Diffuse large B-Cell Lymphoma

ESMO Summary of recommendations

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DIAGNOSIS

- Diagnosis should be carried out in a reference haematopathology laboratory with expertise in morphological interpretation and the facilities to carry out the full range of phenotypic and molecular investigations.
- Surgical biopsy is the optimal method of diagnosis.
- Needle-core and endoscopic biopsies should be reserved for patients for whom a surgical approach is impractical or would entail excessive risk.
- A fine-needle aspirate should not be used as the sole basis for a diagnosis of DLBCL.
- A morphological diagnosis of DLBCL should be confirmed in all cases by immunophenotypic investigations.
- If there is doubt in the diagnosis, demonstration of B-cell monoclonality by a PCR-based method should be considered.
- Assessment of MYC and BCL2 rearrangement is recommended (whenever technically possible) in newly diagnosed and relapsed patients treated with curative intent, using interphase FISH.

STAGING AND RISK ASSESSMENT

- Physical exam, performance status and assessment of B symptoms are necessary.
- A complete blood count, routine blood chemistry including LDH and uric acid, as well as screening tests for HIV, HBV and HCV are required.
- Protein electrophoresis is recommended.
- FDG-PET/CT scan is recommended as the gold standard for staging DLBCL patients.
- If CeCT is not carried out before PET/CT, a full diagnostic high-dose CeCT should be carried out when necessary, in combination with PET/CT.
- Biopsy may be avoided when PET/CT scans demonstrate bone or marrow involvement indicating advanced-stage disease but is appropriate in the case of negative PET, when its results would change prognosis and treatment, especially when a shortened number of immune-chemotherapy cycles is proposed.
- For suspected CNS lymphoma, MRI is the modality of choice.
- A diagnostic lumbar puncture should be considered in high-risk patients.
- Cardiac function (LVEF) should be assessed before treatment.

- The staging is established according to the Ann Arbor classification system.
- For prognostic purposes, the IPI and aa-IPI should be calculated.

TREATMENT

• Treatment strategies should be stratified according to age, IPI and feasibility of dose-intensified approaches.
• Whenever available, inclusion in a clinical trial is recommended.
• In cases with high tumor load, precautions are advised to avoid tumor lysis syndrome.
• Dose reductions due to hematological toxicity should be avoided whenever possible.
• The risk of febrile neutropenia justifies prophylactic use of hematopoietic growth factors in patients treatment with curative intent and in patients >60 years of age.
• *For young, low-risk patients (aa-IPI = 0) without bulky disease:*
    ○ six cycles of combination chemotherapy with CHOP treatment combined with six doses of rituximab given every 21 days is the current standard;
    ○ Consolidation by radiotherapy to initial non-bulky sites has no proven benefit in patients treated with rituximab or not.
• *For young low-intermediate-risk patients (aa-IPI = 1) or IPI low risk (aa-IPI = 0) with bulky disease:*
    ○ Either R-CHOP21 × 6 with radiotherapy to the sites of previous bulky disease or the intensified regimen R-ACVBP is recommended.
• *For young high- and high-intermediate-risk patients (aa-IPI ≥ 2):*
    ○ Enrolment in clinical trials should be a priority;
    ○ Six to eight cycles of chemotherapy with CHOP combined with eight doses of rituximab given every 21 days are most frequently applied;
    ○ Dose dense treatment with R-CHOP given every 14 days has not demonstrated a survival advantage over standard R-CHOP given every 21 days;
    ○ Intensive treatment with R-ACVBP or R-CHOEP is frequently used but these regimens have not been directly compared with R-CHOP in this category;
    ○ HDC with ASCT in first line remains experimental or may be proposed for selected high-risk patients;
    ○ the role of interim PET to select patients who could benefit from consolidative ASCT or from radiotherapy is under evaluation.
• *For patients aged 60–80 years:*
    ○ six to eight cycles of combination chemotherapy with CHOP plus eight doses of rituximab given every 21 days is the current standard;
    ○ If R-CHOP is given every 14 days, six cycles of CHOP with eight cycles of rituximab are sufficient;
    ○ a comprehensive geriatric assessment in order to ascertain comorbidities and functional decline is recommended to guide the choice of treatment in elderly poor-prognosis patients;
    ○ R-CHOP treatment can usually be used up to 80 years of age in fit patients, but modulation of treatment according to geriatric assessment is recommended.
• *For patients aged >80 years:*
    ○ the combination of rituximab with attenuated chemotherapy, such as R-mini CHOP, can induce complete remission and long survival in fit patients older than 80 years;

○ Substitution of doxorubicin by gemcitabine, etoposide or liposomal doxorubicin, or even its omission, can be considered from the beginning or after a few cycles in patients with cardiac dysfunction or who are frail or unfit

CNS PROPHYLAXIS:

- Should be recommended for patients with high-intermediate-risk and high-risk IPI, especially those with more than one extranodal site or elevated LDH or for patients with testicular, renal or adrenal involvement;
- Intravenous high-dose methotrexate has been shown to be associated with efficient disease control.
- Patients with human immunodeficiency virus (HIV) infection should usually receive the same treatment as HIV-negative patients in association with antiviral therapy.
- Antiviral prophylaxis or periodic HBV DNA monitoring and antiviral treatment are recommended for patients previously exposed to HBV who experience reactivation of the virus during treatment.

RESPONSE EVALUATION

- FDG-PET/CT is the recommended standard for post-treatment assessment in DLBCL.
- In the presence of residual metabolically active tissue, where salvage treatment is being considered, a biopsy is recommended.
- Interim evaluation:
  - ○ Mid-treatment imaging after three to four cycles may be used to rule out progression in clinical practice;
  - ○ Changing treatment solely on the basis of interim PET/CT is discouraged, unless there is clear evidence of progression;
  - ○ Early PET evaluation carried out after one to two cycles of treatment has been shown to be predictive of outcome, but should be reserved for clinical trials at the present time.

FOLLOW-UP

- Careful history and physical examination every 3 months for 1 year, every 6 months for 2 further years and then once a year with attention to development of secondary tumors or other long-term side-effects of chemotherapy is recommended.
- Blood count should be carried out 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.
- Minimal radiological examinations at 6, 12 and 24 months after end of treatment, by CT scan, is common practice, but there is no definitive evidence that routine imaging in patients in complete remission provides any outcome advantage and it may increase the incidence of secondary malignancies
- Routine surveillance with PET scan is not recommended

Diffuse large B-cell lymphoma (DLBCL): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Annals of oncology 2015; 26(5):116-125.