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Improving the treatment outcome in follicular lymphoma using rituximab maintenance

"...maintenance treatment with rituximab should be considered for all [follicular lymphoma] patients responding to first-line therapy, as a new standard of care in previously untreated [follicular lymphoma] patients."

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Follicular lymphoma (FL) is the second most frequent lymphoma, representing approximately 70% of all indolent lymphomas and approximately 20% of all non-Hodgkin's lymphomas (NHLs) in adults [1]. Patients with FL usually have a long overall survival (OS) time, but disease progression typically occurs 3–5 years after initiation of treatment.

There is no commonly accepted standard frontline therapy for FL patients. For several years a broad range of therapeutic options were available; however, historical studies did not show a survival benefit of one particular regimen. The real progress in FL treatment has been made after the introduction of immunochemotherapy with rituximab, an anti-CD20 monoclonal antibody. The CD20 antigen is expressed on the surface of both normal and NHL B-cells, although it is in especially high density on FL tumor cells [2]. The addition of rituximab to standard polychemotherapy regimens such as cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) or cyclophosphamide, vincristine and prednisone (CVP), resulted in a significant increase in overall response (OR), complete response (CR) and time-to-progression (TTP) rates in FL [3–6]. In a study conducted by Hiddemann *et al.*, 428 patients with untreated, advanced-stage FL were randomly assigned to therapy with CHOP alone or CHOP combined with rituximab (R-CHOP) [7]. R-CHOP reduced the relative risk for treatment failure by 60% and significantly prolonged TTP ($p < 0.001$). In addition, patients treated with R-CHOP had a significantly higher OR rate (96 vs 90%; $p = 0.011$) and prolonged time of remission ($p = 0.001$), as well as superior OS ($p = 0.016$). In a large, randomized, multicenter study, the combination of rituximab with a CVP regimen (R-CVP) resulted in a significant increase in both OR and CR rates compared with patients treated with CVP alone (81 and 41 vs 57 and 10%, respectively; $p < 0.0001$) [8]. According to the current recommendations, immunochemotherapy with rituximab used in combination with CVP or CHOP regimens, but also with purine nucleoside analog-based schemes or bendamustine, should be applied in FL patients with progressive, symptomatic disease [9]. However, despite distinct progress in FL treatment, the disease still remains incurable.

Different maintenance regimens were assessed to provide means for improving progression-free survival (PFS) and OS of indolent NHL patients. Numerous randomized trials examined the benefit of IFN-α consolidation or maintenance therapies for indolent NHL, including FL [10,11]. In the Southwest Oncology Group (SWOG) study, 279 indolent lymphoma patients in advanced clinical stage III and IV, who responded to the induction treatment with prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide, mechlorethamine, vincristine and procarbazine (ProMACE-MOPP), were randomly assigned either to consolidation with IFN-α or to the observation

Table 1. Trials of rituximab maintenance therapy in indolent lymphoma.

Study (year)	No. of patients	Type of lymphoma	Induction treatment	Rituximab maintenance	Median follow-up	PFS, maintenance vs control	OS, maintenance vs control	Grade 3/4 infections maintenance vs control	Ref.
Salles *et al.* (2010)	1217	Untreated FL	R-CHOP, R-CVP, R-FCM	A single infusion every 8 weeks for 4 years	36 months	74.9 vs 57.6% p < 0.0001	26 vs 30 deaths p = NS	18 (4%) vs 5 (1%)	[11]
Hochster *et al.* (2009)	311[†]	Untreated FL, SLL	CVP	Weekly for 4 weeks every 6 months for 2 years	3.7 years	68 vs 33% p = 0.4	92 vs 86% p = 0.05	1 vs 1%	[12]
van Oers *et al.* (2010)	465	Relapsed/ resistant FL	CHOP vs R-CHOP	A single infusion every 3 months for 2 years	6 years	3.7 vs 1.3 years p < 0.001	5-year OS 74 vs 64% p = 0.07	9.7 vs 2.4% p = 0.01	[13]
Forstpointner *et al.* (2006)	195[‡]	Relapsed FL, MCL	FCM ± R	Weekly for 4 weeks at 3 and 9 months	26 months	Median not reached vs 17 months p < 0.001	3-year OS 77 vs 57% p = 0.1	4 vs 3%	[14]
Ghielmini *et al.* (2004)	185	Untreated/ relapsed FL	Rituximab	A single infusion every 2 months for four doses	35 months	EFS: 23 vs 12 months p = 0.02	NR	NR	[15]
Hainsworth *et al.* (2005)	114	Previously treated FL, SLL	Rituximab	Weekly for 4 weeks every 6 months for 2 years	41 months	31.3 vs 7.4 months p = 0.007	3-year OS 72 vs 68%	NR	[16]

[†]FL: 282 patients. [‡]FL: 113 patients, MCL: 57 patients.

