with limited stage of disease have been confirmed.⁴ Addition of radiotherapy after eight courses of CHOP for patients with limited stage disease showed a better PFS but not OS compared with patients treated with chemotherapy only.⁵ In another randomised study in elderly, limited stage, low risk patients (GELA LNH93-4), the addition of radiotherapy after four courses of CHOP did not result in improved disease free or OS.⁶ The GELA LNH 93-1 study compared dose-intensified ACVBP (doxorubicin, vindesine, cyclophosphamide, bleomycin, prednisolone) chemotherapy with three courses of CHOP followed by involved field radiotherapy in young patients (<61 year) with localised, low risk disease. The ACVBP regimen resulted in a better five year survival (90% versus 81%), but was significantly more toxic.⁷

Several trials have studied the combination of chemotherapy and rituximab (R). Randomised studies between R-CHOP with or without additional radiotherapy are lacking. Three courses of R-CHOP and IFR in patients with limited disease resulted in a four year overall survival of 92%, better than a historical comparison in patients treated without rituximab.⁸ In the randomised MabThera International Trial (MInt) comparing six courses of CHOP with or without rituximab, 72% of patients had limited stage II without risk factors or stage I bulky disease. They reported a trend for a better three year OS for the rituximab arm: 98% versus 92%.⁹ Young low-intermediate risk patients (aaIPI 1) or IPI low risk (aaIPI 0) patients with bulky disease received additional IFR. Long-term follow up of this study confirms the previously reported survival data.³² For young

patients (<61 year) with localised disease (stage I or II), chemotherapy with the more toxic and aggressive ACVBP alone (three cycles followed by consolidation) significantly improved event-free and OS, as compared with the standard treatment with CHOP plus radiotherapy.⁷

Recommendations

For limited stage, good risk patients (age-adjusted IPI 0, 1, non-bulky, no B-symptoms): R-CHOP 21 days x 6 [1]. R-CHOP x 3 and involved field radiation is an alternative treatment option (often used in USA, but rarely used in Europe) with a different toxicity profile for early stage, good risk patients compared to R-chemotherapy alone, dependent on location of the disease. Young patients (<61 years) IPI low risk with bulk or IPI low-intermediate risk should receive R-CHOP x 6 + IFR on bulk. For young patients (age 18-59) with IPI 1 who can tolerate the additional toxic effects, four courses of R-ACVBP with subsequent consolidation is an alternative for centers with experience in ACVBP chemotherapy.¹⁵

Initial treatment of advanced stage (young poor-risk, age adjusted IPI ≥ 2 , bulky >10 cm), stage IIB, III-IV

Several randomised studies in advanced stage DLBCL have shown a higher OS in patients treated with the combination of rituximab and CHOP compared to CHOP only. In the LNH98-5 study 399 patients (age 60-80 years) with DLBCL received 8 cycles of R-CHOP or CHOP.¹⁰ Long-term follow-up of this study showed a statistically significant OS of 43.5% versus 28% in favor of R-CHOP at a median follow-up of 10 years.^{11,12} These data in elderly patients were confirmed in the ECOG/CALB study and the RICOVER-60 study.^{13,14} The MInT study confirmed these findings in young patients with 0 or 1 risk factor.⁹ Twenty eight percent of 824 patients had stage III/IV and 48% had bulky disease. Patients assigned to R-CHOP-(like) had increased three year OS of 79% versus 59% for CHOP only. Choice of regimen, number of cycles and schedule of administration have been investigated in a number of studies. In the LNH03-2B study, intensified chemotherapy with four cycles of ACVBP and consolidation plus rituximab versus standard eight courses R-CHOP was investigated in young patients (18-59 years), all stages (I-IV) and age-adjusted IPI 1.¹⁵ The three year

