An overview of the current clinical use of the anti-CD20 monoclonal antibody rituximab

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The chimeric anti-CD20 monoclonal antibody rituximab has become part of the standard therapy for patients with non-Hodgkin’s lymphoma (NHL). To date, more than 300,000 patients have been treated with rituximab worldwide, including patients with indolent and aggressive NHL, Hodgkin’s disease and other B-cell malignancies. Combination of rituximab with cytotoxic agents or cytokines has been explored in a number of different studies. Rituximab is now also approved for patients with diffuse large B-cell lymphoma when combined with standard CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisone). The monoclonal antibody is generally well tolerated. Most adverse events are infusion-associated, including chills, fever and rigor related to the release of cytokines.

Key words: chronic lymphocytic leukemia, clinical studies, Hodgkin’s disease, non-Hodgkin’s lymphoma, rituximab

Introduction

Since the initial description by Köhler and Milstein [1], monoclonal antibodies have increasingly been used in the diagnosis of malignant diseases. However, many problems were encountered when monoclonal antibodies were developed as specific antitumor reagents. This has changed with the advent of rituximab, a chimeric human/mouse monoclonal antibody directed against the CD20 antigen. The use of rituximab in the treatment of relapsed or refractory indolent CD20+ B-cell non-Hodgkin’s lymphoma (NHL) was endorsed by the US Food and Drug Administration in December 1997. Shortly thereafter, rituximab was also approved in Europe under the trade name MabThera® (Hoffmann-La Roche AG) for patients with advanced stage chemoresistant or relapsed follicular NHL. More recently, rituximab was also approved in the USA and in Europe for the treatment of aggressive NHL when combined with standard chemotherapy. Worldwide, more than 300,000 patients have been treated so far, including patients with other malignancies and autoimmune disorders. The rapidly increasing bulk of data makes it difficult to keep abreast of the most recent developments. Here, we review the current clinical results with rituximab.

Biological activity

Rituximab is a chimeric human/mouse antibody with human constant regions and mouse variable regions (Figure 1) isolated from a murine anti-CD20 antibody (IDEC 2B8) [2]. The murine 2B8 antibody and the chimeric C2B8 antibody (rituximab) are very similar in terms of specificity and affinity. Compared with its murine counterpart, however, rituximab has a longer half-life in humans, interacts with human effector cells [2, 3], and is less immunogenic [4]. Rituximab binds avidly to the CD20 antigen, which is expressed on 95% of B-cell lymphoma cells and on normal B-cells. Importantly, CD20 is not present on precursor B-cells or stem cells. The antigen is expressed at lower levels on chronic lymphocytic leukemia (CLL) and plasma cells [5, 6]. The CD20 antigen is appealing for a selective immunotherapy for several reasons: CD20 does not circulate in the plasma [5], it is not shed from the surface of CD20+ cells after antibody binding and it is not internalized or downregulated [3]. Although the function of CD20 is not fully understood, factors such as complement-dependent lysis [2], effector cell-mediated lysis [7], induction of apoptosis and interference with calcium influx into the cell contribute to the antitumor activity [8].

Indolent and follicular lymphoma

The efficacy and safety of rituximab given as a single agent in relapsed indolent and follicular lymphoma were established in an international pivotal multicenter trial [9]. A total of 166 patients received four weekly doses of 375 mg/m². In the intention-to-treat group the overall response rate (ORR) was 48%, including 6% complete responses (CR) and 42% partial responses (PR). A recently performed retrospective re-analysis of these data using newly standardized response criteria [10] showed a higher ORR (62%) and more CRs (32%). The majority of the non-responders had a mean decrease of measurable disease of 32%. Overall, only...
13% of patients had no response or progressive disease, as shown in Figure 2. Median time to progression (TTP) was 13.2 months for responders and duration of response (DR) 11.6 months.

Adverse events such as fever, chills, nausea and aches were mainly associated with the first infusion and were typically modest. Most patients (55%) had no toxicity at subsequent infusions. The median values for hemoglobin, platelets, leucocytes and granulocytes remained within normal limits throughout the treatment period. Apart from a nearly complete elimination of B-lymphocytes in 86% of patients, other cells were mainly unaffected. No significant changes were observed in serum immunoglobulin levels. Infections that occurred for up to 1 year after therapy were mainly of bacterial origin (37 of 68) and generally mild (61 of 68 grade 1/2). Bcl-2 became negative in the peripheral blood in 62% and in the bone marrow in 56% of patients after 3 months. These data suggest that rituximab has a superior potency to induce molecular remissions when compared with cytotoxic agents.

