Hodgkin’s lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

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On behalf of the ESMO Guidelines Working Group*

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incidence

• The crude incidence of Hodgkin’s lymphoma (HL) in the European Union is 2.2, the mortality 0.7 cases/100 000/year.

diagnosis

• Pathological diagnosis should be made according to the WHO classification from a sufficiently large surgical specimen or excisional lymph node biopsy to provide enough material for fresh frozen and formalin-fixed samples.
• Classical Hodgkin lymphoma (cHL) includes nodular sclerosing (NS), mixed cellularity (MC), lymphocyte-rich (LR) and lymphocyte-depleted (LD) subtypes and represents ~95% of all HL cases. It is distinguished from nodular lymphocyte predominant Hodgkin lymphoma (NLPHL), which accounts for ~5% of all HL cases.

staging and risk assessment

• Chest X-ray and a computed tomography (CT) scan of neck, chest and abdomen are mandatory as well as bone marrow aspiration and histology.
• Additional positron emission tomography (PET) scan may be considered according to the revised response criteria.
• Staging laparotomy is not recommended [II, A].
• Full blood cell count, erythrocyte sedimentation rate (ESR) and blood chemistry including glucose, alkaline phosphatase (AP), lactate dehydrogenase (LDH), liver enzymes, albumin and thyroid-stimulating hormone (TSH) are obligatory [II–III, A]. Screening for hepatitis B (HBV), hepatitis C (HCV) and human immunodeficiency virus (HIV) is compulsory.
• Staging is carried out according to the Ann Arbor system in consideration of the risk factors listed in Table 1. After completion of staging, patients are allocated and treatment is chosen according to three categories (limited, intermediate or advanced stages) [II–III, A].

examinations before treatment

• To identify patients at increased risk for acute and/or long-term complications, cardiac and pulmonary function tests are mandatory before treatment.
• Consultation of an ear, nose and throat specialist should be considered, particularly in patients with involvement of the head and neck region.
• Since chemo- and radiotherapy can potentially cause permanent fertility damage, reproductive counselling (semen cryopreservation, ovarian tissue/function preservation) should be offered to young patients of both genders before treatment.

limited stage patients

Combined modality treatment consisting of a brief chemotherapy followed by radiotherapy was shown to result in superior tumour control compared with radiotherapy alone.

• Therefore, chemotherapy consisting of two or three cycles of adriamycin/bleomycin/vinblastine/dacarbazine (ABVD) (Table 2) followed by 30 Gy involved-field radiotherapy (IF-RT) is currently considered standard for limited stage HL [I, A].
• The question of whether radiotherapy can be omitted in selected patients is a matter of debate and could not be answered yet. Several trials addressing this issue are ongoing and evaluate whether treatment can be stratified on the basis of FDG-PET. However, none of these trials has been finally analysed to date.

intermediate stage patients

• Intermediate stage HL is usually treated with combined modality approaches.
• Four cycles of ABVD followed by 30 Gy IF-RT are widely considered standard for intermediate stage HL [I, A]. In patients up to age 60 years who are eligible for a more intensive treatment, this standard is currently challenged by
a protocol consisting of two cycles of bleomycin/etoposide/adriamycin/cyclophosphamide/vincristine/procarbazine/prednisone in escalated dose (BEACOPPescalated) (Table 3) followed by two cycles of ABVD and 30 Gy IF-RT. At 3 years, freedom from treatment failure (FFTF) with this new protocol was superior in comparison with four cycles of ABVD followed by 30 Gy IF-RT. However, long-term results including data on possible late toxicity (e.g. infertility) associated with the regimen are lacking.

Similar to limited stage HL, the question of whether radiotherapy is dispensable in selected patients could not be answered yet. Ongoing trials evaluate whether treatment might be stratified on the basis of FDG-PET, but none of the trials has been finally analysed.

advanced stage patients

- Advanced stage HL is usually treated with chemotherapy alone. Radiotherapy is confined to patients having large residual masses after chemotherapy.
- Patients up to age 60 years are treated with either six [complete remission (CR) after four cycles] or eight cycles [partial remission (PR) after four cycles] of ABVD or eight cycles of BEACOPPescalated followed by localized radiation with 30 Gy to residual lymphoma >1.5 cm [I–II, A]. Treatment with BEACOPPescalated leads to superior FFTF and overall survival (OS) rates but is associated with increased toxicity requiring granulocyte colony-stimulating factor (G-CSF) support.

relapsed cHL

- For most patients with refractory or relapsed HL, high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) can be regarded as treatment of choice [I, A].

Table 1.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>EORTC/GELA</th>
<th>GHSG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited stage patients</td>
<td>CS I–II without risk factors (supradiaphragmatic)</td>
<td>CS I–II without risk factors</td>
</tr>
<tr>
<td>Intermediate stage patients</td>
<td>CS I–II with ≥1 risk factors (supradiaphragmatic)</td>
<td>CS I, CS IIA with ≥1 risk factors</td>
</tr>
<tr>
<td>Advanced stage patients Risk factors</td>
<td>CS III–IV</td>
<td>CS IIB with risk factors C/D, but not A/B</td>
</tr>
<tr>
<td></td>
<td>(A) large mediastinal mass</td>
<td>(A) large mediastinal mass*</td>
</tr>
<tr>
<td></td>
<td>(B) age ≥50 years</td>
<td>(B) extranodal disease</td>
</tr>
<tr>
<td></td>
<td>(C) elevated ESR</td>
<td>(C) elevated ESR</td>
</tr>
<tr>
<td></td>
<td>(D) ≥4 nodal areas</td>
<td>(D) ≥3 nodal areas</td>
</tr>
</tbody>
</table>

GHSG, German Hodgkin Study Group; EORTC, European Organisation for Research and Treatment of Cancer; GELA, Groupe d’Etude des Lymphomes de l’adulte; CS, clinical stage.

