newly diagnosed diffuse large B-cell non-Hodgkin’s lymphoma

incidence
Diffuse large B-cell non-Hodgkin’s 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. 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 has to be guaranteed. The histological report should give the diagnosis according to the current 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 should be considered in high-risk patients [V, D]. [18F]deoxyglucose positron emission tomography (FDG-PET) scanning is strongly recommended to better delineate the extent of the disease and with a view to the evaluation of 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 tumour load, special precautions are required to avoid tumour 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- and low–intermediate-risk patients (aaIPI ≤1).
Six to eight cycles of combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) treatment combined with six to eight doses of rituximab given every 21 days is the current standard for CD20+ diffuse large-cell non-Hodgkin’s lymphoma of all stages [I, A]. Dose-dense/dose-intensive regimens remain experimental. Consolidation by radiotherapy to initial sites has no clear proven benefit [I, A].

young high- and high–intermediate-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 chemotherapy with CHOP combined with eight doses of rituximab given every 21 days are most frequently applied [I, A]. Dose-dense (R-CHOP-14; R-CHOP given every 2 weeks)
or dose-intensive (like R-ACVBP; rituximab, doxorubicin, vindesine, cyclophosphamide, bleomycin, prednisolone given every 2 weeks followed by sequential consolidation) regimens could also be proposed. High-dose chemotherapy with stem-cell transplantation as consolidation treatment after immunochemotherapy remains experimental in first-line therapy but recent phase II trials have shown promising results. Consolidation by radiotherapy to sites of bulky disease has proved to be of no benefit [III, C]. The role of radiotherapy in partial remission remains to be established in patients treated with rituximab abd evaluated with PET.

patients aged 60–80 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–CHOP is given every 14 days, six cycles of CHOP with eight cycles of rituximab are sufficient. In patients with localized disease, consolidation by radiotherapy has proved to be of no benefit [I, A].

patients aged >80 years. R-CHOP treatment could usually be used until 80 years of age in fit patients. Small series have shown that the combination of rituximab with attenuated chemotherapy could induce complete remission and long survival in some very elderly patients.

CNS prophylaxis. Patients with high–intermediate- and high-risk IPI, especially those with more than one extranodal site or elevated LDH are at higher risk of CNS relapse. CNS prophylaxis should be recommended in this population but intrathecal injections of methotrexate are probably not an optimal method. Whether some specific involvement sites such as paranasal sinus, upper neck or bone marrow should receive prophylaxis remains to be established. Testicular lymphoma must receive CNS prophylaxis.

some extra-nodal DLBCLs require special consideration. Treatment of primary DLBCL of the central nervous system must contain high-dose methotrexate. Addition of high-dose cytarabine seems to improve complete remission rate and outcome. CNS irradiation is usually associated.

Primary DLBCL of the testis is characterized by an increased risk of extranodal relapse. CNS prophylaxis is mandatory. Prophylactic irradiation of the contralateral testis should be considered in localized disease.

Primary mediastinal large B-cell lymphoma (PMBL) is probably a distinct entity. R-CHOP 21 is not established as the definitive treatment option and radiotherapy remains controversial.

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 and biopsy should only be repeated at the end of treatment if initially involved.

PET is highly recommended for post-treatment assessment to define complete remission according to the revised criteria of response. In the case of therapeutic consequences a histological confirmation of PET positivity at this time is strongly recommended. Early PET, performed after one to four cycles of treatment, could be predictive of clinical outcome but its results should not lead to treatment change outside of a clinical trial.

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 tumours 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 is usual practice but there is no definitive evidence that routine imaging in patients in complete remission provides any outcome advantage. 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 DLBCL will ultimately relapse. The incidence in the European Union is therefore estimated to be ~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 with adequate, rituximab-associated anthracycline-containing first-line therapy.

In suitable patients with adequate performance status (no major organ dysfunction, age <65–70 years) a salvage regimen with association of rituximab and chemotherapy followed in responsive patients by high-dose treatment with stem-cell support is recommended [II, A]. Salvage regimens such as R-DHAP (rituximab, cisplatin, cytosine–arabinoside, dexamethasone) or R-ICE (rituximab, ifosfamide, carboplatin, etoposide) may be adequate. The choice of the high-dose regimen depends on local experience; BEAM (carmustine, etoposide, cytosine–arabinoside and melphalan) is the more frequently used. Additional involved-field radiation or iceberg radiation may be used especially in the few cases with limited stage disease, but it has been never evaluated in controlled trials.

Patients not suitable for high-dose therapy may be treated with the same or other salvage regimens such as R-GEMOX (rituximab, gemcitabine, oxaliplatin), which may be combined with involved-field radiotherapy.
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 with 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