clinical practice guidelines

Newly diagnosed and relapsed follicular 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

- Follicular lymphomas are the second most frequent subtype of nodal lymphoid malignancies in Western Europe.
- The annual incidence of this disease has rapidly increased during recent decades and has risen from 2–3/100 000 during the 1950s to 5–7/100 000 recently.

staging and risk assessment

- Since treatment substantially depends on the stage of the disease, initial staging should be thorough particularly in the small proportion of patients with early stages I and II (5–10%) (Table 2). Initial work-up should include a computed tomography (CT) scan of the neck, thorax, abdomen and pelvis, and a bone marrow aspirate and biopsy. An additional positron emission tomography (PET) scan is not recommended according to the updated consensus [2]. In rare cases PET scan may be useful to confirm localized stage I/II [IV, C].
- A complete blood count, routine blood chemistry including lactate dehydrogenase (LDH) and uric acid as well as screening tests for human immunodeficiency virus (HIV) and hepatitis B and C are required.
- The staging is given according to the Ann Arbor system (Table 2) with mention of bulky disease, when appropriate.
- For prognostic purposes, a Follicular Lymphoma-specific International Prognostic Index (FLIPI, Table 3: >4 involved nodal sites, elevated LDH, age >60 years, advanced stage III/IV, hemoglobin <12 g/dl) should be determined [I, A] [3, 4]. A revised FLIPI2 (incorporating β2 microglobuline, diameter of largest lymph node, bone marrow involvement and hemoglobin level) has been recently suggested for patients requiring treatment [5].
- RNA expression analysis suggests a more favorable clinical course in cases with infiltrating T cells in comparison with cases with unspecific macrophage bystander cells [6]. However, this technique is not yet applicable in clinical routine, and immunohistochemistry studies have reported conflicting data recently.

diagnosis

- Diagnosis is only based on a surgical specimen/excisional lymph node biopsy. Core biopsies should only be performed in patients without easily accessible lymph nodes (e.g., retroperitoneal bulk), keeping in mind the possible heterogeneity of follicular lymphoma grading difficult to appreciate on core biopsies. Fine needle aspirations are inappropriate for a reliable diagnosis.
- The histological report should give the diagnosis according to the World Health Organization (WHO) classification. Grading of lymph node biopsies is performed according to the number of blasts/high power field (Table 1). Follicular lymphoma grade 3B (with sheets of blasts) is considered an aggressive lymphoma and treated alike (see clinical recommendation DLBCL) [1].
- When possible, additional biopsy material should be stored fresh frozen to allow additional molecular (currently still investigational) analyses.

RNA expression analysis suggests a more favorable clinical course in cases with infiltrating T cells in comparison with cases with unspecific macrophage bystander cells [6]. However, this technique is not yet applicable in clinical routine, and immunohistochemistry studies have reported conflicting data recently.

treatment plan

first line

stage I–II.

- In the small proportion of patients with limited non-bulky stages I–II, radiotherapy (involved or extended field, 30–36
Table 1. Grading of follicular lymphoma

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>≤5 blasts/high power field</td>
</tr>
<tr>
<td>2</td>
<td>6–15 blasts/high power field</td>
</tr>
<tr>
<td>3A</td>
<td>&gt;15 blasts/high power field, centroblasts with intermingled centrocytes</td>
</tr>
<tr>
<td>3B</td>
<td>&gt;15 blasts/high power field, pure sheets of blasts</td>
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Table 2. Ann Arbor classification

<table>
<thead>
<tr>
<th>Stage</th>
<th>Area of involvement</th>
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<tbody>
<tr>
<td>I (Ia)</td>
<td>One lymph node region or extralymphatic site (Ia)</td>
</tr>
<tr>
<td>II (Ib)</td>
<td>Two or more lymph node regions or at least one lymph node region plus a single localized extralymphatic site (IIb) on the same side of the diaphragm</td>
</tr>
<tr>
<td>III (IIIC, IIIs)</td>
<td>Lymph node regions or lymphoid structures (e.g. thymus, Waldeyer’s ring) on both sides of the diaphragm with optional localized extranodal site (IIIC) or spleen (IIIs)</td>
</tr>
<tr>
<td>IV</td>
<td>Diffuse or disseminated extralymphatic organ involvement</td>
</tr>
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</table>

Table 3. FLIPI risk factors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition of risk factors</th>
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<tbody>
<tr>
<td>FLIPI 1</td>
<td>FLIPI 2</td>
</tr>
<tr>
<td>Nodal sites</td>
<td>&gt;4 lymph node regions</td>
</tr>
<tr>
<td>Age</td>
<td>Above 60 years</td>
</tr>
<tr>
<td>Serum marker</td>
<td>Elevated lactate</td>
</tr>
<tr>
<td>stage</td>
<td>Advanced (III–IV)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>&lt;12 g/dl</td>
</tr>
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</table>

With 0–1 risk factors, low risk; 2, intermediate risk; 3–5, high risk.

