

# The evaluation and optimal use of rituximab in lymphoid malignancies

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**Abstract:** Rituximab is an IgG1, chimeric monoclonal antibody (mAb) containing murine light- and heavy-chain variable-region sequences and human constant-region sequences. Rituximab targets the CD20 molecule expressed on normal and malignant B-lymphocytes. At present, rituximab is the most important mAb of clinical value in patients with B-cell lymphoid malignancies. Since approval in 1997, rituximab has become widely used in chronic lymphocytic leukemia (CLL), follicular lymphoma (FL), mantle cell lymphoma (MCL), and diffused large B-cell lymphoma (DLBCL) when combined with chemotherapy. Currently, rituximab is commonly combined with first-line chemotherapy for FL and should be offered as maintenance therapy to all appropriate patients with this disease. Randomized Phase III trials demonstrated the superiority of rituximab added to CHOP chemotherapy against CHOP chemotherapy alone in patients with DLBCL. Rituximab alone has limited activity in MCL but can be used in MCL in combination with chemotherapy, despite the benefits not being as impressive as when used against other lymphoma entities. In addition, for the less frequent B-cell lymphomas, small series show considerable activity for most of these entities. Fludarabine and rituximab combination therapies in CLL yielded promising results in several studies. Two large Phase III randomized trials demonstrated the superiority of chemoimmunotherapy with rituximab compared with chemotherapy alone in previously untreated and refractory/relapsed patients with CLL. Therefore, it can be concluded that rituximab, with only few exceptions, can generally be accepted as a standard component of anti B-cell non-Hodgkin's lymphoma therapies. In this review, the pharmacology, mode of action, pharmacokinetics, and current place in the therapy of B-cell lymphoid malignancies of rituximab are presented. In addition, an overview of studies conducted to date and optimal use of this drug, including timing and doses, is presented.

**Keywords:** chronic lymphocytic leukemia, combined therapy, rituximab, DLBCL, follicular lymphoma, NHL, side effects, pharmacokinetics

## Introduction

Lymphoid malignancies comprise a heterogeneous group of disorders originating from clonal proliferation of B or T lymphocytes.<sup>1</sup> B-cell lymphoid malignancies are more common than T-cell neoplasms, accounting for approximately 85%–90% of all non-Hodgkin's lymphomas (NHL).<sup>2</sup> The incidence of NHL has been increasing steadily over the past several decades. At present it is the fifth most common cancer in the US, with an estimated 66,360 new cases and 19,320 deaths.<sup>3</sup> The most common subtypes of B-cell NHL are diffused large B-cell lymphoma (DLBCL) and follicular lymphoma (FL).<sup>4</sup> DLBCL accounts for approximately 30% of all new diagnosed cases and more than 80% of aggressive lymphomas. FL is the second most common

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lymphoma, representing approximately 70% of all indolent lymphomas and 22% of all lymphomas.<sup>5</sup> In addition, mantle cell lymphoma (MCL) is a distinct disease entity in the WHO classification of malignant neoplasms, and comprises 7% of NHLs.<sup>4</sup>

In DLBCL, the era of mAbs has transformed treatment practices and R-CHOP (rituximab plus cyclophosphamide, adriamycin, vincristin, prednisone) is now the new standard of care.<sup>6</sup> Patients with FL can have long survival times, but disease progression typically occurs 3–5 years after initial treatment, and there is no universally accepted standard front-line therapy. A broad range of therapeutic options is available, but historical studies have not shown a survival benefit of one regimen over another. However, the addition of rituximab to chemotherapeutic combinations (CVP – cyclophosphamide, vincristin, prednisone; CHOP) has resulted in a significant increase in overall response (OR) rate, complete response (CR) rate, and progression free survival (PFS).<sup>7</sup>

Chronic lymphocytic leukemia (CLL) is a clonal disease characterized by proliferation and accumulation of small CD5 positive B-cells. It is the most common form of leukemia in the Western world with an annual incidence rate of three to five cases per 100,000.<sup>8</sup> The management of CLL is determined by the stage, activity of the disease age, and comorbidities. For many years, chlorambucil has been the drug of choice in previously untreated patients with CLL.<sup>9,10</sup> Subsequently, purine nucleoside analogs (PNAs) – fludarabine (FA), cladribine (2-CdA, 2-chlorodeoxyadenosine), and pentostatin (DCF, 2'-deoxycoformycin) have been introduced for the treatment of this disease and have become standard drugs for the majority of patients. Significantly higher OR, CR, and a longer PFS in patients with CLL treated with FA or 2-CdA were confirmed in randomized, multicenter trials.<sup>11,12</sup> Cyclophosphamide (CY) was the cytotoxic agent most frequently combined with PNA. The higher efficacy of FA combined with cyclophosphamide (FC) compared with FA alone was confirmed in randomized trials in treatment naïve patients.<sup>13</sup> Cladribine combined with CY (CC) is similarly active in previously untreated CLL patients.<sup>14</sup> Several randomized trials indicate that chemotherapy alone does not prolong the survival time of CLL patients.<sup>9–13</sup> Several recent reports have suggested that in patients with CLL, rituximab combined with PNA, or PNA, and cyclophosphamide may improve the results with acceptable toxicity, both in previously untreated and refractory/relapsed patients.<sup>15,16</sup> At present, rituximab is the most important monoclonal antibody (mAb) of clinical value in patients with B-cell lymphoid malignancies.

## Pharmacology and mode of action

Rituximab (IDEC-C2B8; Mabthera®, Roche, Basel, Switzerland; Rituxan®, Biogen Idec, San Diego and Genentech, Inc, San Francisco, CA) is an IgG1, chimeric mAb containing murine light- and heavy-chain variable region sequences and human constant region sequences. Rituximab targets the CD20 molecule, expressed on normal and malignant B-lymphocytes.<sup>18</sup> The variable murine region of rituximab binds specifically to the CD20 antigen. The CD20 (B1) antigen is a 33–35 kDa integral membrane protein expressed on the surfaces of non-malignant and most malignant B cells<sup>19</sup> consisting of cytoplasmic N- and C-termini and four hydrophobic regions for anchoring the molecule in the membrane. Some evidence indicates that CD20 might function as a calcium ion channel.<sup>20</sup> The intensity of CD20 antigen expression is lower on CLL cells than in patients with NHL and appears to correlate with the level of clinical response.<sup>21</sup> The characteristics that make CD20 a good target antigen include its relatively high level of expression and close location of the extracellular epitopes to the cell surface.<sup>20</sup> The CD20 circulating form has been detected in patients with CLL, Hodgkin's disease, and NHL, as well as in healthy individuals.<sup>22</sup>

## Mode of action

The variable murine region of rituximab binds specifically to the CD20 antigen. The Fc domain recruits the immune effect or functions to mediate B-cell lysis.<sup>18,23</sup> The anti-tumor activity of rituximab is attributed to complement dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), apoptosis, and possible direct growth arrest.<sup>24–26</sup> CDC and ADCC are considered the main effects. CDC involves fixation of the complement by the Fc portion of immunoglobulin and the subsequent activation of the complement cascade.<sup>27,28</sup>

