# Therapy for patients with follicular lymphoma

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Follicular lymphoma (FL) is a heterogeneous disease, characterised biologically by t(14;18) translocation causing an over-expression of the bcl-2 protein, which inhibits apoptosis of the lymphoid tumour cells. Clinical stage, prognostic factors, such as the Follicular Lymphoma International Prognostic Index (FLIPI) [1], and histological grading are of help in choosing the best therapeutic option. During the course of the disease, 30–70% of indolent FL cases transform to aggressive lymphoma [2]. New data on the clinical importance of immune cells, such as T-cells, in the micro-environment of the tumour may affect the outcome and might be valuable in developing new biological therapies [3].

Patients with advanced FL (stage III–IV) are usually not treated until symptoms appear (wait-and-watch policy). Initial treatment has often consisted of an alkylating agent, such as chlorambucil, alone or in combination with prednisone, with a response rate of 50–60% [4,5]. Cyclophosphamide is usually used in combination therapy, such as CVP (cyclophosphamide, vincristine (Oncovin), prednisolone), or for patients with high tumour burden in CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) or CHOP-like regimens. CHOP or CHOP-B (cyclophosphamide, doxorubicin, vincristine, prednisone, bleomycin) showed a better response quality than chlorambucil/prednisone or single cyclophosphamide, respectively, as first-line treatment in patients with low-grade lymphoma, but without prolonged survival [5,6]. A high response rate has been reported with fludarabine alone and in combination with other cytostatic drugs, such as mitoxantrone and corticosteroids, or with cyclophosphamide the response rate increases [7,8]. The impact on survival with these drug combinations is, however, uncertain. Resistance to chemotherapy tends to increase over time, with lower response rates and duration of response after each new treatment. Therefore, high-dose chemotherapy with autologous transplantation has been used in young patients who relapse or show evidence of transformation. However, few patients are cured even with intensive therapy, which also has late myelotoxic side-effects; thus allogeneic transplantation is sometimes an alternative for young patients.

A great improvement in therapeutic options for FL has been achieved with the use of the chimeric monoclonal anti-CD20 antibody rituximab. In pre-clinical studies, rituximab was shown to induce complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC) and direct apoptosis of $CD20^+$ B-lymphocytes. Rituximab has also been shown to sensitise drug-resistant human B-cell lymphoma cell lines to the cytotoxic effects of chemotherapeutic agents. The clinical effect of the antibody was first shown in patients with relapsing FL. In the pivotal study, including 166 patients, the objective response rate was 48%, with 6% complete responses (CRs), with a median progression-free survival of approximately 13 months in responding patients [9]. Later phase II and III trials have shown that a prolonged course of rituximab alone or combination with chemotherapy could further enhance the efficacy. The combination of rituximab with CVP, CHOP or fludarabine combinations has been shown to extend both progression-free (PFS) and overall survival (OS) when used as first-line and/or second-line therapy in randomised phase III trials [10–12]. There is insufficient data to decide which particular chemotherapy to combine with rituximab, although in one randomised trial a higher CR rate was seen with R-FM (rituximab, fludarabine, mitoxantrone) compared with R-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) [13]. Common side-effects of rituximab are transient fevers, chills, mild hypotension and hypoxia, urticaria or other rash, which are mostly seen only with the first rituximab infusion.

The combination of rituximab with chemotherapy has the disadvantage of being myelotoxic. Another approach to augment the activity of rituximab is therefore combination with biologicals, such as interferon-α2a (IFN-α2a), interleukins and growth factors [14]. IFN, a cytokine with anti-proliferative, antiviral and immunomodulatory effects, has shown response rates of 30–50% as a single agent in FL and has been shown to increase response rate and progression-free survival when given in combination with chemotherapy or as single maintenance therapy after chemotherapy. An overall meta-analysis for survival showed a significant difference in favour of IFN-α2, when given in the

context of relatively intensive chemotherapy and at a relatively high dose [15]. Moreover, three out of the four randomised up-front trials with rituximab in combination with chemotherapy used IFN as maintenance therapy.

Rituximab has recently demonstrated benefit when used as maintenance therapy after effective induction in patients with relapsed FL. Four randomised phase III studies have investigated the benefit of rituximab maintenance therapy compared with observation alone [16,17]. In the European Organisation for Research and Treatment of Cancer (EORTC) 20981 Intergroup Study [17], patients with a CR or partial response (PR) after six cycles of CHOP or R-CHOP underwent a second randomisation to no further treatment (observation) or maintenance treatment with rituximab (375 mg/m$^2$ once every 3 months) until relapse or for a maximum of 2 years. Both induction treatment arms yielded similar PR rates, but a significantly higher CR rate with R-CHOP. In patients randomised to maintenance therapy, an advantage was observed both in PFS and OS compared with the observation arm. The benefit of rituximab maintenance for patients with first-line immunochemotherapy will be determined in ongoing randomised studies.