In the majority of patients with advanced stage III and IV disease, no curative therapy is yet established. Since the natural course of the disease is characterized by spontaneous regressions in up to 25% of cases and varies significantly from case to case, therapy should be initiated only upon the occurrence of symptoms including B-symptoms, hematopoietic impairment, bulky disease, vital organ compression, ascites, pleural effusion or rapid lymphoma progression [I, A]. In four randomized trials an early initiation of therapy in asymptomatic patients did not result in any improvement of disease-specific survival or overall survival (OS) [9]. In a recent study, early initiation of rituximab resulted in improved progression-free survival (PFS; 80% vs 48%, P <0.001), but the benefit on long-term outcome has to be determined [10].

- If complete remission and long PFS are to be achieved, rituximab in combination with chemotherapy [such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), CVB (cyclophosphamide, vincristine and prednisone), purine analog-based schemes: FC (fludarabine and cyclophosphamide) or FM (fludarabine and mitoxantrone) or Bendamustine] should be used [I, B] [11]. In cases with (histologically or clinically) suspected transformation to aggressive lymphoma, an anthracycline-based regimen should be preferred. Four prospective first-line trials and two salvage trials as well as a systematic meta-analysis confirmed an improved overall response, PFS and OS when rituximab was added to chemotherapy (Table 4) [12–16].

- Antibody monotherapy (rituximab, radioimmunotherapy) or chlorambucil plus rituximab remains an alternative in patients with low risk profile or contraindications for a more intensive chemoimmunotherapy [III, B] [17, 18].

- In hepatitis B patients, specific recommendations (HBV monitoring, antiviral therapy) should be followed [19].

consolidation/maintenance.

- Meta-analysis of the pre-rituximab era suggests a potential benefit of interferon-α maintenance therapy that has to be balanced against toxicity [20].

- Rituximab maintenance for 2 years improves PFS (75% vs 58% after 3 years, P <0.0001) [I, B] [21].

- Radioimmunotherapy consolidation prolongs PFS after chemotherapy but its benefit following rituximab combinations has not been established [I, B] [22].

- Myeloablative radiochemotherapy followed by autologous stem cell transplantation prolongs PFS but not OS in four randomized trials and therefore represents no standard of care outside of trials [I, A] [23–26].
relapsed disease

- A repeated biopsy is strongly recommended to rule out a secondary transformation into aggressive lymphoma.
- Selection of salvage treatment depends on efficacy of prior regimens. In early relapses (<12 months), a non-cross-resistant scheme should be preferred (e.g. Bendamustine after CHOP or vice versa). Rituximab should be added if the previous antibody-containing scheme achieved >6–12 months duration of remission [IV,C].
- Radioimmunotherapy represents an effective therapeutic approach especially in elderly patients with co-morbidities not appropriate for chemotherapy. Otherwise, it should be applied preferably as consolidation [27].
- Rituximab maintenance for up to 2 years has a favorable side effect profile and, based on a systematic meta-analysis, substantially prolongs PFS and OS in relapsed disease even after antibody-containing induction in patients who have not received antibody as first-line therapy [I, A] [28].
- High-dose chemotherapy with autologous stem cell transplantation prolongs PFS and OS and should be especially considered in patients with short-lived first remissions after R-containing regimens, but its role has to be redefined in the rituximab era [I, B] [29, 30].
- In selected younger patients with high-risk profile, a potentially curative allogeneic stem cell transplantation

Table 4. Combined chemoimmunotherapy in follicular lymphoma (first line)