CHOP: Cyclophosphamide, doxorubicin, vincristine, prednisone; CVP: Cyclophosphamide, vincristine, prednisone; EFS: Event-free survival; FCM: Fludarabine, chlorambucil, mitoxantrone; FL: Follicular lymphoma; MCL: Mantle-cell lymphoma; NR: No response; OS: Overall survival; PFS: Progression-free survival; R: Rituximab; SLL: Small-lymphocytic lymphoma.

arm [10]. No statistically significant differences in either PFS nor OS were noted between IFN-α-treatment and observatory groups at 4 years of follow up. Meta-analysis of the IFN-α maintenance therapy in FL suggests a benefit of this agent, especially longer remission duration for such treated patients [11]. By contrast, comparison of OS showed no advantage for IFN-α maintenance therapy and that the toxicity of this agent was not negligible. Thus, IFN-α maintenance is not generally approved for management in FL patients.

More recently, data concerning the use of rituximab in maintenance therapy for FL patients who responded to induction treatment were reported. Induction therapies included chemotherapy alone [12], chemotherapy combined with rituximab [13,14] or with rituximab alone (Table 1) [15,16]. These randomized trials documented longer PFS in patients receiving rituximab maintenance. Unfortunately, the studies failed to show a significant OS benefit of rituximab maintenance. A meta-analysis of randomized trials included analysis of 1143 adult FL patients treated in five trials. Of these, 985 patients were available for OS assessment [17]. Interestingly, previously treated FL patients (refractory or relapsed) were found to have a survival benefit from the rituximab maintenance (HR = 0.58). By contrast, previously untreated patients had no survival benefit from such treatment. In addition, infection-related adverse events were significantly more frequent in the rituximab maintenance arm (HR = 1.99) [17].

Most recently, Salles *et al.* evaluated maintenance treatment with rituximab in patients with grade 1, 2 and 3A FL after first-line therapy with rituximab and chemotherapy regimens, known as the PRIMA study [18]. In this multicenter international study, 1217 patients with grade 1, 2 or 3A FL requiring systemic therapy were assessed. Almost 80% of these patients had advanced disease with intermediate- or high-risk scores according to validated Follicular Lymphoma International Prognostic Index (FLIPI). They received one of the three nonrandomized immunochemotherapy induction regimens commonly used in routine practice. The majority of them (75%) were treated with six courses of R-CHOP (885 patients), 272 (22%) patients received eight cycles of R-CVP and 45 (3%) of them received six cycles of R-FCM (rituximab, fludarabine, cyclophosphamide and mitoxantrone) regimen induction. Patients who obtained CR or partial response (PR; overall 1018 patients) were randomly assigned, in equal proportions, to receive rituximab maintenance therapy at a dose of 375 mg/m^2 every 8 weeks for a total period of 24 months (505 patients) or to the observation arm (513 patients). With a median follow-up of 36 months from randomization, PFS (primary end point of the study) and time to next antilymphoma treatment were significantly longer in patients

who received rituximab maintenance in comparison with those from the observation-only group. Namely, at 3 years from randomization, patients maintained on rituximab had significantly longer PFS (74.9%; 95% CI: 70.9–78.9), than patients from the observation arm (57.6%; 95% CI: 53.2–62·0) (HR 0.55; 95% CI: 0.44–0.68; p < 0.0001). Maintenance with rituximab reduced the risk of lymphoma progression by 50% (HR = 0.5; 95% CI: 0.39–0.64; p < 0.0001). Moreover, in the rituximab maintenance group, a significant reduction in the risk of starting a new antilymphoma treatment (p = 0.0001) or starting a new course of chemotherapy (p = 0.0004) was noticed. Importantly, more patients who were in PR before randomization converted to CR or unconfirmed CR after 2 years of the rituximab maintenance (52%), compared with patients from the observation group (30%; p = 0.0001). After 2 years from randomization, 361 patients (71.5%) on rituximab maintenance were in CR or unconfirmed CR in comparison with 268 patients (52·2%) on observation only (p = 0·0001).