Prognostic factors

Patients who had received only one prior treatment showed an ORR of 57%. In contrast, those who had three or more regimens before treatment with rituximab had an ORR of 38%. The ORR was 35% in patients with lesions >7 cm. This contrasts with most of the available literature documenting a clear relationship between bulky disease and both shorter survival and lower response to chemotherapy [11]. Davis et al. [12] treated 31 patients with bulky disease of ≥10 cm with four weekly infusions of rituximab and reported an ORR of 43% with a median TTP for the responders of 8.1 months. More grade 3/4 events were reported compared with the pivotal trial, but no patient developed a tumor lysis syndrome.

First-line treatment of indolent and follicular lymphoma

Colombat et al. [13] treated a group of 50 previously untreated patients with follicular NHL with a standard four-dose course of rituximab. Of the 36/49 patients who were responders on day 78, 10 patients progressed during the first year of follow-up. Of note, seven of 23 patients in PR on day 78 were in CR/CR (unconfirmed) (CRu) at 12 months after treatment. If the response rates
at any staging during the first year of follow-up are considered, the ORR was 80% and the CR/CRu rate 41%, respectively. Thirty-two of 48 patients had been positive for the t(14;18) translocation before treatment. Interestingly, 17 of 30 (57%) were negative on day 50 after rituximab treatment in the peripheral blood, with 31% negative in bone marrow.

Hainsworth [14] conducted a phase II trial in 62 patients with indolent lymphoma also using the 4-dose schedule as first-line therapy. Treatment was repeated every 6 months in responding patients for a maximum of up to four courses. At week 6 after the first course, 47% of the patients had objective responses (7% CR). Forty-six patients received two or more rituximab courses (two courses, 10; three courses, 13; four courses, 23) with response rates increasing to 65% (27% CR). Repeated courses of the antibody at 6-month intervals improved responses in 30% of the patients without increasing toxicity. The 1- and 2-year progression-free survival (PFS) for all patients were 69% and 67%, respectively.

Retreatment

Davis et al. [15] conducted a clinical trial evaluating rituximab in the retreatment of 58 patients with relapsed low-grade or follicular B-cell NHL who had responded to at least one prior course of rituximab. In general, rituximab was well tolerated in this setting. Significant clinical activity was observed with an ORR of 38% (10% CR, 28% PR) in the intention-to-treat group. The median TTP was 17.8 months and DR was 16.3 months. This was longer than the TTP and DR achieved in these patients prior to treatment with rituximab (TTP 12.4 months and DR 9.8 months). The median interval between the courses was 14.5 months (range 3.8–35.6 months). These results were confirmed by Igarashi et al. [16], suggesting that retreatment with rituximab is save and feasible.

Development of resistance is characteristic for B-cell lymphoma upon repeated treatment with conventional chemotherapy. In contrast, the selection of CD20− lymphoma cells in patients treated with rituximab is rarely observed. Therapeutical trials showed a primary response rate of 50%, and a secondary response rate of 44% in prior responders [17]. Possible mechanisms of resistance include uncoupling of the apoptotic signal initiated by rituximab, an inhibited immune response by complement-resistance proteins, or reduction of CD20 expression below a critical threshold. The most relevant clinical trials of rituximab in low-grade and follicular NHL are shown in Table 1.

Combined modality treatment of rituximab and chemotherapy

Preclinical studies have indicated that rituximab can sensitize resistant malignant cells to the effect of cytotoxic agents [18].

