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 non-Hodgkin’s 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 3–4/100 000/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 enough material for formalin-fixed samples. Core biopsies may be appropriate as the only diagnostic test in the rare patients requiring emergency treatment. Immunohistochemistry is mandatory with description of minimal antibody panel results (CD45, CD20 and CD3). The determination of CD10, BCL-2 and MUM1 expression for differentiation of germinal center derivation (GCB) or activated B-cell (ABC) type is optional. 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 has to 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 a screening test for human immunodeficiency virus and hepatitis B and C are required. Protein electrophoresis is recommended.

Patients amenable to 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 directly combined with a first prophylactic instillation of cytarabine and/or methotrexate should be considered in high-risk patients [V, D]. 18F-deoxyglucose positron emission tomography (PET) scanning can be performed to better delineate the extent of the disease and with a view to the evaluation of future treatment response.

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 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 proposed.

In cases with high tumor load, special precautions (e.g. corticosteroid pre-phase) 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 low-risk patients (aaIPI ≤1)
Six to eight cycles of combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) combined with eight doses of rituximab given every 21 days is the current standard for CD20+ BLBCL of all stages [I, A]. Consolidation by radioimmunotherapy to initial sites has no proven benefit [I, A].
young high-risk patients (aaIPI ≥2)

There is no current standard with sufficient efficacy. Thus, especially this patient population should be treated preferably in clinical trials. However, six to eight cycles of combination chemotherapy with CHOP treatment combined with eight doses of rituximab given every 14–21 days are most frequently applied. Dose-intensive regimens and high-dose chemotherapy with stem-cell transplantation, as part of first-line therapy, remain experimental. Central nervous system relapse prophylaxis is recommended in high-risk patients. Consolidation by radiotherapy to sites of bulky disease has not proved of benefit [III, C].

patients older than 60 years

Eight cycles of combination chemotherapy with CHOP treatment combined with eight doses of rituximab given every 21 days is the current standard [I, A]. If rituximab (R)-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 repeated only at the end of treatment if initially involved.

PET, when positive at baseline, is part of the updated response criteria. However, in case of therapeutic consequences a histological confirmation of PET positivity is strongly recommended. 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 as needed for evaluation of suspicious symptoms or clinical findings in those patients suitable for further therapy [V, D]. Minimal adequate radiological examinations at 6, 12 and 24 months after end of treatment by CT scan are indicated [V, D]. Routine surveillance with PET scan is not recommended. High-risk patients with still curative options may mandate more frequent controls.

relapsed and refractory DLBCL

incidence

Overall, >30% of DLBCL will ultimately relapse. The incidence in the European Union is therefore estimated to be around 2/100 000/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 initial phase.

treatment

The following recommendations apply to patients with adequate, rituximab-associated anthracycline-containing first-line therapy. Phase II studies combining rituximab with salvage or high-dose chemotherapy clearly suggest superior response and disease-free survival over chemotherapy alone [II, A], but the advantage after first-line therapy containing rituximab is not established. In suitable patients with adequate performance status (no major organ dysfunction, age <65 years) salvage regimen followed by high-dose treatment with stem-cell support in responsive patients is recommended [II, A]. Any of the published salvage regimens such as R-DHAP, R-ESHAP, R-ICE, etc. may be adequate until results of comparative trials are known. The choice of the high-dose regimen depends on local experience with BEAM (carmustine, etoposide, cytosine–arabinoside and melphalan) being most frequently used. Additional involved-field radiation or iceberg radiation may be used especially in the few cases with limited-stage disease, but has been never evaluated in controlled trials.

Patients not suitable for high-dose therapy may be treated with the same or other salvage regimens (e.g. R-IMVP16, R-GEMOX, etc.) and 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 the end of all 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