OS was increased in the R-ACVBP group compared with R-CHOP (92% versus 84%). However, the three year EFS in the R-CHOP arm was only 67%, which seems slightly low on the basis of previous studies in this population of patients where a range between 70-80% would be expected. The R-ACVBP regimen showed an expected higher rate of toxicities with significantly increased hematologic toxic effects. The optimal defined number of treatment cycles compared to R-CHOP-21 is still unclear and awaits the results of two randomised studies. In the RICOVER study 6 courses of R-CHOP-14 (+2R) in elderly patients (61-80 years) was at least as good as eight courses of R-CHOP-14 but with less deaths.¹⁴ A paucity of data exists concerning the relative efficacy of R-CHOP-14 with R-CHOP-21. Results of the final analysis of LNH03-6B GELA trial demonstrate similar efficacy and safety profile between the two treatment arms.^{16,17} However, this trial was not powered enough to compare different clinical subgroups. Although there are no strong data to support autologous transplantation in first line, some centers are using autologous stem cell transplantation (ASCT) as a consolidation after remission induction in selected, high risk patients. GELA investigators have recently reported a 78% four-year OS in high-risk (IPI 2 or 3) patients. In addition, they recommend consolidation with ASCT in patients with slow PET response.³⁹ A US/Canadian intergroup trial demonstrated a significantly higher rate of PFS, but no differences in OS.⁴⁰ They indicated that some high-risk patients could benefit from upfront ASCT. Consolidation by radiotherapy to sites of bulky disease has proven no benefit. The role of radiotherapy in partial remission remains to be established in patients treated with R-CHOP and evaluated with PET. The role of rituximab maintenance is still experimental, as is the addition of lenalidomide.

Recommendations

for initial treatment of 'Fit' advanced stage (young poor-risk, age adjusted IPI ≥ 2 , bulky (>10 cm) stage II, stage IIB, III-IV): 6 courses of R-CHOP-14+2R or 8 courses of R-CHOP-21 [1]. Four courses of R-ACVBP and consolidation is an alternative treatment option in centers with ACVBP experience. 'Fit' elderly patients: six courses of R-CHOP-14+2R or 8 courses of R-CHOP-21. Autologous transplantation might be considered as a

consolidation after remission induction by standard chemotherapy is selected patients or slow-responders, but preferentially in a clinical trial.

Advanced older patients 'unfit' for R-CHOP: Elderly patients need thorough evaluation (including a geriatric assessment) before starting chemotherapy. Rigorous supportive care including anti-infectious prophylaxis and growth factor support are mandatory. Nutritional status should be monitored carefully. A prephase with corticosteroids should be considered to limit lysis syndrome. The treatment with chemotherapy should be adapted to (cardiac, pulmonary, renal, neurological) comorbidities, knowing that less than 85% of the dose significantly reduces the efficacy. In very elderly (>80 yr) patients: consider R-miniCHOPx 6 after pre-phase with steroids +/- vincristine, in case of poor performance status.¹⁸

There is no uniform consensus concerning CNS prophylaxis. CNS prophylaxis with four doses of intrathecal metotrexate and/or cytarabine is recommended during the course of treatment in patients with involvement of paranasal sinus, testis, bone marrow and \geq one extranodal sites. LySA recommends 4 injections of intrathecal MTX to any patient with IPI \geq 1. The alternative of replacing IT MTX by two courses of IV MTX at the end of therapy is studied in ongoing trial of GELA. However, the value of prophylactic therapy has been raised, especially in the rituximab era.

Unusual localisations

CNS disease: see separate article on treatment of CNS lymphoma

Testicular localisation: outcome of testicular lymphoma had in the past a worse prognosis. No randomised studies are available. A combination of systemic chemotherapy, radiotherapy and intrathecal treatment is advised based on several non-randomised studies.¹⁹⁻²¹ Recently, an international phase II study treated patients with stage I disease after unilateral orchidectomy with six courses of R-CHOP, CNS prophylaxis with IT-MTX, 12mg total dose, weekly for four times. At the end of chemotherapy, all patients received prophylactic irradiation to the contralateral testis (25-30 Gy). Patients with stage II disease received additional IFR. They reported excellent results with a five year PFS of 74% and OS of 85%.⁴⁴

Recommendations

For initial treatment of localised stage I testicular lymphoma: Unilateral orchidectomy on side of the disease, six courses of R-CHOP/21, IT-MTX (x4) and irradiation to the contralateral testis. Patients with stage II: 6-8 courses of R-CHOP, IT-MTX (x4), IFR and irradiation of the contralateral testis.