Table 1. Current studies using single-agent rituximab in indolent and follicular NHL

<table>
<thead>
<tr>
<th>Indication</th>
<th>No. of pts (n)</th>
<th>Schedule</th>
<th>Response rate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>l-g NHL (n = 15, relapsed) and intermediate-/high-grade NHL (n = 5, relapsed)</td>
<td>20</td>
<td>4×125 mg/m² R weekly; or 4×250 mg/m² R weekly; or 4×375 mg/m² R weekly (phase I multiple-dose trial)</td>
<td>ORR 33% (l-g/foll. NHL 40%)</td>
<td>Maloney et al. [46]</td>
</tr>
<tr>
<td>l-g/foll. NHL (relapsed)</td>
<td>37</td>
<td>Standard dose</td>
<td>CR 8%; PR 38%</td>
<td>Maloney et al. [47]</td>
</tr>
<tr>
<td>l-g/foll. NHL (relapsed or refractory)</td>
<td>166</td>
<td>Standard dose (pivotal study)</td>
<td>CR 6%; PR 42%; DR 11.6 m (re-analysis: CR 32%; PR 30%)</td>
<td>McLaughlin et al. [9]</td>
</tr>
<tr>
<td>foll. NHL (untreated and pretreated)</td>
<td>76</td>
<td>Standard dose</td>
<td>CR 6%; PR 46%</td>
<td>Ghielemi et al. [48] (data about MCL also shown in ‘Mantle cell lymphoma’)</td>
</tr>
<tr>
<td>foll. NHL (relapsed)</td>
<td>38</td>
<td>Standard dose</td>
<td>CR 17%; PR 30%</td>
<td>Feuring-Buske et al. [49]</td>
</tr>
<tr>
<td>l-g/foll. NHL with bulky disease &gt;10 cm (relapsed or refractory)</td>
<td>31</td>
<td>Standard dose</td>
<td>CR 4%; PR 39%</td>
<td>Davis et al. [12]</td>
</tr>
<tr>
<td>foll. NHL with low tumor burden (first-line therapy)</td>
<td>50</td>
<td>Standard dose</td>
<td>CR/CRu 26%; PR 47%; 57% became bcl-2-negative in PB and 31% in BM</td>
<td>Colombat et al. [13]</td>
</tr>
<tr>
<td>indol. NHL (first-line therapy)</td>
<td>62</td>
<td>Standard dose, repeated every 6 in responding/stable pts for a maximum of 4 courses after the 1st course: CR 7%, PR 47%; after 2 or more courses: CR 27%, PR 38%</td>
<td></td>
<td>Hainsworth [14]</td>
</tr>
<tr>
<td>l-g/foll. NHL (relapsed)</td>
<td>35</td>
<td>8×375 mg/m² R</td>
<td>CR 14%; PR 46%; 9/18 became bcl-2-negative</td>
<td>Piro et al. [52]</td>
</tr>
<tr>
<td>l-g/foll. NHL, relapse after prior course of R (retreatment)</td>
<td>58</td>
<td>Standard dose</td>
<td>CR 10%; PR 28%</td>
<td>Davis et al. [15]</td>
</tr>
<tr>
<td>indol. NHL, relapse after prior course of R (retreatment)</td>
<td>13</td>
<td>Standard dose</td>
<td>CR 0%; PR 38%</td>
<td>Igarashi et al. [16]</td>
</tr>
</tbody>
</table>

*Four weekly doses of rituximab 375 mg/m².*

R, rituximab; l-g, low-grade; foll., follicular; ORR, overall response rate; CR, complete response; PR, partial response; m, months; indol., indolent; pts, patients; PB, peripheral blood; BM, bone marrow.
Underlying mechanisms for a possible synergism were analyzed for the combination of fludarabine and rituximab, showing that fludarabine downregulates the membrane expression of CD55, which serves as an anticomplement protein [19]. In preclinical studies, rituximab was subsequently shown to potentiate the cytotoxicity of fludarabine [20]. Thus, the concept of concomitant administration of the antibody and chemotherapy is appealing.

Czuczman et al. [21] published data on the combined use of rituximab and fludarabine in 40 patients with follicular lymphoma. The ORR was 90% in the intention-to-treat group (CR/CRu 82.5%, PR 7.5%). The first report demonstrating the efficacy and safety of rituximab in combination with standard-dose CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) in low-grade lymphoma patients was published by the same group [22]. Two antibody infusions were administered before CHOP with the rationale of making use of a possible rituximab-induced sensitization to cytotoxic agents and also to saturate CD20 binding sites. The third and fourth rituximab infusion were given together with the chemotherapy. Thirty-eight of 40 patients responded, 55% with a CR, which compares favorably with similar studies when CHOP was given alone [23]. In an update, 21 patients were in remission between 46.8 and 86.3 months after treatment [24]. Median DR was 63.3 months with median PFS not reached after a median observation time of 65.1 months. Seven of the eight bcl-2-positive patients converted to PCR negativity after the combined treatment. Importantly, there was no evidence of additive toxicity. When rituximab was administered after CHOP, response rates appeared to be lower (CR/CRu 54%, PR 18%), but possible additional antitumor activity was demonstrated as measured by the clearance of bcl-2 [25].