*Large mediastinal mass: more than one-third of the maximum horizontal chest diameter.

Table 2. The ABVD regimen

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adriamycin</td>
<td>25 mg/m²</td>
<td>i.v.</td>
<td>1–15</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>10 mg/m²</td>
<td>i.v.</td>
<td>1–15</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>6 mg/m²</td>
<td>i.v.</td>
<td>1–15</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>375 mg/m²</td>
<td>i.v.</td>
<td>1–15</td>
</tr>
</tbody>
</table>

Recycle: day 29

Table 3. The BEACOPP escalated regimen

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin</td>
<td>10 mg/m²</td>
<td>i.v.</td>
<td>Day 8</td>
</tr>
<tr>
<td>Etoposide</td>
<td>200 mg/m²</td>
<td>i.v.</td>
<td>Days 1–3</td>
</tr>
<tr>
<td>Adriamycin</td>
<td>35 mg/m²</td>
<td>i.v.</td>
<td>Day 1</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>1250 mg/m²</td>
<td>i.v.</td>
<td>Day 1</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.4 mg/m²</td>
<td>i.v.</td>
<td>Day 8</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>100 mg/m²</td>
<td>p.o.</td>
<td>Days 1–7</td>
</tr>
<tr>
<td>Prednisone</td>
<td>40 mg/m²</td>
<td>p.o.</td>
<td>Days 1–14</td>
</tr>
<tr>
<td>G-CSF</td>
<td>s.c.</td>
<td></td>
<td>From day 8</td>
</tr>
</tbody>
</table>

Recycle: day 22.

- Patients >60 years old should be treated with six to eight cycles of ABVD followed by localized radiation with 30 Gy to residual lymphoma of >1.5 cm. BEACOPPescalated should not be used in elderly patients since increased toxicity has been observed in this age group [I–II, A].
- Treatment options in medically non-fit patients should be discussed individually.
- Ongoing trials aim to reduce treatment intensity without compromising efficacy. In most trials, interim FDG-PET is used to distinguish between those patients who can potentially be cured with reduced therapy and those who require standard or even more intensive treatment. This approach seems promising since some trials suggest that interim FDG-PET is a good predictor of treatment failure in patients with advanced HL treated with ABVD. However, treatment stratification on the basis of interim FDG-PET cannot be considered standard yet and further evidence from randomized trials is necessary.
Salvage regimens such as dexamethasone/high-dose ara-C/cisplatin (DHAP) or ifosfamide/gemcitabine/vinorelbine/dexamethasone (IGEV) are given to reduce the tumour burden and mobilize stem cells before high-dose chemotherapy and ASCT.

A subset of low-risk patients relapsing after primary treatment with two cycles of chemotherapy followed by radiotherapy can be successfully salvaged with a second, more intensive conventional chemotherapy such as BEACOPPescalated [IV, B].

In some patients with localized late relapse, salvage radiotherapy alone can be considered [IV, B].

There is no standard treatment for patients relapsing after high-dose chemotherapy and ASCT. The decision how to treat these patients has to be made individually.

Reduced-intensity conditioning allogeneic stem cell transplantation (RIC-allo) can be considered in young, chemosensitive patients in good general condition [II–III, B]. However, RIC-allo is no standard approach in HL and should be conducted within clinical trials.

In a palliative setting, acceptable remission rates, satisfying quality of life and prolonged survival can be achieved by gemcitabine-based chemotherapy and/or regional radiotherapy. Classical palliative chemotherapy approaches are increasingly challenged by novel agents such as small molecules, antibodies or immunotoxins. These drugs are currently being evaluated in clinical trials either as single agent or in combination with conventional chemotherapy. Patients who might benefit from such novel treatment strategies should be referred to centres participating in studies.

treatment of NLPHL

stage IA without risk factors

30 Gy IF-RT alone is the standard treatment for stage IA NLPHL patients without risk factors [III, A].

other stages

NLPHL is treated identically to cHL in all stages except for stage IA without risk factors.

relapsed NLPHL patients

In contrast to most cHL cases, the malignant cells of NLPHL are characterized by a strong expression of CD20. Therefore, localized NLPHL relapses can be effectively treated with rituximab alone [III, B].

NLPHL patients with more advanced relapses require a more aggressive salvage therapy possibly combined with rituximab.

response evaluation

Response evaluation should be done after four cycles and after completed chemo- or chemo-/radiotherapy. Physical examination, laboratory analysis and CT scans are mandatory. In studies with advanced stage patients, interim FDG-PET was shown to identify poor-risk patients. However, treatment stratification on the basis of interim PET should be reserved for clinical trials and cannot be considered standard. After completed treatment, positive PET scans may reveal persistent disease activity but false-positive PET scan has to be excluded.

follow-up

- History, physical examination and laboratory analysis including full blood cell count, ESR and blood chemistry should be performed every 3 months for the first half year, every 6 months until the 4th year and once a year thereafter [V, D].
- Additional evaluation of the thyroid function (TSH) after irradiation of the neck at 1, 2 and at least 5 years is recommended [III, A].
- CT scans and previously pathologic radiographic tests must be performed to confirm the remission status. Thereafter, they are indicated if suspicious clinical symptoms occur.
- PET is not recommended in routine follow-up of patients.
- Patients should be asked for symptoms indicating the existence of long-term toxicity, particularly of heart and/or lung.
- Cancer screening (e.g. mammography in irradiated patients) should be conducted regularly due to the increased risk of haematological and solid secondary malignancies after HL treatment.

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