Breast localisation

Recommendations

Initial treatment of extranodal lymphomas: R-CHOP x 3 and IFR or 6-8 R-CHOP, Stage IIE: 6-8 R-CHOP. For both stages, consider CNS prophylaxis since there is a high incidence of CNS recurrence up to 27%.^{22,23} However, no prospective randomised trials are available.

Primary mediastinal lymphomas (PMLBCL)

In the absence of prospective randomised trials, there is no established optimal treatment for patients with primary mediastinal large B-cell lymphoma (PMLBCL). In the pre-rituximab era, a higher refractoriness rate and early relapse rate was noted compared to other DLBCLs following CHOP chemotherapy.²⁴⁻²⁶ Retrospective studies suggest better outcome with more intensive chemotherapy than CHOP and the addition of radiotherapy, but the use of radiotherapy remains controversial.^{27,28} However, the addition of rituximab to chemotherapy improved response rates and seems to overcome the poor prognostic features of PMLBCL. In the MInt trial 11% of patients had PMLBCL.⁹ Sub-analysis of these patients showed an increase in CR (90% versus 54%) and increase in the three year event-free survival (78% versus 52%) and a trend towards increased overall survival (89% versus 78%).³¹ We could not find a Belgian consensus for the treatment of PMLBCL.

Recommendations

For initial treatment of PMLBCL: 6 cycles of R-CHOP/14. If PET/CT is negative at the end of treatment, patients may enter follow-up or will receive consolidation radiotherapy according to local guidelines. In the case of a positive PET/CT, biopsy is recommended and, if

residual disease is confirmed, additional radiotherapy is advised +/- ASCT according to local guidelines. We advise 8 cycles of R-CHOP for patients with bulky disease, pleural effusion or pericardial effusion. R-ACVBP is an alternative option.

High-proliferative variants of DLBCL

The presence of translocations of both c-myc and bcl-2 characterizes double-hit lymphoma (5% of DLBCLs). Patients with high expression of c-myc and bcl-2 by immunohistochemistry constitute a much larger group (29%) who also have a poor prognosis, independently of the IPI score and cell-of-origin subtype.⁴¹ In these patients, R-CHOP is unsatisfactory, but alternative options are lacking.

Recommendations

Outside a clinical trial R-EPOCH and CNS prophylaxis is a reasonable option.

Response assessment and follow up

Evaluation by CT scan should be performed after three to four courses of therapy in order to identify patients with refractory disease. Standard evaluation of PET response by IHC criteria ('Cheson criteria') are not adequate for interim evaluation of metabolic response. Alternative methods using other background or quantitative measurements (by calculation delta SUVmax) are being studied. Preliminary data suggest that early FDG-PET/CT has a prognostic value in terms of PFS and OS, but cannot be recommended on a routine base. Clinical studies are still on going.⁴³

Six to eight weeks after completion of planned therapy (twelve weeks after radiotherapy) response to therapy should be documented, preferable by PET-CT scan. Response should also include a bone marrow aspirate/biopsy if initially involved, physical examination and laboratory studies.

History and physical examination, complete blood count and chemistry including LDH will be scheduled every three months, during the first year, every three to six months during the second year and then every six months up to five years. Repeated CT scan is performed at 6, 12 and 24 months after end of therapy or as clinically indicated. Continuous

follow-up with FDG-PET scanning is not advised in patients who have achieved complete metabolic response.