The combination of FND (fludarabine, mitoxantrone and dexamethasone) with rituximab was shown to be effective and associated with modest side-effects in the treatment of indolent lymphoma [26, 27]. A prospective, randomized multicenter trial of the German Low Grade Lymphoma Study Group randomized between FCM (fludarabine, cyclophosphamide, mitoxantrone) or FCM in combination with rituximab [29]. To date, 43 patients with relapsed follicular lymphoma are evaluable. The ORR was 95% in the combined immunochemotherapy group and 68% in the FCM group.

Other trials using rituximab combined with different regimens such as cyclophosphamide/dexamethasone [29], fludarabine/mitoxantrone [30], bendamustine [31, 32] or mitoxantrone/chlorambucil/prednisone (MCP) [33] suggest that a combined immuno-chemotherapy is generally safe and might give superior clinical results.

Table 2 summarizes the clinical trials in which rituximab was combined with chemotherapy in patients with low-grade and follicular NHL.

**Rituximab combined with interferon**

Interferon (IFN)-α has a potential synergistic antitumor effect with monoclonal antibodies [34]. This synergism is probably related to an IFN-induced upregulation of antigen expression [35], which results in a better targeting of antibodies to tumor cells [36] and possibly enhanced cytotoxicity [37]. Therefore, different trials investigated safety and efficacy of rituximab in combination with IFN (Table 3).

Davis et al. [38] performed a 12-week trial involving 38 patients with relapsed or refractory low-grade or follicular lymphoma. IFN was given three times each week [weeks 1–12, 5 million International Units (MIU)]; rituximab was administered at standard doses (weeks 5–8). The ORR of 45% (CR 11%) compares to the response rates observed with rituximab alone [9], but TTP was more durable (25.2 months). No unexpected toxicities occurred, and most adverse events were classified as IFN-related.

In other low-grade lymphoma studies, the response rate ranged from 49% (F. Offner, presented at the rituximab meeting in Montreux, 2001) to 70% [39] and median DR was ~20 months.

Kimby et al. [40] treated 69 patients with low-grade or follicular lymphoma who had a PR or minor response after a first course of rituximab with additional four doses of the antibody with or without IFN in a randomized fashion. Co-administration resulted in more CRs (48% versus 23%).

Although the current evidence is rather limited, combining IFN with rituximab might be an option for patients who have difficulty tolerating chemotherapy. In addition, this is an interesting combination for possible use as maintenance therapy in patients with minimal residual disease after induction treatment.

**Stem cell transplantation**

A number of trials in which rituximab was used both before stem cell collection and after transplantation have been published (Table 4), and indicate that this approach is safe as far as mobilization and engraftment is concerned. The amount of tumor cell contamination in the stem cell product can be reduced and an increase in molecular remission following transplant has been suggested [41–45]. The use of rituximab in combination with autologous peripheral stem cell transplantation (ASCT) is also promising in patients with aggressive NHL.

**Dosing and scheduling**

The standard dose of rituximab is 375 mg/m² given once a week for a total of four applications. In the pivotal trial [9], the mean serum half-life after the first infusion was shorter than after the fourth infusion (76.3 versus 205.8 h), and the maximum observed concentration was higher after the fourth compared with the first infusion (mean 465 versus 206 µg/ml). Median serum antibody levels were higher compared with non-responders (502.8 versus 412.4 µg/ml, respectively; \( P = 0.010 \)).

