incidence

- Follicular lymphomas present the second most frequent subtype of nodal lymphoid malignancy 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.

diagnosis

- Diagnosis should always be 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). Fine-needle aspiration is inappropriate for a reliable diagnosis.
- The histological report should give the diagnosis according to the WHO classification. Grading is performed according to the number of blast per high-power field (grade 1–2: ≤15 blasts, grade 3: >15 blasts). Follicular lymphoma grade 3B (with sheets of blasts) is considered an aggressive lymphoma and treated alike (see Clinical Practice Guidelines for diffuse large B-cell lymphoma).
- When possible additional biopsy material should be stored fresh frozen to allow additional molecular (currently still scientific) analyses.

staging and risk assessment

- Since treatment depends substantially on the stage of the disease initial staging should be thorough particularly in the small proportion of patients with early stages I and II (15%–20%). Initial work-up should include a CT scan of the neck, thorax, abdomen and pelvis, and a bone marrow aspirate and biopsy. An additional PET is not recommended according to the updated consensus except in rare cases to confirm localized stage I/II disease [IV, C].
- A complete blood count, routine blood chemistry including lactate dehydrogenase (LDH) and uric acid as well as screening tests for HIV and hepatitis B and C are required.
- The staging is given according to the Ann Arbor system with mention of bulky disease.
- For prognostic purposes, a Follicular Lymphoma-specific International Prognostic Index (FLIPI: >4 envolved nodal sites, elevated LDH, age >60 years, advanced stage III/IV, haemoglobin <12 g/dl) should be determined [I, A]. A revised FLIPI2 (incorporating β2 microglobulin, diameter of largest lymph node, bone marrow involvement and haemoglobin level) has recently been suggested.
- RNA expression analysis suggests a more favourable clinical course in cases with infiltrating T-cells in comparison with cases with non-specific macrophage bystander cells. However, this technique is not yet applicable in clinical routine.

first line

stage I–II.

- In the small proportion of patients with limited stages I–II, radiotherapy (involved or extended field, 30–40 Gy) is the preferred treatment having a curative potential [II, B].
- In patients with large tumour burden systemic therapy as indicated for advanced stages may be applied before radiation [IV, B].
• stage III–IV. 

Induction: 
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 regression in up to 25% of cases and varies significantly from case to case, chemotherapy should be initiated only upon the occurrence of symptoms including B symptoms, haematopoietic impairment, bulky disease, vital organ compression, ascites, pleural effusion or rapid lymphoma progression [I, A]. In four randomized trials early initiation of therapy in asymptomatic patients did not result in any improvement of disease-specific or overall survival. 

• If complete remission and long progression-free survival (PFS) is to be achieved, rituximab in combination with chemotherapy [such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), CVP, purine analogue-based schemes: FC or FM, bendamustin] should be applied [I, B]. Four prospective first-line trials and two salvage trials as well as a systematic meta-analysis confirmed an improved overall response, PFS and overall survival when rituximab was added to chemotherapy. 

• Antibody monotherapy (rituximab, radioimmunotherapy) or single-agent alkylators remain an alternative in patients with a low risk profile or contraindications for a more intensive immunochemotherapy [III, B]. 

• Consolidation/maintenance. Meta-analysis of the pre-rituximab era suggests a limited benefit of interferon-α maintenance therapy that has to be balanced against toxicity. 

• Rituximab maintenance for 2 years improves PFS [I, B]. 

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

• Myeloablative radiochemotherapy followed by autologous stem cell transplantation prolonged PFS but not overall survival in four randomized trials and therefore represents no standard of care outside of trials [I, A]. 

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. fludarabine after CHOP). Rituximab should be added if the previous antibody-containing scheme achieved a >6-month duration of remission [IV, C]. 

• Radioimmunotherapy represents an effective therapeutic approach especially in elderly patients with comorbidities not appropriate for chemotherapy. Otherwise, it should be applied preferably as consolidation. 

• Rituximab maintenance for up to 2 years has a favourable side-effect profile and based on a systematic meta-analysis, substantially prolongs PFS and overall survival in relapsed disease even after antibody-containing induction [I, A]. 

• Myeloablative consolidation followed by autologous stem cell transplantation prolongs PFS and overall survival but its role has to be redefined in the rituximab era [I, B]. 

• A potentially curative allogeneic stem cell transplantation (optionally with dose-reduced conditioning) may be discussed in relapsed disease. 

Response evaluation 
Adequate radiological tests should be performed mid-term and after completion of chemotherapy. Patients with insufficient or no response should be evaluated for early salvage regimens. 

Follow-up 
• History and physical examination every 3 months for 2 years, every 4–6 months for 3 additional years, and subsequently twice 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. 

• 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 


9. Hiddemann W, Kneba 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.