ADCC is positively regulated by activating Fc receptors that are expressed on NK cells, macrophages, and dendritic cells. These two mechanisms are categorized into “immune-mobilizing” mechanisms or direct effects. It has been shown recently that human macrophages promote phagocytic killing of rituximab-opsonized CLL cells. In addition, accumulating evidence suggests that rituximab can also directly induce apoptosis.<sup>29</sup>

Rituximab preferentially inhibits the expression of the antiapoptotic gene products Bcl-2/Bcl-xL, X-linked inhibitor of apoptosis protein, and myeloid cell leukemia sequence 1 in B-cell NHL cells through downregulating the p38 mitogen-activated protein kinase (MAPK), nuclear factor (NF)-κB,

ERK-1/2, and Akt survival pathways.<sup>24</sup> In addition, rituximab enhances apoptosis by a caspase-independent mechanism.<sup>30</sup> Furthermore, rituximab sensitizes malignant B cells to the cytotoxic effects of chemotherapy.<sup>31</sup>

## Pharmacokinetics of rituximab

Several studies have analyzed the pharmacokinetics (PK) of rituximab in patients receiving four or eight doses of the antibody for the treatment of active, relapsed, or refractory NHL.<sup>32,33</sup> The results of these studies indicate that serum rituximab levels are highly variable in patients receiving similar doses. Rituximab pharmacokinetics are best described by a two-compartmental model, with mean half-lives of about 1.3 (distribution) and 19 days (elimination).<sup>17</sup> In a pivotal trial, PK assessment of rituximab was performed in 147 patients with relapsed or refractory indolent NHL treated with 4 weekly infusions of rituximab at 375 mg/m<sup>2</sup>.<sup>32,33</sup> The rituximab level increased throughout the course of treatment, reaching mean concentrations of 206 µg/mL after the first infusion and 465 µg/mL after the fourth infusion. The estimated half-life of rituximab increased from 76.3 hours after the first infusion to 205.8 hours after the fourth infusion, with a concomitant marked decrease in the antibody clearance.

In another study, in which rituximab was given in four consecutive weekly doses of 375 mg/m<sup>2</sup> to NHL patients, the serum concentration was seen to increase with each infusion from a median C<sub>max</sub> of 239 µg/mL after the first infusion to 460 µg/mL after the fourth one.<sup>34</sup> Levels of the drug remained detectable in the serum for up to 3–6 months following completion of treatment. Serum rituximab levels have been shown to be proportional to the antibody dose infused.<sup>35</sup> A receptor binding and saturation mechanism may be involved in the PK process. A study using noncompartmental analysis showed that from the first to the fourth infusion of rituximab, clearance decreased more than 4-fold and the half-life increased almost 3-fold in patients with NHL treated with weekly infusions of rituximab 375 mg/m<sup>2</sup>.<sup>33</sup> It is possible that these observations reflected depletion by rituximab of CD20-positive B-cells.<sup>32</sup> In addition, higher and more sustained serum levels were achieved after multiple doses than after single doses.<sup>36</sup> When the drug was administered at doses of 375 mg/m<sup>2</sup> weekly for 8 weeks, the median post-infusion serum levels peaked higher than in studies using only four doses.<sup>37</sup> However, a plateau was achieved after the sixth infusion. Moreover, higher mean serum antibody levels were observed in responders than in non-responders.<sup>33,34,38</sup>

The PK of rituximab have been characterized by wide inter-individual variability, with high serum drug concentrations appearing to correlate with the clinical response. In the study of Berinstein et al,<sup>33</sup> patient serum rituximab levels correlated inversely with the degree of tumor bulk and the number of circulating B cells before treatment. In one study, steady-state plasma concentrations of rituximab were reached after 6–8 weekly infusions.<sup>39</sup> However, in another study, Mangel et al<sup>40</sup> found no differences in pharmacokinetic parameters between patients who were in clinical remission and historical controls treated with rituximab who exhibited a tumor burden. They also found that the level of rituximab exposure is similar after four infusions in patients treated for minimal disease states and patients with active disease.<sup>40</sup> In addition, population pharmacokinetic studies by Regazzi et al<sup>39</sup> showed that the PK characteristics of rituximab are similar for autoimmune disorders and relapsed or refractory FL or MCL. These results indicate that the PK profile of this drug does not necessarily correlate with disease burden. The PK studies should allow the best dosing regimen to be defined for the optimal efficacy of rituximab in an individual patient.<sup>41</sup> Ternant et al<sup>42</sup> used pharmacokinetic–pharmacodynamic (PK–PD) modeling to design an optimized rituximab dose regimen in FL patients. They suggest a benefit of increasing doses of rituximab in FL, both during induction and maintenance. The model predicted a potential benefit of 1500 mg/m<sup>2</sup> maintenance doses of rituximab for both rituximab monotherapy and in R-CHOP combination. In addition, the authors have found that the PFS of FCGR3A-F carriers remains lower than that of homozygous FCGR3A-VV patients, even when higher rituximab doses were used. Few studies have investigated the pharmacokinetics of rituximab when administered with other drugs or at different intervals.<sup>42,43</sup> The PK profile of rituximab when administered as part of an R-CHOP chemotherapy was recently reported by Blasco et al.<sup>44</sup> They found that PK parameters were similar to those described for studies in the absence of chemotherapy. In addition, the authors did not observe any intra-subject variation in pharmacokinetic parameters over the treatment period. Rituximab is widely distributed to body organs, including heart, liver, lungs, spleen, and kidneys of patients with NHL. The drug is degraded in the liver and other organs by a process of nonspecific catabolism and is mainly excreted renally.<sup>45</sup> The proportion of radiolabeled rituximab excreted in the urine was 47.5%.<sup>45</sup>

## Side effects

Treatment with rituximab is usually well tolerated. However, infusion-related reactions occur in the majority of patients.

These adverse effects are usually of mild or moderate severity, and only 10% of patients have shown a severe infusion-related reaction which may be accompanied by fever, bronchospasm, hypotension, and angioedema. The symptoms are usually brief and occur during the first infusion.<sup>46</sup> Infusion-related adverse effects occur within the first 30 minutes to 2 hours of starting the first infusion, and are usually reversible with interruption or discontinuation of rituximab along with supportive care. In addition, patients may be susceptible to the development of human anti-mouse antibody (HAMA). However, in clinical practice HAMA and human anti-chimeric antibody are rarely detected.<sup>47</sup>

Several reports suggest that rituximab increases the risk of viral and bacterial infections due to prolonged impairment of antibody production. In a retrospective analysis of 215 NHL patients performed by Casulo et al,<sup>48</sup> patients receiving rituximab maintenance had a significantly higher risk of developing hypogammaglobulinemia, and 10% required intravenous immune globulin infusion for infection. Recent data indicates that rituximab increases the risk of hepatitis B virus reactivation (HBV in patients with resolved infection).<sup>49–51</sup> Elderly patients, particularly those without anti-HBs, seemed particularly at risk. However, the true incidence and mechanism of reactivation are still being elucidated and greater adherence to recommendations for screening and prophylaxis is necessary.