Several investigators have evaluated modifications of the current schedule. For patients with CLL or bulky tumor, other schedules might be more suitable. Alternative approaches included higher doses [50] or an increase of the number of applications given [51]. Piro et al. [52] conducted a phase II trial in which eight weekly infusions of rituximab were evaluated in patients with refractory or relapsed indolent NHL. Of 35 evaluable patients, 14% achieved CR and 46% PR. Patients with bulky disease also responded including 25% of those with lesions >7 cm.
The median post-infusion serum levels plateaued after the sixth infusion (range 518.1–558.1 µg/ml). Most adverse events were mild and similar to those seen in previous studies.

Rituximab in aggressive NHL

A single-arm, open-label phase II study evaluated the clinical activity of rituximab in combination with CHOP as first-line treatment of aggressive NHL [53]. The patient population consisted of histologically documented aggressive lymphoma excluding patients with mantle cell, lymphoblastic or Burkitt’s lymphoma. Treatment was administered at 21-day intervals, with rituximab given on days 1 and 3 of each cycle at standard doses.

Table 2. Clinical studies using rituximab combined with chemotherapy in indolent and follicular NHL

<table>
<thead>
<tr>
<th>Indication</th>
<th>No. of pts (n)</th>
<th>Schedule</th>
<th>Response rate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>foll. NHL (67% relapsed, 33% untreated)</td>
<td>40</td>
<td>7× 375 mg/m² R + 6 cycles flu</td>
<td>CR 82.5%; PR 7.5%</td>
<td>Czuczman et al. [21]</td>
</tr>
<tr>
<td>indol. NHL (77.5% untreated, 22.5% pretreated)</td>
<td>40</td>
<td>6× 375 mg/m² R + 6 cycles CHOP</td>
<td>CR 55%; PR 40%; 7/8 pts became bcl-2-negative</td>
<td>Czuczman et al. [22]</td>
</tr>
<tr>
<td>indol. NHL (untreated, all were bcl-2-positive in PB and/or BM)</td>
<td>128</td>
<td>Pts who were in CR/PR after CHOP, but still bcl-2-positive by PCR, were eligible for a standard dose* of R (77 pts received R)</td>
<td>74% became bcl-2-negative after R</td>
<td>Rambaldi et al. [25]</td>
</tr>
<tr>
<td>indol. NHL (relapsed or untreated)</td>
<td>16</td>
<td>4× FND + standard dose* R; for pts with PR after the 1st cycle: 2× FND + 2× 375 mg/m² R</td>
<td>At the end of the whole treatment program: CR/CRI 81%; PR 12.5%; 8/12 pts became bcl-2-negative</td>
<td>Vitolo et al. [27]</td>
</tr>
<tr>
<td>l-g/foll. NHL (relapsed or refractory)</td>
<td>43</td>
<td>Two arms: (A) FCM days 1–3; (B) FCM days 1–3, R one day before FCM</td>
<td>(A) CR 21%, PR 47%; (B) CR 35%, PR 60%</td>
<td>Hiddemann et al. [28] (data about MCL also shown in ‘Mantle cell lymphoma’)</td>
</tr>
<tr>
<td>indol. NHL (pretreated)</td>
<td>10</td>
<td>day 1: 1× 375 mg/m² R; day 2: cyclophosphamide; days 1–7: decadron; cycles were repeated every 4 weeks till a maximum response (median 6 cycles)</td>
<td>CR 40%; PR 60%</td>
<td>Patel et al. [29]</td>
</tr>
<tr>
<td>indol. NHL (untreated)</td>
<td>19</td>
<td>4–6 cycles flu/mitoxantrone + standard dose* R</td>
<td>CR 53%; PR 42%</td>
<td>Gregory et al. [30]</td>
</tr>
<tr>
<td>indol. NHL (relapsed)</td>
<td>20</td>
<td>Days 1–3: bendamustine; day 1: mitoxantrone; weeks 2–5: standard dose* R; followed by a maximum of 5 courses of bendamustine/mitoxantrone</td>
<td>CR 35%; PR 60%</td>
<td>Weide et al. [31]</td>
</tr>
<tr>
<td>indol. NHL (pretreated)</td>
<td>25</td>
<td>days 1–3: flu + bendamustine; weeks 2–5: standard dose* R; followed by a maximum of 4 courses of flu/bendamustine</td>
<td>CR 28%; PR 48%</td>
<td>Kirchner et al. [32]</td>
</tr>
<tr>
<td>indol. NHL</td>
<td>124</td>
<td>Two arms: (A) 8× MCP; (B) 8× MCP + standard dose* R</td>
<td>CR 40%; PR 41% (evaluation has to be continued)</td>
<td>Herold et al. [33]</td>
</tr>
<tr>
<td>foll. NHL (untreated)</td>
<td>38</td>
<td>3–8 cycles CHOP + standard dose* R</td>
<td>Histological grade I/II: (after CHOP) CR 41%; (after R) CR 86%; Histological grade III: (after CHOP) CR 81%; (after R) R 93%</td>
<td>Jäger et al. (presented at the rituximab meeting in Montreux, 2001)</td>
</tr>
</tbody>
</table>