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Detailed analysis showed improvements in all age subgroups, FLIPI risk scores, induction immunochemotherapy regimens and quality of responses to induction treatments in the rituximab maintenance arm. However, OS did not differ significantly between examined groups (HR = 0.87; 95% CI: 0.51–1.47). To date, the toxicity of rituximab maintenance seems to be acceptable; however, adverse events were more frequent in patients maintained on rituximab. Grade 3 and 4 adverse events were observed in 24% of the patients in the rituximab maintenance and 17% in the observation groups (HR = 1.46; 95% CI: 1.14–1.87; p = 0.0026). Similarly, grade 2–4 infections were more common in the rituximab maintenance group (39%) than in the control group (24%; HR = 1.62; 95% CI: 1.35–1.96; p < 0·0001). Moreover, quality of life was evaluated at the end of maintenance treatment using adjusted Functional Assessment of Cancer Therapy-General (FACT-G). The adjusted FACT-G total scores in the rituximab maintenance group were 86.6 and 87.2 in the control arm. The European Organization for Research and Treatment of Cancer quality of Life group (EORTC QLQ-C30) global health status mean scores were also similar in both the study arms (75.5 and 75.2, respectively; p = 0.89) [18].

In summary, several previous trials have suggested that maintenance treatment with rituximab after induction therapy might improve results in patients with FL [17]. In our opinion, evidence from the PRIMA study, the largest clinical trial performed in FL patients to date, fully supports those findings. The PRIMA study is particularly important because rituximab maintenance therapy was introduced after induction with immunochemotherapy regimens in previously untreated patients, which has recently become a treatment of choice for patients with FL. The results from this trial should influence conclusively the favorable role of rituximab in maintenance therapy in FL.

On the other hand, the advantage of PFS in a rituximab maintenance group has to be balanced against higher toxicity, the potential of long-term adverse consequences, no difference in OS and no difference in the quality of life compared with responders to the frontline treatment from the observational arm. The survival data concerning OS is relatively immature and post-trial treatment with rituximab-containing therapies in the observational arm may cause difficulty in demonstrating a survival benefit in a longer follow-up. In addition, it is not known whether maintenance treatment has an advantage over re-treatment with rituximab-containing regimens upon relapse.

Longer observation of the patients analyzed in the PRIMA trial is particularly important because of the safety profile connected with prolonged B-cell depletion. In the PRIMA study, median serum immunoglobulin concentrations were similar in both rituximab maintenance and control arms at the end of 2 years. However, in a retrospective analysis of NHL patients treated with rituximab performed by Casulo *et al.* [19], hypogammaglobulinemia was noted in 39% of 215 patients who had normal baseline serum immunoglobulin levels. In this study, patients receiving rituximab maintenance had a significantly higher risk of developing hypogammaglobulinemia and 10% of them required intravenous immunoglobulin infusion. Available data also suggests an increased risk of progressive multifocal leukoencephalopathy in NHL patients treated with rituximab. Recent retrospective single-center cohort analysis indicated that inclusion of rituximab into standard chemotherapy regimens caused a significantly higher incidence of progressive multifocal leukoencephalopathy cases (rate difference, 2.2 every 1000 patient-years; 95% CI: 0.1–4.3) [20]. The risk of this complication and other rarer adverse events in patients receiving prolonged maintenance therapy with rituximab should be carefully monitored for the follow-up longer than that reported in the PRIMA study [18].

The long-term costs or cost–effectiveness of rituximab maintenance therapy in FL should also be taken into consideration. In the USA, the cost to Medicare of maintenance strategy according to the PRIMA protocol would be more than US$60,000 per patient [21]. On the

other hand, the French analysis showed that rituximab maintenance therapy may be a cost-effective strategy in the management of relapsed/refractory FL [22]. This study showed that the cost of rituximab therapy was partially offset by the lower cost of further patient management due to lower relapse rates, thus a longer period of disease-free survival.

Despite these limitations, the results of the PRIMA study indicate that rituximab maintenance in FL is efficacious and well tolerated. Thus, in our opinion, maintenance treatment with rituximab should be considered for all FL patients responding to first-line therapy, as a new standard of care in previously untreated FL patients.

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