Problems with other viruses have also been reported in association with rituximab-containing regimens. Severe herpes virus reactivation including cytomegalovirus and varicella zoster has been reported in several patients.<sup>52</sup> Some reports have indicated that Parvovirus B19 with pure red cell aplasia and West Nile virus may be linked to treatment with rituximab,<sup>53,54</sup> in addition to progressive multifocal leukoencephalopathy (PML).<sup>55</sup> A lethal, progressive demyelinating disorder of the central nervous system (CNS) characterized by the destruction of oligodendrocytes due to the reactivation of the John Cunningham (JC) virus (a type of human polyoma virus). A review of literature published recently revealed that 57 cases of rituximab-associated PML had been reported to date, mostly in patients who had lymphoproliferative disorders.<sup>56</sup> Recent retrospective, monocentric cohort analysis indicates that inclusion of rituximab into standard chemotherapy regimens caused a significantly higher incidence of PML cases (rate difference, 2.2 every 1000 patient-years; 95% confidence interval: 0.1–4.3).<sup>55</sup> Importantly, a recent systematic review and meta-analysis of randomized controlled trials comparing rituximab combined with chemotherapy indicates that the addition of rituximab does not increase

the overall risk of severe infections nor increases the risk of dying as a consequence of infection.<sup>57</sup> However, the addition of rituximab to standard chemotherapy increases the risk of severe leukopenia and granulocytopenia.

## Overview of studies conducted to date in CLL and NHL

Rituximab was the first mAb approved in 1997 by the Food and Drug Administration (FDA) for the treatment of FL. Since approval, rituximab has become the standard of care in FL, CLL, and aggressive lymphomas when combined with chemotherapy. In addition, for the less frequent B-cell lymphomas, small series show considerable effectiveness for most of these entities. Therefore it can be concluded that rituximab, with only few exceptions, can today be generally accepted as a standard component of anti B-cell non-Hodgkin lymphoma (B-NHL) therapies.

## Rituximab in follicular lymphoma

There is no universally accepted standard frontline therapy for FL. A broad range of therapeutic options is available but historical studies have not shown a survival benefit of one regimen over another. However, the addition of rituximab to chemotherapeutic combinations (CHOP, CVP) has resulted in a significant increase in OR and CR rates, and time to progression (TTP). Rituximab in combination with chemotherapy improves PFS and OS compared to chemotherapy alone when used for induction therapy for patients with newly diagnosed or relapsed indolent lymphoma.<sup>58,59</sup> Currently, an immunochemotherapy regimen based on a combination of rituximab with chemotherapy such as CHOP, CVP, or purine analog-based schemes should be applied in FL patients with progressive, symptomatic disease.<sup>60</sup> In a large, randomized, multicenter study, the addition of rituximab to CVP (R-CVP) resulted in a significant increase in CR rate: 41% with rituximab versus 10% without.<sup>61</sup>

A number of promising trials have suggested that the addition of rituximab maintenance treatment after induction therapy might improve results in patients with FL. Induction therapies included chemotherapy alone,<sup>62</sup> chemotherapy with rituximab,<sup>63,64</sup> and rituximab alone (Table 1).<sup>65,66</sup> These randomized trials documented longer PFS in patients receiving rituximab maintenance therapy. Unfortunately, these trials have failed to demonstrate a survival benefit with maintenance rituximab. A meta-analysis of randomized trials included 1143 adult patients with FL for response duration and 985 patients for overall survival.<sup>67</sup> Previously treated patients had a survival benefit with rituximab



**Table I** Trials of rituximab maintenance therapy in indolent lymphoma

Study	No of pts	Type of lymphoma	Induction treatment	Rituximab maintenance	Median follow-up	PFS maintenance vs control	OS maintenance vs control
Salles et al <sup>68</sup>	1217	Untreated FL	R-CHOP R-CVP R-FCM	A single infusion every 8 wk for 4 y	36 m	74.9% vs 57.6% $P < 0.0001$	26 deaths vs 30 deaths $P = \text{NS}$
Hochster et al <sup>62</sup>	311*	Untreated FL, SLL	CVP	Weekly for 4 wk every 6 m for 2 y	3.7 y	68% vs 33% $P = 0.4$	92% vs 86% $P = 0.05$
van Oers et al <sup>63</sup>	465	Relapsed/resistant FL	CHOP vs R-CHOP	A single infusion every 3 m for 2 y	6 y	3.7 y vs 1.3 y $P < 0.001$	5-y OS 74% vs 64% $P = 0.07$
Forstpointner et al <sup>64</sup>	195**	Relapsed FL, MCL	FCM $\pm$ R	Weekly for 4 wk at 3 and 9 m	26 m	Median not reached vs 17 m $P < 0.001$	3-y OS 77% vs 57% $P = 0.1$
Ghielmini et al <sup>65</sup>	185	Untreated/relapsed FL	Rituximab	A single infusion every 2 m for 4 doses	35 m	EFS: 23 m vs 12 m $P = 0.02$	NR
Hainsworth et al <sup>66</sup>	114	Previously treated FL, SLL	Rituximab	Weekly for 4 wk every 6 m for 2 y	41 m	31.3 m vs 7.4 m $P = 0.007$	3-y OS 72% vs 68%

**Notes:** \*FL-282pts; \*\*FL-113pts, MCL-57pts.

**Abbreviations:** FL, follicular lymphoma; SLL, small lymphocytic lymphoma; MCL, mantle cell lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristin, prednisone; CVP, cyclophosphamide, vincristin, prednisone; FCM, fludarabine, chlorambucil, mitoxantrone; R, rituximab; m, months; y, years; wk, weeks; NS, no significant changes; NR, not reported.

maintenance treatment (hazard ratio: 0.58). Recently Salles et al<sup>68</sup> evaluated maintenance treatment with rituximab in patients with FL after first-line therapy with rituximab and chemotherapy regimens. This multicenter study, known as PRIMA, included 1217 patients with grade 1, 2, or 3A FL needing systemic therapy. They received one of three non-randomized immunochemotherapy induction regimens used in routine practice. Patients who obtained CR or PR were then randomly assigned to receive either rituximab maintenance therapy at a dose of 375 mg/m<sup>2</sup> every 8 weeks or observation. With a median follow-up of 36 months, the primary study endpoint, PFS from randomization, and time to next anti-lymphoma treatment were significantly longer in patients who received maintenance therapy with rituximab in comparison with the observation-only group. However, OS did not differ significantly between groups.