\*Four weekly doses of rituximab 375 mg/m².

R, rituximab; l-g, low-grade; foll., follicular; ORR, overall response rate; CR, complete response; PR, partial response; m, months; indol., indolent; pts, patients; flu, fludarabine; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; PB, peripheral blood; BM, bone marrow; FND, fludarabine, mitoxantrone, dexamethasone; MCP, mitoxantrone, chlorambucil, prednisone; TTP, time to progression; DR, duration of response.

The median post-infusion serum levels plateaued after the sixth infusion (range 518.1–558.1 µg/ml). Most adverse events were mild and similar to those seen in previous studies.

Rituximab in aggressive NHL

A single-arm, open-label phase II study evaluated the clinical activity of rituximab in combination with CHOP as first-line treatment of aggressive NHL [53]. The patient population consisted of histologically documented aggressive lymphoma excluding patients with mantle cell, lymphoblastic or Burkitt’s lymphoma. Treatment was administered at 21-day intervals, with rituximab given on days 1 and 3 of each cycle at standard doses.

Toxicity was similar to that expected with each treatment alone. ORR was 94% (31 of 33 patients), with a CR rate of 61%. Intermediate- and high-risk patients (International Prognostic Index (IPI) score ≥2) had remissions sustained for at least 2 years.

The first large, prospectively randomized multicenter trial in previously untreated patients with aggressive NHL was performed by the French GELA, comparing CHOP alone with a rituximab–CHOP combination (R-CHOP) [54]. This study involved 399 elderly patients (aged 60–80 years) with diffuse large cell lymphoma (stage II–IV). With a median follow-up of 24 months, R-CHOP led to significantly more CRs (76% versus 63%, P = 0.005), 2-year event-free survival (EFS) (57% versus 38%, P < 0.001) and overall survival (OS) (70% versus 57%, P = 0.007).
compared with CHOP alone (Figure 3). This study documented a significant benefit of the combined immunochemotherapy in both patients with low-risk IPI \( (P < 0.001) \) and those with high-risk IPI \( (P < 0.03) \). There was no major difference between the two arms in terms of toxicity or severe infections. Thus, this ‘proof of concept’ study showed that the addition of rituximab to conventional CHOP is associated with superior results, and therefore suggests R-CHOP as the new standard for elderly patients with aggressive NHL.

In the USA, a similar study conducted by the Eastern Cooperative Oncology Group (ECOG), Cancer and Leukemia Group B (CALGB) and the Southwest Oncology Group (SWOG) is currently underway. In addition, a large international study (MINT) is also evaluating the combination of rituximab and CHOP-like chemotherapy in previously untreated younger patients with aggressive NHL.

Table 3. Clinical studies using rituximab combined with interferon in indolent and follicular NHL

