

Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

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incidence

Follicular lymphomas present 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.

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 aspirations are inappropriate for a reliable diagnosis.

The histological report should give the diagnosis according to the World Health Organization classification. Grading is performed according to number of blast/high power field (grade 1–2: ≤15 blasts; grade 3: >15 blasts). Follicular lymphoma grade 3B (with sheets of blasts) is considered to be an aggressive lymphoma and treated as such (see clinical recommendation DLCL).

When possible additional biopsy material should be stored fresh frozen to allow additional molecular (currently still scientific) analyses.

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 (15–20%). Initial work-up should include a computed tomography (CT) scan of the neck, thorax, abdomen and pelvis, and a bone marrow aspirate and biopsy [IV, C]. An additional positron emission tomography (PET) scan is not recommended according to the updated consensus.

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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 mentioning of bulky disease.

For prognostic purposes, a Follicular Lymphoma-specific International Prognostic Index (FLIPI: >4 involved nodal sites, elevated LDH, age >60 years, advanced stage III/IV, hemoglobin <12 g/dl) should be determined [I, A].

treatment plan

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 with a curative potential [II, B].

In patients with large tumor burden systemic therapy as indicated for advanced stages may be applied prior to optional 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 regressions 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, hematopoietic impairment, bulky disease or rapid lymphoma progression [I, A].

If complete remission and long progression-free survival is to be achieved, rituximab in combination with chemotherapy (such as CHOP—cyclophosphamide, doxorubicin, vincristine, prednisone, CVP, purine analogue-based schemes: FC(M) or bendamustin) should be applied [I, B].

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

stage III–IV, consolidation

Meta-analysis suggests a limited benefit of interferon- α maintenance therapy, which has to be balanced against toxicity.

Rituximab maintenance is currently tested in first line therapy.

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

Myeloablative radiochemotherapy followed by autologous stem cell transplantation prolongs progression-free survival but remains investigational in first line therapy [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 >12 months duration of remission [IV, C].

Rituximab maintenance has a favourable side effect profile and substantially prolongs progression-free survival with a strong tendency towards improved overall survival in relapsed disease even after antibody-containing induction [I, A].

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

Radio-immunotherapy (preferable as consolidation) and 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 midterm and after completion of chemotherapy. Patients with insufficient or lacking 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 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.

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 experts and the ESMO faculty.

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