## Diffuse large B-cell lymphoma

Rituximab was originally used in relapsed/refractory DLBCL patients in monotherapy in a Phase II clinical trial.<sup>69</sup> Subsequently, several multicenter clinical trials have documented that the addition of rituximab to a standard CHOP regimen (R-CHOP) increases the efficacy of this first-line treatment, both in older (>60 years)<sup>70,71</sup> and younger<sup>72</sup> DLBCL patients (Table 2). Firstly, Vose et al<sup>74</sup> showed that six cycles of R-CHOP resulted in 89% of OR, including 56% CR. Subsequently, a randomized Phase III trial of GELA (Groupe d'Etudes des Lymphomes de l'Adulte) assessed

the effectiveness of eight courses of R-CHOP vs the same number of CHOP regimens in elderly DLBCL patients. Both R-CHOP and CHOP were given every 21 days. Patients treated with R-CHOP demonstrated a better OS than those from the CHOP arm (median OS not reached after 5 years, vs 3.1 years,  $P = 0.007$ ).<sup>70</sup> The CR rates and PFS were also higher in R-CHOP treated patients (76% vs 63% and 3.8 years vs 1.1 years, respectively). A further study, MInT (Mabthera International Trial), was addressed to low-risk DLBCL patients, younger than those in the GELA trial.<sup>73,75</sup> As in the GELA trial, they were randomly treated with either CHOP-like or R-CHOP-like regimens. Patients in the R-CHOP arm showed higher 3-year EFS (79% vs 59%,  $P < 0.0001$ ) and, most importantly, OS (93% vs 84%,  $P = 0.0001$ ).

Ongoing studies assess the effects of R-CHOP given every 14 days (R-CHOP-14) and every 21 days (R-CHOP-21). In the RICOVER-60 trial, Pfreundschuh et al<sup>72</sup> compared CHOP-14 and R-CHOP-14 regimens in elderly patients with DLBCL. The R-CHOP-14 program showed advantage over CHOP-14 in regard to PFS and OS. Eight courses of R-CHOP-14 did not improve the outcome (namely, 3-year EFS) compared to six cycles of this regimen (66.5% vs 63%, respectively). Moreover, any statistical advantage of R-CHOP-21 vs R-CHOP-14 was shown in elderly DLBCL patients.

High-dose chemotherapy (HDC) with autologous stem cell transplantation (ASCT) is actually a standard of care in the case of younger patients with relapsed/refractory DLBCL.<sup>76</sup> There are few non-randomized studies on the

**Table 2** Larger studies evaluating the efficacy of rituximab combined with first-line treatment or salvage chemotherapy in patients with DLBCL

Study	Treatment	Patients	OR	CR	Median TTF/PFS/ EFS	OS
Pfreundschuh et al <sup>72</sup>	6 vs 8 × R-CHOP-14 ± R	Untreated n = 1222 age 61–80	76% vs 63% P = 0.005	NR	3-year EFS: 6 × CHOP-14 vs 8 × CHOP 47.2% vs 53% 6 × CHOP-14 vs 8 × R-CHOP 66.5% vs 63.1%	3-year OS: 6 × CHOP-14 vs 8 × CHOP 67.7% vs 66.0% 6 × CHOP- 14 vs 8 × R-CHOP 78.1% vs 72.5%
Coiffier et al <sup>70</sup>	8 × R-CHOP vs 8 × CHOP	Untreated n = 399 age 60–80	82% vs 69% P < 0.05	72% vs 37% P = 0.005	EFS: 3.8 vs 1.1 years P < 0.001	Median OS not reached after 5 years vs 3.1 years P = 0.007
Pfreundschuh et al <sup>73,75</sup>	6 × CHOP-like vs 6 × R-CHOP-like	Untreated n = 824 age 18–60	NR	NR	3-year EFS: 79% vs 59% P < 0.0001 6-year EFS 56% vs 74% P < 0.0001	3-year OS: 93% vs 84% P = 0.00001
Kewalramani et al <sup>77</sup>	R-ICE vs historical ICE cohort	Relapsed/ refractory n = 36 vs 147 median age 45 vs 48	78% vs 71% P = 0.53	53% vs 27% P = 0.01	PFS at 2 years 54% vs 43%	OS after 2 years 67% vs 56% (ns)
Habermann et al <sup>71</sup>	R-CHOP vs CHOP, then R-maintenance (MR) or observation (O)	Untreated n = 632	NR	NR	3-year FFS: R-CHOP vs CHOP 53% vs 46% P = 0.04 2-year FFS: MR vs O 76 vs 61% P = 0.009	3-year OS R-CHOP vs CHOP 67% vs 57% P = 0.05

**Abbreviations:** DLBCL, diffuse large B-cell lymphoma; PFS, progression free survival; TTF, time to treatment failure; NR, not reported; ns, no significant differences; R, rituximab; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone; ICE, ifosfamide, carboplatin, etoposide; EFS, event-free survival; HDS, high-dose sequential chemotherapy regimen; MR, maintenance; O, observation arm; OS, overall survival.

role of rituximab combined with salvage HDC regimens, based on comparisons with historical cohorts of patients. Kewalramani et al<sup>77</sup> reported an improvement of CR rates after R-ICE (rituximab, ifosfamide, carboplatin, etoposide), when compared to patients treated with ICE only (53% vs 27%, respectively). PFS after 2 years was slightly better in patients treated with ASCT after R-ICE (54% vs 43%). An R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin) regimen generated higher overall response rate (ORR) than in DHAP treated patients (63% vs 42%). PFS at 2 years and OS were significantly better with R-DHAP receiving patients than in the historical DHAP treated group (57% vs 18% and 77% vs 37%, respectively).<sup>78</sup> Moreover, rituximab in combination with a DexaBEAM regimen (dexamethasone, BCNU, etoposide, cytarabine, melphalan) and further conditioning treatment with BEAM or total body irradiation and cyclophosphamide (TBI/Cy) was distinctly better than in patients without rituximab, with an OS after 4.5 years in

the rituximab group (67% vs 45% in historical control).<sup>79</sup> The CORAL (Collaborative trial in Relapsed Aggressive Lymphoma) study is the first randomized trial comparing the activities of the R-ICE and R-DHAP regimens as a HDC before ASCT, however, the final results are still not yet available.<sup>80</sup> Recently, Tarella et al<sup>81</sup> showed the advantage of a combination of rituximab with HDC administered prior to ASCT in regard to OS (64% in patients with R-HDC vs 38% in HDC group).

Habermann et al,<sup>71</sup> studying the role of rituximab in DLBCL maintenance after first-line treatment, showed that only CHOP-treated patients benefited from the maintenance in regard to PFS. The final results of the CORAL trial concerning the role of rituximab maintenance after ASCT are yet to be known.

## Mantle cell lymphoma

Rituximab has been studied both in combination with existing chemotherapeutic regimens and as monotherapy

in the treatment of MCL (Table 3). A study by Ghelmini et al<sup>82</sup> showed that rituximab as a single agent had rather low activity in MCL. The OR of 88 analyzed patients was 27%, including CR in 2.3% of the study group. The duration of remission was only 6–12 months. In 2005, the German Low Grade Lymphoma Study Group (GLSG) conducted a randomized trial comparing R-CHOP and CHOP in first-line therapy.<sup>83</sup> In the cohort of 122 MCL patients, OR was found to be better in the R-CHOP group (94% vs 75% in CHOP arm;  $P = 0.0054$ ). Also the CR rate and median time to treatment failure (TTF) were better in R-CHOP patients (34% vs 7%,  $P = 0.0002$  and 21 vs 14 months, respectively). However, no difference was found in regard to both PFS and OS.

