clinical recommendations

Diffuse large B-cell non-Hodgkin’s lymphoma: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

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newly diagnosed diffuse large B-cell lymphoma

incidence
Diffuse large B-cell lymphoma (DLBCL) constitutes 30–58% of non-Hodgkin’s lymphoma series. The crude incidence in the European Union is 5–6/100 000/year. The incidence increases with age from 0.3/100 000/year (35–39 years) to 26.6/100 000/year (80–84 years).

diagnosis
Diagnosis should be made on the basis of a surgical specimen/excisional lymph node or extranodal tissue biopsy providing sufficient material for formalin-fixed samples. Core biopsies may be appropriate in the rare patients requiring emergency treatment. Minimal immunohistochemistry (CD45, CD20 and CD3) is mandatory. The collection of fresh frozen material for molecular characterization is recommended although gene expression profiling remains investigational. To ensure adequate quality, processing by an experienced pathology institute must be guaranteed. The histological report should give the diagnosis according to the World Health Organization classification.

staging and risk assessment
A complete blood count, routine blood chemistry including lactate dehydrogenase (LDH) and uric acid as well as screening for human immunodeficiency virus and hepatitis B and C are required. Protein electrophoresis is recommended.

Patients with curative therapy should have at least a computed tomography (CT) scan of the chest and abdomen, as well as a bone marrow aspirate and biopsy. A diagnostic spinal tap combined with prophylactic instillation of methotrexate and/or cytarabine should be considered in high-risk patients [V, D]. [18F]deoxyglucose positron emission tomography (PET) scanning is recommended to better delineate the extent of the disease and in order to evaluate the treatment response according to the revised criteria. Performance status and cardiac function (left ventricular ejection fraction) should be assessed before treatment.

The staging is established according to the Ann Arbor system [I, A]. For prognostic purposes, IPI and age-adapted IPI (aaIPI) should be calculated [I, A].

treatment
Treatment strategies should be stratified according to age, age-adapted IPI and feasibility of dose-intensified approaches. Whenever available, the inclusion in a clinical trial should be considered.

In cases with high tumor load, special precautions are required to avoid tumor lysis syndrome. Dose reductions due to hematological toxicity should be avoided. Febrile neutropenia justifies prophylactic use of hematopoietic growth factors in patients treated with curative intent.

Young good-risk patients (aaIPI 0, 1). Six cycles of combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) treatment combined with eight doses of rituximab given every 14 days is the current standard for CD20⁺ diffuse large-cell non-Hodgkin’s lymphoma of all stages [I, A]. Alternatively, patients in early stages (I, II) may be treated with three cycles R-CHOP and involved field radiation. Dose-dense/dose-intensive regimens remain experimental. Consolidation by radiotherapy to initial sites has proven no clear benefit [I, A].

Young poor-risk patients (aaIPI ≥2). There is no current standard with sufficient efficacy. Thus, this patient population should be treated preferably in clinical trials. However, rituximab and six to eight cycles of dose-dense combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP-14) treatment combined with eight doses of rituximab given every 14 days or dose-intensive regimens (R-ACVBP) are most frequently applied. High-dose chemotherapy with stem-cell transplantation remain experimental in first-line therapy. Central nervous system prophylaxis may be recommended in this population based on...
data before the rituximab era. Consolidation by radiotherapy to sites of bulky disease has no proven benefit [III, C].

**Patients aged >60 years.** Eight cycles of combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) treatment combined with eight doses of rituximab given every 21 days is the current standard [I, A]. If rituximab-CHOP is given every 14 days, six cycles are sufficient.

**response evaluation**
Abnormal radiological tests at baseline should be repeated after three to four cycles and after the last cycle of treatment. Bone marrow aspirate/biopsy should be only repeated at the end of treatment if initially involved.

PET is highly recommended for the post-treatment assessment to define complete remission according to the revised response criteria. In case of therapeutic consequences a histological confirmation of PET positivity is strongly recommended. Early PET, performed after one to four cycles of treatment, is predictive of clinical outcome but should be restricted to clinical trials.

**follow-up**
History and physical examination every 3 months for 1 year, every 6 months for 2 more years, and then once a year with attention to development of secondary tumors or other long-term side-effects of chemotherapy [V, D].

Blood count and LDH at 3, 6, 12 and 24 months, then only in case of suspicious symptoms or clinical findings in patients suitable for further therapy [V, D].

Minimal adequate radiological examinations by CT scan at 6, 12 and 24 months after end of treatment are indicated [V, D]. Routine surveillance with PET scan is not recommended.

High-risk patients with curative options may potentially mandate more frequent controls.

**relapsed and refractory DLBCL**

**incidence**
Overall, >30% of diffuse large B-cell non-Hodgkin’s lymphoma will ultimately relapse. The incidence in the European Union is therefore estimated to be around 1/100 000/year.

**diagnosis**
Histological verification should be obtained whenever possible, and is mandatory in relapses >12 months after the initial diagnosis, especially in order to ensure CD20 positivity. Image-guided core biopsy may be appropriate in this context.

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

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

In suitable patients with adequate performance status (no major organ dysfunction, age <65–70 years), salvage regimen (rituximab and chemotherapy) followed in responsive patients by high-dose treatment with stem-cell support is recommended [II, A]. Any of the published salvage regimens such as R-DHAP, R-EHAP, R-ICE, etc. may be adequate until results of comparative trials are available. The choice of the high-dose regimen depends on local experience with BEAM (carmustine, etoposide, cytosine-arabinoside and melphalan) being the most frequently used. Additional involved-field radiation may be used, especially in the few cases with limited stage disease, but this treatment has been never evaluated in controlled trials.

Patients not suitable for high-dose therapy may be treated with similar or other salvage regimens (e.g. R-GEMOX, etc.) which may be combined with involved-field radiotherapy.

**response evaluation**
Response criteria are identical to those of first-line treatment evaluation. An evaluation should be performed after three to four cycles of salvage regimen (before high-dose treatment) and after completed therapy. Results of PET before high-dose treatment are correlated to clinical outcome.

**follow-up**
Follow-up of patients in second response could be the same as first response.

**note**
Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

**literature**
8. Pfreundschuh MG, Trumper L, Osterborg A et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma—a randomized controlled trial by the