<table>
<thead>
<tr>
<th>Study</th>
<th>Total no. of patients</th>
<th>Median follow-up</th>
<th>Overall response</th>
<th>Time to treatment failure (months)</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marcus 2008 [14] R-CVP</td>
<td>321</td>
<td>53 months</td>
<td>81% (P &lt;0.0001)</td>
<td>27 (P &lt;0.0001)</td>
<td>83% (4 years)</td>
</tr>
<tr>
<td>Hiddemann 2005 [12] R-</td>
<td>428</td>
<td>58 months</td>
<td>96%</td>
<td>NR (P &lt;0.001)</td>
<td>90% (2 years)</td>
</tr>
<tr>
<td>CHOP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herold 2007 [13] R-MCP</td>
<td>201</td>
<td>48 months</td>
<td>92% (P = 0.0009)</td>
<td>NR (P &lt;0.001)</td>
<td>87% (P = 0.0096)</td>
</tr>
<tr>
<td>Salles 2008 [15] R-CHVP-Ifn</td>
<td>558</td>
<td>60 months</td>
<td>81% (P = 0.055)</td>
<td>NR (P &lt;0.001)</td>
<td>(high FPLIPI: P = 0.025)</td>
</tr>
<tr>
<td>Rummel 2009 [11]</td>
<td>279</td>
<td>34 months</td>
<td>92.7%</td>
<td>NR</td>
<td>84% (4 years)</td>
</tr>
</tbody>
</table>

P, significance levels in comparison with chemotherapy only.

Table 5. Recommended treatment strategies outside of clinical studies

<table>
<thead>
<tr>
<th>Low tumor burden</th>
<th>High tumor burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I/II</td>
<td>Stage III/IV (≤65 years)</td>
</tr>
<tr>
<td>Radiotherapy (involved field) 30–36 Gy</td>
<td>Watch and wait</td>
</tr>
<tr>
<td>In selected cases: watchful waiting</td>
<td>In symptomatic cases: consider rituximab monotherapy</td>
</tr>
</tbody>
</table>

Relapse/progress

Chemoimmunotherapy (e.g. R-CHOP, R-CVP, BR) | Chemoimmunotherapy (e.g. R-CHOP, R-CVP, BR, FC) | Dependent on first-line regimen and remission duration: Chemoimmunotherapy: e.g. BR, R-CHOP, R-FC Discuss high dose consolidation with autologous ASCT Rituximab maintenance (single application every 3 months, up to 2 years) Alternatively radioimmunotherapy In selected cases: discuss allogeneic transplantation | Dependent on first-line regimen and remission duration: Chemoimmunotherapy: e.g. BR, R-CHOP, R-FC Rituximab maintenance (single application every 3 months, up to 2 years) Alternatively radioimmunotherapy |

| Study Total no. of patients Median follow-up Overall remission Time to treatment failure (months) Overall survival |
|------------------------|------------------|------------------|------------------|------------------------------------|-----------------|
| Marcus 2008 [14] R-CVP | 321 | 53 months | 81% (P <0.0001) | 27 (P <0.0001) | 83% (4 years) (P = 0.029) |
| Hiddemann 2005 [12] R-CHOP | 428 | 58 months | 96% | NR (P <0.001) | 90% (2 years) (P = 0.0493) |
| Herold 2007 [13] R-MCP | 201 | 48 months | 92% (P = 0.0009) | NR (P <0.001) | 87% (P = 0.0096) (high FPLIPI: P = 0.025) |
| Salles 2008 [15] R-CHVP-Ifn | 558 | 60 months | 81% (P = 0.055) | NR (P <0.001) | 84% (4 years) |
| Rummel 2009 [11] | 279 | 34 months | 92.7% | NR | |
response evaluation

- Adequate radiological tests should be performed midterm and after completion of chemotherapy. Patients with insufficient or lacking response should be evaluated for early salvage regimens.
- PET scan-CT to evaluate response quality remains investigational in this disease, until future study confirms its predictive value [33].
- Minimal residual disease (MRD) analysis at the end of the treatment has some prognostic impact, but should not guide therapeutic strategies outside of clinical studies [34].

follow-up

The following recommendation are based on consensus rather than on evidence:

- History and physical examination every 3 months for 2 years, every 4–6 months for an additional 3 years, and subsequently once a year with special attention to transformation and secondary malignancies including secondary leukemia [V, D].
- Blood count and routine chemistry every 6 months for 2 years, then only as needed for evaluation of suspicious symptoms.
- Evaluation of thyroid function in patients with irradiation of the neck at 1, 2 and 5 years.
- Minimal adequate radiological or ultrasound examinations every 6 months for 2 years and annually thereafter. Regular CT scans are not mandatory outside of clinical trials.
- MRD screening may be performed in clinical studies but should not guide therapeutic strategies.

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 expert authors and the ESMO faculty.

literature

12. Hiddemann W, Krebs M, Dreyling M et al. Front-line therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) significantly improves the outcome of patients with advanced stage follicular lymphomas as compared to CHOP alone—results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG). Blood 2005; 106: 3725–3732.