The combination of rituximab with a hyper-CVAD regimen (three cycles high dose methotrexate and cytarabine alternating with three cycles cyclophosphamide, vincristine, doxorubicin, and dexamethasone), produced a longer PFS after 3 years (64%) than hyper-CVAD only.<sup>84</sup> The OR was 97%, including 87% of CR. As a matter of fact, the benefit of rituximab on OS in MCL patients was indicated by the results of a meta-analysis by Schultz et al.<sup>85</sup> This analysis included data from three separate trials<sup>83,86</sup> with a total cohort of 260 MCL patients. In this meta-analysis, the hazard ratio for death was 0.6, which indicated a significant advantage for

patients receiving rituximab plus chemotherapy, compared to chemotherapy alone.

Additionally, indirect evidence of a survival benefit for rituximab in MCL comes from a historical comparison of patients treated by CLSG with patients treated by the Kiel Lymphoma Study Group (KLSG).<sup>87</sup> The GLSG patients were treated with MCP (mitoxantrone, chlorambucil, prednisone), CHOP, or R-CHOP regimens, whereas KLSG patients received either COP or CHOP. Patients from those two groups were matched and the OS was compared. The median OS rate was 2.7 years in the KLSG study compared to 4.8 years in the GLSG study ( $P < 0.0001$ ), and the 5-year survival rates were 22% and 47%, respectively. However, the only already published randomized trial on combined rituximab-chemotherapy regimens in previously untreated patients with MCL showed no difference in OS, with a 2-year probability of 76.6% OS ( $P > 0.05$  for the difference between the two groups).<sup>83</sup> On the other hand, the addition of rituximab to chemotherapy alone as first-line therapy was found to improve OS in elderly patients with MCL in an analysis recently published by Griffiths et al.<sup>88</sup> Median OS was 27 months for chemotherapy alone compared to 37 months for rituximab combined with first-line regimens ( $P < 0.001$ ). Hence, it seems that first-line chemotherapy

**Table 3** Larger studies evaluating the efficacy of rituximab combined with first-line treatment or salvage chemotherapy in patients with mantle cell lymphoma

Study	Treatment	Patients	OR	CR	Median TTF/PFS	OS
Lentz et al (GLSG) <sup>83</sup>	R-CHOP vs CHOP	Untreated n = 122	94% vs 75% $P = 0.0054$	34% vs 7% $P = 0.00024$	TTF – 21 vs 14 months PFS ns	ns
Romaguera et al <sup>84</sup>	R-hyper-CVAD/HDMC	Untreated n = 97	97%	87%	At 10 years of follow-up (median 8 years), TTF – 4.6 years	At 10 years of follow-up (median 8 years), OS for all patients had not been reached
Griffiths et al <sup>88</sup>	R-CHOP/R-CHOP-like vs CHOP/CHOP-like	Untreated n = 638 median age 75 years	NR	NR	NR	37 months for chemotherapy alone vs 27 months for R combined with first-line regimens $P < 0.001$
Forstpointer et al <sup>89</sup>	R-FCM vs FCM	Relapsed/refractory n = 48	58% vs 46% ns	13% vs 0% $P < 0.01$	PFS 8 vs 4 months $P = 0.389$	Median OS R-FCM was not reached; for FCM – 11 months $P = 0.042$
Forstpointer et al <sup>92</sup>	R-FCM vs FCM maintenance (MR)	Relapsed/refractory FCM vs R-FCM n = 50 MR n = 57 median age 62	46% vs 58% ns	29% vs 0%	Alive at 3 years 14 vs 12 months $P = 0.049$ Remissions beyond 2 years 45% vs 9%	Median OS for RCM not reached. The estimated proportion of patients alive at 3 years is 77% after MR vs 57% with O $P = 0.100$

**Abbreviations:** GLSG, German Lymphoma Study Group; PFS, progression free survival; TTF, time to treatment failure; ns, no significant differences; R, rituximab; CHOP, cyclophosphamide, adriamycin, vincristine, prednisone; OR, overall response; CR, complete response; PFS, progression free survival; TFS, treatment-free survival; OS, overall survival; hyper-CVAD /HDMC regimen, 3 cycles cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with 3 cycles high dose methotrexate and cytarabine; MCP, mitoxantrone, chlorambucil, prednisone; KLSG, Kiel Lymphoma Study Group; FCM, fludarabine, cyclophosphamide, mitoxantrone; FL, follicular lymphoma; MR, rituximab maintenance; O, observation only group; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone; FCM, fludarabine, cyclophosphamide, mitoxantrone; NR, not reported.

including rituximab is associated with significantly improved survival in older patients diagnosed with MCL.

In a randomized study by GLSG, a combination of rituximab with the FCM (fludarabine, cyclophosphamide, mitoxantrone) regimen was examined in comparison with FCM in relapsed/refractory patients with MCL.<sup>89</sup> R-FCM showed a distinct OR improvement compared to FCM (58% vs 46%), however the CR rates were low in both treatment arms (13% vs 0%). However, the R-FCM regimen led to significantly prolonged PFS and OS after 2 years (8 vs 4 months and 65% vs 35%, respectively). Hoerr et al<sup>90</sup> assessed the activity of treatment after addition of rituximab to the salvage HDC scheme, showing a significant benefit with regard to PFS and OS. In another study, a combination of rituximab with TBI/Cy, applied prior to alloSCT, improved EFS (median not reached vs 43 months in no rituximab group) and OS after 4 years (87% vs 77%, respectively).<sup>91</sup>

Rituximab in maintenance therapy was assessed in a trial of the GLSG. MCL patients randomly treated with R-FCM vs FCM regimens with rituximab maintenance showed a benefit of maintenance.<sup>92</sup> Although the median response duration did not differ between rituximab maintenance and observation only (14 vs 12 months), a higher proportion of patients in this evaluation experienced ongoing remissions beyond 2 years (45% vs 9%).

## Rituximab in CLL

When used as a single agent at a dose of 375 mg/m<sup>2</sup>, Rituximab demonstrated limited activity in previously treated CLL.<sup>92,93</sup> However, in a study performed by O'Brian et al,<sup>94</sup> a correlation was found between the dose of rituximab and the clinical response. In this trial, CLL patients received an initial dose of rituximab of 375 mg/m<sup>2</sup> which was then increased to a fixed dose of between 500 and 2250 mg/m<sup>2</sup> once weekly for 4 weeks. The OR rate was 36% and ranged between 22% for lower doses and 75% for the highest doses. Byrd et al reported a dose-dense (thrice weekly) rituximab study in 83 previously treated CLL patients. The patients received different doses of rituximab (250–375 mg/m<sup>2</sup>) three times weekly for 4 weeks.<sup>95</sup> The OR rate was 45% including 3% CR and 42% PR. Single-agent rituximab was also evaluated in patients with previously untreated CLL. In the study performed by Hainsworth et al,<sup>96</sup> 44 previously untreated, symptomatic patients received four weekly doses of rituximab 375 mg/m<sup>2</sup>. The OR rate was 51% and CR 4%. Recently, Ferrajoli et al<sup>97</sup> reported the results of an early intervention with standard-dose rituximab (375 mg/m<sup>2</sup> intravenously weekly for 8 consecutive weeks) in 34 asymptomatic, untreated, early-stage

CLL patients. The OR rate in 34 patients was 82% including 9% CR. Median time to progression (TTP) in the 28 responders was 23 months and the 8-year OS rate was 74%. Although rituximab is active as a single agent, responses are poorer than in other B-cell NHL.