Relapse or refractory disease

The majority of relapses occur during the first two years after completing therapy. A biopsy should be obtained whenever possible to document relapse, especially in patients with prior complete remission. Patients should undergo a staging procedure as at first diagnosis.

Treatment of 'FIT' patients (good performance status and good physiological age)

Patients with chemotherapy-responsive disease should proceed to high-dose chemotherapy and ASCT. The PARMA, phase III study randomised patients to chemotherapy only (DHAP; cisplatin, cytosine arabinoside, dexamethason) or to DHAP followed by high-dose chemotherapy and ASCT for patients with sensitive relapse.³³ five year OS was 53% for the transplant group versus 32% for the non-transplant group. A pre-transplant PET scan has been identified as a predictive factor following autologous stem cell transplantation.³⁴ However, even patients with a positive pre-transplant PET but still chemotherapy-sensitive disease remain candidates for ASCT.^{35,36} Several studies have explored different chemotherapy regimens before ASCT. For example, the CORAL study compared rituximab and DHAP compared to rituximab in combination with ICE (ifosfamide, carboplatin, etoposide) and followed by high dose chemotherapy and ASCT.³⁷ No differences in three year EFS or OS were detected. Patients with the germinal center B(GCB)-like DLBCL subtype who were treated with R-DHAP had a better PFS (52 versus 32%) than patients with the non-germinal center B-like subtype. Patients treated with R-ICE had a poor PFS, with no significant differences between GCB and non-GCB types. R-DHAP is thus preferred before ASCT.⁴² The addition of rituximab as a standard component of second line chemotherapy is controversial. In the HOVON randomised trial in patients with relapsed aggressive CD20-positive lymphoma, the combination arm of R-DHAP resulted in a higher response rate.³⁸ However, most patients did not receive rituximab as part of their initial induction therapy. Others reserve rituximab for those patients who are ritux-

imab-naive or in the case of a late relapse in patients previously treated with rituximab.

An allogeneic SCT may be considered in the case of mobilization failure, refractory disease or relapse after autologous SCT, preferable in a clinical trial.

Treatment for patients not eligible for high dose chemotherapy and ASCT

Patients not eligible for transplantation should be encouraged to participate in a clinical trial. Gemcitabine and oxaliplatin with or without rituximab (GemOX-+/-R) might be an alternative. Promising drugs currently evaluated in DLBCL are lenalidomide (combined with Rituximab), everolimus, immunotoxin (anti-CD22-calicheamycin) and BTK inhibition (ibrutinib).

Recommendations

For relapsed/refractory patients who are candidates for ASCT, second-line chemotherapy with DHAP (especially in germinal center B-type) or ICE with or without rituximab followed by high dose chemotherapy and ASCT in the case of chemosensitive disease.¹ Patients not eligible for transplantation should be encouraged to participate in a clinical trial. GemOX-+/-R might be an alternative.

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List of abbreviations

DLBCL: diffuse large B-cell lymphoma **BHS:** Belgian Hematology Society **IPI:** International Prognostic Index **CHOP:** cyclophosphamide, doxorubicin, vincristine, prednisone **IFRT:** involved field radiotherapy **PFS:** progression-free survival **EFS:** event-free survival **OS:** overall survival **ACVBP:** doxorubicin, vindesine, cyclophosphamide, bleomycine, prednisolone **R:** rituximab **ASCT:** autologous stem cell transplantation **MTX:** methotrexate **CNS:** central nervous system **IT:** intrathecal **PMLBCL:** primary mediastinal large B-cell lymphoma **EPOCH:** dose adjusted Etoposide, doxorubicin, vincristine, prednisone, and cyclophosphamide **SUVmax:** Maximum standard uptake value **ICE:** ifosfamide, carboplatin, etoposide **DHAP:** cisplatin, cytosine arabinoside, dexamethasone **HOVON:** Hematologie Oncologie voor Volwassenen Nederland **GELA:** Groupe de l'Etude des Lymphomas de l'Adulte **GemOx:** gemcitabine, oxaliplatin