<table>
<thead>
<tr>
<th>Indication</th>
<th>No. of pts ((n))</th>
<th>Schedule</th>
<th>Response rate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-g/foll. NHL (relapsed or refractory)</td>
<td>38</td>
<td>Weeks 1–12: IFN 3× weekly; weeks 5–8: standard dose(^a) R</td>
<td>CR 11%; PR 34%; TTP 25.2 m</td>
<td>Davis et al. [38]</td>
</tr>
<tr>
<td>I-g NHL (CD20-positive)</td>
<td>70</td>
<td>Weeks 1–4: standard dose(^a) R; until week 6: IFN 3× weekly for 6 m</td>
<td>Maximum response: CR 20%; PR 29%; DR 20 m</td>
<td>Offner et al. (presented at the rituximab meeting in Montreux, 2001)</td>
</tr>
<tr>
<td>L-g/foll. NHL (relapsed)</td>
<td>64</td>
<td>Week 1: IFN 1.5 Mio U/day; weeks 2 + 3: IFN 3 Mio U/day; weeks 4 + 5: IFN 6 Mio U/day; weeks 2–5: standard dose(^a) R</td>
<td>CR 33%; PR 37%; DR 19 m</td>
<td>Sacchi et al. [39]</td>
</tr>
<tr>
<td>L-g/foll. NHL (pts had a PR or minor response to a first course of R)</td>
<td>69</td>
<td>Two arms: (A) standard dose(^a) R; (B) week 1: IFN 3 Mio U/day; weeks 2–5: IFN 4.5 Mio U/day; weeks 3–6: standard dose(^a) R</td>
<td>(A) CR 11%, PR 65%; (B) CR 54%, PR 46%</td>
<td>Kimby et al. [40]</td>
</tr>
</tbody>
</table>

\(^a\)Four weekly doses of rituximab 375 mg/m\(^2\).  
R, rituximab; I-g, low-grade; foll., follicular; ORR, overall response rate; CR, complete response; PR, partial response; m, months; indol., indolent; pts, patients; flu, fludarabine; IFN, interferon; TTP, time to progression; DR, duration of response.

Table 4. Clinical studies using rituximab in patients undergoing high-dose chemotherapy and stem cell transplantation

<table>
<thead>
<tr>
<th>Indication</th>
<th>No. of pts ((n))</th>
<th>Schedule</th>
<th>Response rate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>indol. NHL</td>
<td>25</td>
<td>Two arms: (A) HDCT; (B) HDCT + standard dose(^a) R, 2× 375 mg/m(^2) R after HDCT</td>
<td>PCR-negative harvests: (A) 40%; (B) 93%</td>
<td>Magni et al. [41]</td>
</tr>
<tr>
<td>indol. NHL (pretreated)</td>
<td>65</td>
<td>1× 375 mg/m(^2) R during mobilization, standard dose(^a) R after transplantation</td>
<td>93% PCR-negative harvests</td>
<td>Flinn et al. [42]</td>
</tr>
<tr>
<td>foll. NHL and MCL</td>
<td>21</td>
<td>In vivo purge: 1× 375 mg/m(^2) R, 8× 375 mg/m(^2) R after transplantation</td>
<td>CR/CRu 86%; 7/7 pts had molecular remission after 1 year, 6/7 after 2 years</td>
<td>Buckstein et al. [43]</td>
</tr>
<tr>
<td>foll. NHL + MCL ((n = 3))</td>
<td>18</td>
<td>HDCT + standard dose(^a) R</td>
<td>7/7 pts became PCR negative</td>
<td>Voso et al. [44]</td>
</tr>
<tr>
<td>foll. NHL + MCL</td>
<td>22</td>
<td>standard dose(^a) R after transplantation</td>
<td>CR 92%; bcl-1/2-negativity 100% after 6 m</td>
<td>Brugger [45]</td>
</tr>
</tbody>
</table>

\(^a\)Four weekly doses of rituximab 375 mg/m\(^2\).  
R, rituximab; I-g, low-grade; foll., follicular; ORR, overall response rate; CR, complete response; PR, partial response; m, months; indol., indolent; pts, patients; PB, peripheral blood; BM, bone marrow; TTP, time to progression; DR, duration of response; HDCT, high-dose chemotherapy.
For patients with relapsed or refractory aggressive NHL, combinations of high-dose chemotherapy and rituximab followed by ASCT are an interesting new option. Recently published data suggest that the addition of rituximab to the ICE (ifosfamide, carboplatin, etoposide) regimen may significantly increase the CR rate achieved with ICE alone (55% versus 28%, respectively) without increasing toxicity [56]. Horwitz et al. [57] suggested that rituximab as adjuvant therapy after ASCT might lead to higher OS and PFS than expected with conventional ASCT regimens.

A rituximab–EPOCH (doxorubicin, etoposide, vincristine, cyclophosphamide, prednisone) regimen was found to be effective and well tolerated both in heavily pretreated patients with aggressive NHL (R. Stahel, presented at the rituximab meeting in Montreux, 2001) and in untreated patients [58]. Several smaller studies with different regimens combined with rituximab also point towards possible superior effects.