Fludarabine and rituximab combination therapies in CLL yielded promising results in several studies, both in previously treated and untreated patients (Tables 4 and 5). Several studies indicated that adding rituximab to FA (FR) in the initial treatment of CLL may produce an increase in the CR rate.<sup>98–100</sup> Del Poeta et al<sup>99</sup> conducted a Phase II study in which FR was given to the patients with symptomatic, untreated CLL. Sixty patients with CLL received 6-monthly courses of FA (25 mg/m<sup>2</sup> for 5 days) followed by 4-weekly doses of rituximab (375 mg/m<sup>2</sup>). Forty-seven of 60 patients (78%) achieved CR and nine of 60 patients (15%) achieved PR.

Similar results were reported by Byrd et al<sup>98,101</sup> from the Cancer and Leukemia Group B (CALGB). In this randomized study, patients received either 6-monthly courses of rituximab concurrently with FA, followed 2 months later by 4-weekly doses of rituximab for consolidation therapy, or sequential FA alone, followed 2 months later by rituximab alone for consolidation. In the concurrent regimen, the OR was 90% with a 47% CR compared with a 77% OR and 28% CR in the sequential regimen. Subsequently, this group retrospectively compared the treatment outcome of patients treated with FR or FA alone enrolled on two multicenter clinical trials performed by the CALGB and the US Intergroup. In this study, patients were treated with FR (CALGB 9712, n = 104) or FA alone (CALGB 9011, n = 178). In multivariate analyses, the patients receiving FR had a significantly better PFS and OS than patients receiving FA alone. Subsequently, the authors reported the updated results of the CALGB 9712 trial with a median follow-up of 117 months.<sup>102</sup> The median PFS was 42 months, and 27% of the patients were progression free at 5 years. The median OS was 85 months, and 71% of patients were alive at 5 years.

Recently, Gerrie et al<sup>103</sup> reported the results of treatment with oral FA combined with rituximab as frontline treatment of CLL in a community-based setting. Ninety-eight patients received FR for CLL/SLL from 2004 to 2009. Two- and 4-year treatment-free survival (TFS) was 69% and 54% (median 4.0 years). Two- and 4-year OS was 90% and 73%, respectively (median not reached). These results indicate that FR with oral fludarabine can be successfully given to community-based patients and is more convenient than R-FC with intravenous FA.



**Table 4** Larger studies evaluating the efficacy of rituximab combined with fludarabine ± cyclophosphamide in previously untreated patients with CLL

Study	Treatment	No of patients	Median age	OR	CR	Median PFS
Schulz et al <sup>100</sup>	R-F	20	59	85%	20%	75 weeks
Woyach et al <sup>104</sup>	R-F	104	63	84% (77%* and 90%**)	28%* and 47%**	42 months
Gerrie et al <sup>103</sup>	R-F***	98	62	NR	NR	TFS – 4 years
Keating et al <sup>106</sup>	R-FC	224	58	95%	70%	NR
Hallek et al <sup>15</sup>	R-FC	408	61	90%	44%	58.1 months
Foon et al <sup>108</sup>	R-FC lite	48	58	100%	79%	22+ months for CR
Faderl et al <sup>111</sup>	R-FCM	30	57	96%	83%	Median PFS not reached
Bosch et al <sup>112</sup>	R-FCM	72	60	93%	82%	NR
Parikh et al <sup>115</sup>	CFAR	60	59	92%	70%	38 months

**Notes:** \*R and F administered sequentially; \*\*R and F administered concurrently; \*\*\*oral F.

**Abbreviations:** NR, not reported; F, fludarabine; C, cyclophosphamide; R, rituximab; M, mitoxantrone; B, bendamustine; A, alemtuzumab; HDMP, high-dose methylprednisolone; OR, overall response; CR, complete response; PFS, progression free survival; TFS, treatment-free survival.

The combination of rituximab with FC (R-FC regimen) demonstrated particularly high rates of OR, CR, and duration of PFS in relapsed/refractory and previously untreated patients with CLL (Table 1).<sup>16,104</sup> Wierda et al<sup>105</sup> evaluated the efficacy, toxicity, and tolerability of R-FC in patients with previously treated CLL. CR was achieved in 25% of 177 patients and the OR rate was 73%. In 12 (32%) of 37 patients with CR, molecular remission in the bone marrow was noted. Prospective, randomized study have recently confirmed the advantage of the R-FC regimen over the FC regimen in previously treated, relapsed, or refractory patients (REACH study).<sup>106</sup> The primary endpoint of the study, PFS, was prolonged by 10 months in the R-FC arm (30.6 months) compared to FC (20.6 months,  $P = 0.0002$ ).

Keating et al<sup>106</sup> evaluated R-FC regimen as front-line therapy in 224 patients with progressive or advanced CLL. The CR rate was 70% and the OR was 95%. Moreover, preliminary analysis suggested that chemotherapy with R-FC improved PFS and OS. These results were subsequently confirmed by the German CLL study group (GCLLSG)

in a randomized, multicenter, multinational Phase III trial.<sup>15</sup> In this study, 817 previously untreated, physically fit patients were randomly assigned to receive six courses of either FC or R-FC. At 3 years after randomization, 65% of patients in the R-FC group were free of progression compared with 45% in the FC group ( $P < 0.0001$ ). At the same time, 87% were alive versus 83%, respectively ( $P = 0.01$ ). However, R-FC treatment was more frequently associated with grade 3 and 4 neutropenia (34% vs 21%;  $P < 0.0001$ ). Retrospective analysis performed by Tsimberidou et al<sup>107</sup> indicated that chemoimmunotherapy with R-FC may overcome the adverse prognostic significance of 11q deletion in previously untreated patients with CLL. Currently, R-FC is becoming the first-line choice for younger, physically fit patients with CLL. Reducing the doses of FA and CY while increasing the dose of rituximab demonstrated good efficacy combined with improved tolerability in previously untreated CLL patients.<sup>108</sup>

Addition of a fourth drug to the R-FC immunochemotherapy of CLL could further improve the treatment outcome.<sup>109</sup>

**Table 5** Larger studies evaluating the efficacy of rituximab combined with fludarabine ± cyclophosphamide in previously treated patients with CLL

Study	Treatment	No of patients	Median age	No of previous treatments	OR	CR	PFS
Schulz et al <sup>85</sup>	R-F	11	59	1–4	90%	27%	75 weeks
Wierda et al <sup>105</sup>	R-FC	179	59	2	73%	25%	28 months
Robak et al <sup>16</sup>	R-FC	276	63	1	69.9%	24.3%	30.6 months
Byrd et al <sup>113</sup>	FCR + L	31	58	2	65%	52%	29 months
Badoux et al <sup>114</sup>	CFAR	80	58	3	65%	29%	10.6 months
Hillmen et al <sup>110</sup>	FCM + R	23	65	2	70%	42%*	NR

**Note:** \*CR + CR with incomplete marrow recovery.

**Abbreviations:** NR, not reported; F, fludarabine; C, cyclophosphamide; R, rituximab; L, lumiliximab; A, alemtuzumab; M, mitoxantrone; B, bendamustine; HDMP, high-dose methylprednisolone; R-C, rituximab, cladribine; R-CC, rituximab, cladribine, cyclophosphamide; OR, overall response; CR, complete response; PFS, progression free survival.

