Is rituximab maintenance therapy useful following rituximab salvage in refractory or relapsed follicular lymphoma?

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A study by the German Low Grade Lymphoma Study Group has shown that rituximab maintenance following salvage with rituximab-containing chemotherapy is the standard of care for advanced-stage refractory or relapsed follicular lymphoma.

Rituximab maintenance therapy following chemotherapy for follicular lymphoma (FL) is the latest permutation in the application of anti-CD20 monoclonal antibody immunotherapy.

Studies of rituximab added to chemotherapy regimens including CVP (cyclophosphamide, vincristine and prednisolone), FCM (fludarabine, cyclophosphamide and mitoxantrone) and CHOP (vincristine, doxorubicin, prednisolone and cyclophosphamide) have revealed improvements in response rates, disease-free survival and overall survival in advanced-stage FL either initially or at relapse. Studies have now established that rituximab maintenance therapy after salvage chemotherapy, rather than traditional observation alone, also delivers substantial clinical benefit.

Forstpointner et al. report, on behalf of the German Low Grade Lymphoma Study Group (GLSG), the impact of rituximab maintenance following rituximab-FCM (R-FCM) therapy in patients with relapsed or refractory FL or mantle-cell lymphoma (MCL). Strikingly, the addition of rituximab maintenance resulted in marked prolongation of response duration in both lymphoma types, with the greatest impact seen in patients with FL (median response duration not reached vs 26 months for observation only; P=0.035). Whilst clearly beneficial compared with observation alone (median response duration 14 months vs 12 months; P=0.049), the results of rituximab maintenance in MCL are less marked than those achieved by aggressive chemotherapy regimens, such as rituximab plus Hyper-CVAD (fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone) alternating with rituximab plus methotrexate–Ara-C (cytarabine). The results reported by Forstpointner et al. in FL are, however, supported by similar recent findings from a European Organisation for Research and Treatment of Cancer Intergroup study, which randomised patients with recurring FL to salvage therapy with CHOP or rituximab-CHOP, followed by a second randomisation to observation or maintenance rituximab (as a single infusion every three months for two years).

The central finding in both the GLSG and the Intergroup studies is that a long-lasting advantage can be achieved with rituximab maintenance – even when the salvage regimens contained rituximab – resulting in the dual benefits of disease control and a reduction in the number of chemotherapy regimens required over time.

Furthermore, the study by Forstpointner et al. confirms the Intergroup findings of no discernable pattern of increased toxicity, promotion of resistant FL subclones or alteration in the

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Synopsis

R Forstpointner, M Unterhalt, M Dreyling et al. (2006) **Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients with recurring and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG).** *Blood 108:4003–4008*

Background. Treatment with a combination of rituximab and chemotherapy improves prognosis in patients with follicular lymphoma (FL) or mantle-cell lymphoma (MCL).

Objectives. To establish whether, in patients with recurrent or refractory FL or MCL, rituximab maintenance therapy is beneficial following induction of remission by rituximab in conjunction with a chemotherapy regimen.

Design. This prospective, phase III, randomised, open-label, multi-centre trial by the German Low Grade Lymphoma Study Group (GLSG) included adult patients with FL or MCL who had experienced lack of response to or relapse after chemotherapy and disease recurrence following autologous stem cell transplantation. Patients who had received rituximab as part of their chemotherapy regimen were not excluded. Women who were pregnant or lactating or who were of childbearing potential were excluded. Patients were enrolled between November 1998 and April 2005.

Intervention. Patients received an induction regimen consisting of the following: rituximab (375 mg/m^2 of body surface area) on day 0, fludarabine (25 mg/m^2/day) intravenously over 30 min. on days 1–3, cyclophosphamide (200 mg/m^2/day) as a 4 h infusion on days 1–3 and mitoxantrone (8 mg/m^2) intravenously over 30 min. on day 1 (R-FCM). A small number of patients received FCM alone. Patients in either group who then achieved a complete or partial response were randomised to rituximab maintenance therapy or to no further treatment. The patients who were randomised to rituximab maintenance received two courses of rituximab (four times weekly) 3 and 9 months after completion of salvage therapy.

Outcome measures. The effects of rituximab maintenance on the relative risk of relapse were studied.

Results. Of the 195 patients randomised to rituximab maintenance or no further treatment following response to R-FCM or FCM, reference histology showed 113 patients (58%) to have FL, 66 patients (34%) to have MCL and 16 patients (8%) to have other subtypes of lymphoma. Among the 176 evaluable patients, all patients in the rituximab maintenance arm had a longer duration of response than the patients who received no maintenance. The median response duration was estimated at 17 months for patients receiving no further treatment but was not reached for the group receiving rituximab maintenance ($P<0.001$). This benefit of rituximab maintenance remained when the analysis was restricted to patients who had received initial R-FCM therapy ($P=0.035$ for patients with FL and $P=0.049$ for patients with MCL). The percentages of patients alive at three years were estimated as 77% after rituximab maintenance therapy and 57% after no maintenance therapy ($P=0.100$). Median survival time had not been reached by the time of evaluation in either study arm. Rituximab-related side-effects were generally mild to moderate. One patient in the rituximab maintenance arm had a severe allergic reaction, requiring early discontinuation of rituximab.

Conclusions. Rituximab maintenance is a promising therapy for patients with MCL or FL.

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rates of large cell transformation or extra-nodal progression with rituximab maintenance.

Some questions do remain unanswered, including which rituximab maintenance schedules are most clinically efficacious. In addition, it is unknown whether rituximab maintenance will deliver the same rates of disease control when given after rituximab-containing frontline therapy. Similarly, the ability of patients to be successfully salvaged by chemotherapy and/or autologous stem cell transplantation if their disease progresses whilst on rituximab maintenance is entirely unknown.

The challenge now is to construct algorithms for cost-effective treatment that encompass these data. Useful risk stratification can be provided by the Follicular Lymphoma International Prognostic Index, which has shown applicability in determining the depth and durability of responses to chemotherapy alone and with rituximab. The addition of rituximab maintenance, however, seems to benefit patients across all subgroups of the prognostic index and flattens its detrimental prognostic impact, suggesting that rituximab maintenance may be of benefit in all patients despite their risk stratification at diagnosis or relapse.

Details of the references cited in this article can be accessed at www.cancerworld.org/cancerworld