

Minimum Clinical Recommendations for diagnosis, treatment and follow-up of newly diagnosed follicular lymphoma

Incidence

- Follicular lymphomas present worldwide the second most frequent subtype of nodal lymphoid malignancies.
- The incidence of this disease has rapidly increased during recent decades and has risen from 2–3/100 000/year during the 1950s to more than 5–7/100 000/year recently.

Diagnosis

- Diagnosis should always be based on a surgical specimen/excisional lymph node biopsy providing enough material for fresh frozen and formalin-fixed samples [II, A]. To ensure adequate quality, immediate processing by an experienced pathology institute has to be guaranteed. Fine needle aspirations or core biopsies are inappropriate for a proper diagnosis and should only be used in the rare patients requiring emergency treatment.
- The histological report should give the diagnosis according to the World Health Organisation classification.

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 CT-scan of the thorax, abdomen and pelvis, and a bone marrow aspirate and biopsy [IV, C]. A complete blood count, routine blood chemistry including 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) has been recently recommended [III, B].

Treatment plan

Stage I

- In the small proportion of patients with limited stages I, radiotherapy is the treatment of choice with a curative potential. Radiotherapy should be performed as extended field irradiation [II, B].
- In selected patients with large tumor burden systemic therapy as developed for advanced stages may also be used [IV, B].

Stage II–IV

- In the large proportion 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 15–20% of cases and varies from case to case, chemotherapy should be initiated only upon the occurrence of symptoms including B-symptoms, hematopoietic impairments, bulky disease or lymphoma progression [II, B].
- If complete remission and long progression-free survival is to be achieved, rituximab in combination with chemotherapy (COP, CHOP and fludarabine-containing schemes such as FCM) should be considered [I, B]. Single agent fludarabine or chlorambucil remain an alternative [III, B]. In selected cases with contraindications for chemotherapy, antibody monotherapy alone may be discussed [II, B].

Consolidation

- Meta-analysis suggests a survival benefit with interferon- α as maintenance therapy that has to be balanced against toxicity. Rituximab prolonged progression-free survival in a randomized trial. Myeloablative radiochemotherapy followed by autologous stem cell transplantation remains investigational [I, B].
- Radio-immunotherapy and potentially curative allogeneic stem cell transplantation may be discussed especially in second and higher relapses.

Response evaluation

- Adequate radiological tests should be done after ever 2–3 cycles of therapy and after completion of chemotherapy. Patients with incomplete or lacking response should be evaluated for early salvage regimens.

Follow-up

- History and physical examination every 3 months for 2 years, every 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 at 3, 6, 12 and 24 months, then only as needed for evaluation of suspicious symptoms.
- Evaluation of thyroid function in patients with irradiation to the neck at 1, 2 and 5 years.

- Minimal adequate radiological or ultrasound examinations at 6, 12 and 24 months after end of 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 expert authors and the ESMO faculty.

Literature

1. Solal-Celigny P, Roy P, Colombat P et al. Follicular lymphoma international prognostic index. *Blood* 2004; 104: 1258–1265.
2. MacManus PM, Hoppe RT. Is radiotherapy curative for stage I and II low grade follicular lymphoma? Results of a long term follow-up study of patients treated at Stanford University. *J Clin Oncol* 1996; 14: 1282–1290.
3. Stuschke M, Hoederath A, Sack H. Extended field and total central lymphatic radiotherapy for early stages nodal centroblastic-centrocytic lymphoma: Results of a prospective multicenter study. *Cancer* 1997; 80: 2273–2284.
4. Horning SJ, Rosenberg SA. The natural history of initially untreated low-grade non-Hodgkin's lymphomas. *N Engl J Med* 1984; 311: 1471–1475.

5. Marcus R, Imrie K, Belch A et al. CVP chemotherapy plus Rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. *Blood* 2005; 105: 1417–1423.
6. Ghilmini M, Schmitz SF, Cogliatti SB et al. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly $\times 4$ schedule. *Blood* 2004; 103: 4416–4423.

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