Hillmen et al<sup>110</sup> compared an FCM (fludarabine, cyclophosphamide, mitoxantrone) regimen with FCM + rituximab in previously treated CLL. The OR rates to FCM and FCM-R were 58% and 65%, respectively. The toxicity of both regimens was similar and acceptable. Faderl et al reported the results of FCM-R regimen in previously untreated patients.<sup>111</sup> In this study, OR was 96% and CR was 83%. However, the efficiency and toxicity of this four-drug combination is similar to the standard R-FC immunochemotherapy used as the historical control. Bosch et al reported a Phase II clinical trial consisting of an initial treatment with R-FCM followed by rituximab maintenance.<sup>112</sup> Patients achieving response after FCM-R immunochemotherapy received rituximab 375 mg/m<sup>2</sup> every 3 months for 2 years. The OR rate was 93%, including 82% CR.

In a Phase I/II study by Byrd et al,<sup>113</sup> an R-FC regimen combined with anti-CD23 mAb lumiliximab was tested in patients with refractory/relapsed CLL. The OR rate was 65%, including 52% CR. The CR rate in this study compared favorably for R-FC and lumiliximab with the activity of R-FC alone in a similar patient population (25% CR) previously reported by Wierda et al.<sup>105</sup>

Alemtuzumab has also been added to R-FC (CFAR) for the treatment of previously treated and untreated CLL patients.<sup>115</sup> In relapsed or refractory patients the OR rate was 65%, including 29% CR. However, there was no significant improvement in PFS and OS in comparison with a similar historical group treated with R-FC in the same center. CFAR was also evaluated in younger untreated patients.<sup>115</sup> However, response rates and survival of the majority of patients treated with CFAR are comparable with those of R-FC-treated patients.

Recent clinical observations reveal that rituximab can be also combined with other PNAs, DCF, or 2-CdA (Table 6). Lemanna et al<sup>116</sup> treated 32 refractory or relapsed patients with DCF, CY, and rituximab (PCR regimen) and found 24 responses (75%) including eight CRs (25%). The median duration of response was 25 months and the median time to treatment failure was 40 months. Kay et al<sup>117</sup> presented the results of PCR in previously untreated patients. Responses occurred in 58 out of 65 patients (91%) with 26 (41%) CR.

A PCR regimen may be a good therapeutic option for older patients and those with modestly decreased renal function.<sup>118</sup> Reynolds et al<sup>119</sup> compared R-FC and PCR regimens in previously untreated or minimally treated CLL in a randomized study. The OR rate was higher in the R-FC group (59%) than in the PCR arm (49%), which demonstrated CR rates of 14% and 7%, respectively. Efficacy and

toxicity of combined therapy consisting of rituximab and 2-CdA (RC protocol) or 2-CdA, CY, and rituximab (RCC protocol) were also evaluated in patients with refractory or relapsed CLL.<sup>120</sup> Among the 46 patients that entered the study, three patients (6.5%) achieved CR and 31 (67%) patients achieved PR.

Combinations of high-dose methyl prednisolone (HDMP) with rituximab were investigated in relapsed/refractory and previously untreated patients.<sup>121,122</sup> In previously untreated patients, the OR rate was 96%, CR rate 32%, and the median PFS was 30.3 months.<sup>122</sup> This treatment can be particularly useful for patients with limited myeloid reserve that might not tolerate other therapies. In one study, 14 refractory or relapsed patients were treated with three cycles of rituximab (375 mg/m<sup>2</sup> weekly for 4 weeks) in combination with HDMP (1 gm/m<sup>2</sup> daily for 5 days). The OR rate was 93% and the CR rate was 36%. The median PFS was 15 months. HDMP and rituximab were well tolerated and had promising activity in this patient population.

Encouraging results were also obtained using rituximab in combination with bendamustine (RB). In a study performed by Fisher et al, 78 relapsed or refractory patients received 70 mg/m<sup>2</sup> of bendamustine on days 1 and 2, and 375 mg/m<sup>2</sup> of rituximab on day 1 of the first cycle and 500 mg/m<sup>2</sup> on day 1 of up to six subsequent 28-day cycles.<sup>123</sup> The OR rate was 59% and CR 9.0%. After a median follow-up time of 24 months, the median event-free survival was 14.7 months. Subsequently, a multicenter Phase II trial (CLL2M) was performed to evaluate the efficacy and toxicity of RB in previously untreated CLL patients.<sup>124</sup> The OR rate was 90.9% with 32.7% CR. After 18 months, 75.8% of the patients were still in remission and median PFS had not been reached. Alemtuzumab was also combined with rituximab, with significant responsiveness and acceptable toxicity.<sup>125–127</sup>

## Optimal use of rituximab

In routine use, rituximab is usually administered intravenously as a single agent or as part of combination chemoimmunotherapy.<sup>128</sup> Rituximab is almost exclusively administered slowly via the intravenous route. The standard dose of rituximab used for the treatment of patients with NHL is 375 mg/m<sup>2</sup> administered as an intravenous infusion once weekly for 4 weeks. However, the results of a Phase I dose-escalation study indicate that higher doses of rituximab are more effective and relatively well tolerated.<sup>129</sup> In CLL, there is clear evidence of a dose-response relationship. In a study performed by O'Brien et al,<sup>94</sup> the OR rate was found to be 22% for patients treated at 500 to 825 mg/m<sup>2</sup>, 43% for those

**Table 6** Larger studies evaluating the efficacy of rituximab combined with other drugs than fludarabine in previously untreated and pretreated patients with CLL

Study	Treatment	No of patients	Median age	No of previous treatments	OR	CR	Median PFS
Kay et al <sup>117</sup>	R-PC	65	63	0	91%	41%	32.6 months
Lamanna et al <sup>116</sup>	R-PC	32	62	2	75%	25%	25 months
Robak et al <sup>120</sup>	R-C/R-CC	46	59	2	67%	7%	12 months
Fischer et al <sup>124</sup>	R-B	117	64	0	90.9%	32.7%	Not reached
Fischer et al <sup>123</sup>	R-B	81	67	2	77%	14%	NR
Castro et al <sup>122</sup>	R-HDMP	28	65	0	96%	32%	30.3 months
Bowen et al <sup>121</sup>	R-HDMP	37	67	2	78%	22%	12 months
Zent <sup>126</sup>	R + A	30	61	0	90%	37%	14.4 months
Faderl et al <sup>127</sup>	R + A	40	59	3	53%	18%	6 months

**Abbreviations:** NR, not reported; F, fludarabine; C, cyclophosphamide; R, rituximab; L, lumiliximab; A, alemtuzumab; M, mitoxantrone; B, bendamustine; HDMP, high-dose methylprednisolone; R-C, rituximab + cladribine; R-CC, rituximab + cladribine + cyclophosphamide; OR, overall response; CR, complete response; PFS, progression free survival.

treated at 1000 to 1500 mg/m<sup>2</sup>, and 75% for those treated at the highest dose of 2250 mg/m<sup>2</sup> ( $P = 0.007$ ).