Achievement of a molecular remission has been shown to be associated with prolonged clinical remission in FL after autologous transplantation and, in a few cases, following single rituximab as first-line treatment of indolent lymphomas. Data on the evaluation of minimal residual disease during maintenance therapy are lacking.

Despite the ability of immunochemotherapy to induce high response rates, and a suggested improvement in survival in patients with FL, the pattern of continuous relapse remains problematic. The best schedule and length of therapy, as well as the long-term effects of rituximab maintenance treatment, need to be evaluated. New monoclonal antibodies and radioimmunoconjugates are under development, but it has not yet been determined which subgroups of patients will benefit most from treatment with these. Furthermore, other new drugs acting on the microenvironment of the lymphoma, such as lenalidomide, and idiotypic vaccination may be shown to have therapeutic activity.

## Conflict of interest statement

None declared.

## References


1 Solal-Celigny P, Roy P, Colombat P, *et al.* Follicular lymphoma international prognostic index. *Blood* 2004, **104**, 1258–1265.

2 Lossos IS. Higher-grade transformation of follicular lymphoma – a continuous enigma. *Leukemia* 2005, **19**, 1331–1333.

3 Wahlin B, Sander B, Christensson B, Kimby E. CD8+ T-cell content in diagnostic lymph nodes measured by flow cytometry is a predictor of survival in follicular lymphoma. *Clin Cancer Res* 2007, **13**, 388–397.

4 Gallagher CJ, Gregory WM, Jones AE, *et al.* Follicular lymphoma: prognostic factors for response and survival. *JCO* 1986, **4**, 1470–1480.

5 Kimby E, Bjorkholm M, Gahrton G, *et al.* Chlorambucil/prednisone vs. CHOP in symptomatic low-grade non-Hodgkin's lymphomas: a randomised trial from the Lymphoma Group of Central Sweden. *Ann Oncol* 1994, **5**, 67–71.

6 Peterson BA, Petroni GR, Frizzera G, *et al.* Prolonged single-agent versus combination chemotherapy in indolent follicular lymphomas: a study of the cancer and leukemia group B. *J Clin Oncol* 2003, **21**, 5–15.

7 Liu Q, Fayad L, Cabanillas F, Hagemeister FB. Improvement of overall and failure-free survival in stage IV follicular lymphoma: 25 years of treatment experience at The University of Texas MDA Cancer Center. *J Clin Oncol* 2006, **24**, 1582–1589.

8 Hagenbeek A, Eghbali H, Monfardin S, *et al.* Phase III Intergroup study of fludarabine phosphate compared with cyclophosphamide, vincristine, and prednisone chemotherapy in newly diagnosed patients with stage III and IV low-grade malignant non-Hodgkin"s lymphoma. *J Clin Oncol* 2006, **24**, 1590–1596.

9 McLaughlin P, Grillo-López AJ, Link BK, *et al.* Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *J Clin Oncol* 1998, **16**, 2825–2833.

10 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.

11 Hiddemann W, Kneba M, Dreyling MH, *et al.* Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German LGL Study Group. *Blood* 2005, **106**, 3725–3732.

12 Schulz H, Bohlius JF, Trelle S, *et al.* Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: a systematic review and meta-analysis. *J Natl Cancer Inst* 2007, **99**, 706–714.

13 Zinzani PL, Pulsoni A, Porotti, *et al.* Fludarabine plus mitoxantrone with and without rituximab versus CHOP with and without rituximabas frontline treatment for patients with follicular lymphoma. *J Clin Oncol* 2004, **343**, 1750–7.

14 Kimby E. Beyond immunochemotherapy: combinations of rituximab with cytokines IFN-α2a and G-CSF. *Sem Oncol* 2002, **29**, 7–10.

15 Rohatiner AZ, Gregory WM, Peterson B, *et al.* Meta-analysis to evaluate the role of interferon in follicular lymphoma. *J Clin Oncol* 2005, **23**, 2215–2223.

16 Ghielmini M, Hsu 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 ×4 schedule. *Blood* 2004, **103**, 4416–4423.

17 Oers MHJ, Klasa R, Marcus RE, *et al.* Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin's lymphoma, both in patients with and without rituximab during induction: results of a prospective randomized phase III intergroup trial. *Blood* 2006, **108**, 3295–3301.