Data relating to the safety, efficacy, and PK of other routes of administration are incomplete. Novel routes of administration include subcutaneous, intrathecal, intraventricular, intrapleural, intralesional, intradermal, and even intravitreal use. Fractionated subcutaneous dosing schedules that limit exhaustion of effector mechanisms may be more effective than current intravenous bolus schedules of rituximab at a dose of 375 mg/m<sup>2</sup>.<sup>130</sup> A pilot trial suggests that low-dose rituximab at 20 mg/m<sup>2</sup> intravenously thrice weekly promotes clearance of leukemic cells without inducing loss of targeted CD20.<sup>131</sup> Lower doses of this antibody (20 mg) administered subcutaneously thrice weekly for up to 12 weeks was well tolerated with minimal injection site reactions.<sup>130</sup> Subcutaneous rituximab largely preserved CD20 expression on leukemic cells. Subcutaneous administration could be more convenient for the patients than intravenous treatment. In fact, higher subcutaneous doses of rituximab could be more effective than lower doses. However, the safety of this approach should be confirmed in a larger cohort of patients and possible development of human anti-chimeric antibodies (HACA) would have to be studied. At present, subcutaneous rituximab administration should not be repeated outside of clinical trials. Intraventricular administration of rituximab has been evaluated in Phase I trials and was effective in some cases with central nervous system (CNS) lymphoma.<sup>132,133</sup>

Intrapleural and intraperitoneal administration of rituximab for the treatment of recurrent malignant pleural effusions or abdominal ascites unresponsive to systemic therapy have been reported in individual cases with NHL.<sup>134–137</sup> The intracavity administration of rituximab seems to be effective in some cases with no significant side effects.

## Conclusions and place in therapy

Rituximab was the first mAb approved in 1997 by the FDA for the treatment of FL. Although the introduction of rituximab has not led to the development of curative treatments, it has markedly prolonged the PFS and OS of patients with FL. Currently, this drug is commonly combined with first-line chemotherapy for FL, and retreatment with rituximab is typically reserved until first relapse. In addition, the results of the PRIMA study showed that rituximab maintenance doubled the PFS of patients with FL compared to those who stopped treatment. The PRIMA study is particularly important because rituximab maintenance therapy was added as a further stage after induction with immunochemotherapy regimens in previously untreated patients, and this combination has recently become a treatment of choice for patients with FL. The results from this trial should conclusively establish the favorable role of rituximab in maintenance therapy in FL. Based on the currently available evidence, rituximab should be offered as maintenance therapy to all appropriate patients with FL rather than waiting until relapse. In January 2011, the FDA approved rituximab for maintenance therapy for patients with previously untreated FL who achieve a response to rituximab in combination with chemotherapy.

Randomized Phase III trials have demonstrated the superiority of R-CHOP over CHOP chemotherapy alone in patients with DLBCL. In February 2006, the FDA granted approval to rituximab for use in combination with CHOP or other anthracycline-based chemotherapy regimens in the first-line treatment of patients with DLBCL. Despite the significant progress in the first-line treatment of DLBCL, up to 50% of patients relapse after chemoimmunotherapy with R-CHOP, especially if they belong to the high-risk population. In younger patients with relapsed or refractory DLBCL, salvage therapy followed by high-dose therapy with

ASCT is currently the treatment of choice. The optimal salvage regimen should be defined on the basis of the ongoing CORAL study (Collaborative trial in Relapsed Aggressive Lymphoma), randomized relapsed patients between R-ICE (rituximab, ifosfamide, carboplatin, etoposide), and R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin) salvage therapy prior to ASCT.

Rituximab alone has limited activity in MCL. However, this agent is currently widely used in MCL in combination with chemotherapy, although benefits are not as impressive as in other lymphoma entities, and other therapeutic strategies are needed in this disease.

Rituximab as a single agent also demonstrates moderate clinical activity in patients with CLL. However, when administered in combination with chemotherapy, rituximab can improve the survival of patients relative to those treated with chemotherapy alone. In 2009, the European Commission approved rituximab in combination with chemotherapy for use in patients with previously untreated and previously treated CLL. In February 2010, the FDA granted approval to rituximab, in combination with fludarabine and cyclophosphamide, for the treatment of both previously untreated and previously treated patients with CLL.<sup>138</sup> These approvals were based on two large Phase III randomized trials that demonstrated the superiority of chemoimmunotherapy with rituximab compared with chemotherapy alone in previously untreated and refractory/relapsed patients with CLL.

Over the last few years, new generations of anti-CD20 mAbs have been developed for potential benefits over the classical, first-generation mAb rituximab.<sup>139</sup> Some of them are potentially useful in the treatment of lymphoid malignancies. Compared with rituximab, new mAbs have enhanced antitumor activity resulting from increased complement-dependent cytotoxicity (CDC) and/or antibody-dependent cellular cytotoxicity (ADCC), and increased Fc binding affinity for the low-affinity variants of the FcγRIIIa receptor on immune effector cells. In particular, ofatumumab specifically recognizes an epitope encompassing both the small and large extracellular loops of CD20 molecule, and is more effective than rituximab at CDC induction and killing target cells.<sup>140</sup> Obinutuzumab (GA-101) was designed for enhanced ADCC and superior direct cell-killing properties, in comparison with currently available type I antibodies.<sup>141</sup> However, an advantage of these new anti-CD20 mAbs over rituximab needs to be further documented in well-designed, randomized trials. Therefore it can be concluded that, until the results from

such trials are available, rituximab is generally accepted as a standard component of therapies for B-cell lymphoid malignancies.<sup>142,143</sup>

In B-cell lymphoid malignancies, rituximab has been combined successfully in chemoimmunotherapy regimens with several standard chemotherapy combinations. Thus, although traditional strategies can still have a role in standard therapies, such approaches must now be placed in perspective with options that have the potential to achieve durable disease control or even cure. It is the hope that potentially curative treatment options may be forthcoming for these patients when rituximab, or newer anti-CD20 monoclonal antibodies, will be combined with emergent targeted drugs such as flavopiridol, lenalidomide, and orally bioavailable tyrosine kinase inhibitors, with potential activity in lymphoid malignancies. Immunotherapy with rituximab and these agents promises increased lymphoma specificity, reduced toxicity, and synergistic efficacy based on their different modes of action.

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