An overview of studies of rituximab in aggressive NHL is given in Table 5.

Mantle cell lymphoma

Rituximab has shown activity in patients with mantle cell lymphoma (MCL) with responses ranging from 20% to 38% [48, 55, 60, 61]. In a study conducted by Foran et al. [60] the ORR was 37% in 67 patients, with CR in 14% of the pretreated patients. The projected median DR in MCL was 1.2 years, with no difference between previously treated and untreated patients.

A phase II trial is ongoing to evaluate the concurrent use of rituximab plus CHOP in patients with newly diagnosed MCL [62]. Preliminary results including 39 patients show response rates of 96% with 48% CR. Nine of 25 patients who were bcl-1-positive at diagnosis showed PCR negativity after therapy. However, patients who achieved molecular remissions in peripheral blood or bone marrow had PFS similar to those without molecular response (16.5 versus 18.8 months; \( P = 0.51 \)). Thus, the possible benefit of this regimen has to be determined in larger studies.

In a randomized German multicenter trial, 37 patients with relapsed MCL were treated with FCM alone or in combination with rituximab [28]. An ORR of 77% was observed in patients treated with the combined immunochemotherapy compared with 27% in the FCM group. The estimated risk reduction for relapse of 63% suggested a superior efficacy of rituximab plus FCM compared with FCM alone (\( P = 0.0107 \)), although the number of patients is too small for final conclusions to be drawn.

Peripheral stem cell transplantation (PSCT) is increasingly being evaluated as first-line treatment for patients with MCL. Results reported thus far using additional treatment with rituximab in this setting are encouraging: all patients achieved clinical CRs after post-transplant therapy with rituximab, and most also had molecular remissions (71.5% to 100%) [41, 42, 63, 64]. For comparison, high-dose chemotherapy alone was effective in only one of nine cases [65], and ex vivo purging failed to eradicate PCR-detectable disease in most patients [66].

More recently, 77 previously untreated MCL patients received rituximab combined with the HyperCVAD-Methotrexate/Ara-C regimen (HCVAD) without PSCT [67]. In this study, the combination of the antibody and HCVAD in retrospective analysis appears equivalent to HCVAD with PSCT in patients <66 years
old, and superior in older patients. Longer follow-up and confirmatory studies are, however, warranted.

Although the data available so far suggest a beneficial role of rituximab in the treatment of MCL (Table 6), randomized trials with larger numbers of patients are recommended to fully determine the role of rituximab as single agent or in combination with chemotherapy in this disease.

### Rituximab in CLL

Several trials have been conducted to determine the efficacy of rituximab in CLL patients using standard doses. However, results were disappointing with only a limited number of short-lived PRs (11% to 25% of cases) [60, 61, 68, 69]. The ORR in the pivotal trial was 13% for patients with small lymphocytic lymphoma (SLL), contrasting with 60% for those with follicular lymphoma [9]. This might be due at least in part to the lower density of CD20 on CLL/SLL cells as compared with follicular lymphoma. Other reasons include the high number of B-cells and circulating CD20 [70]. In an attempt to improve on these results, a thrice-weekly dosing schedule was evaluated reporting higher response rates (CR 4%, PR 48%) [51].

An alternative strategy might be to increase the dose administered. Previously treated CLL patients received escalating doses of rituximab ranging from 500 up to 2250 mg/m² per infusion [50]. The response rates were 22%, 43% and 75% (P = 0.03) when response was correlated with dose (500–825, 1000–1500 and 2250 mg/m²). All responses were PRs. Ninety-four per cent of the patients had side-effects including fever, chills and nausea with the first rituximab infusion, but severe toxicity (grade 3/4) was only seen in 12%. At the highest dose level a significant number of side-effects were observed without severe toxicity.

Different combination therapy trials have been conducted. Four cycles of rituximab, cyclophosphamide and decandron induced 36% CR and 41% PR in 22 evaluable patients [71]. In fludarabine and anthracycline-naïve patients, concurrent use of rituximab and fludarabine resulted in an ORR of 90%, with CR of 32% to 47% [72, 73] and a median TTP for the responders of 11 months [73]. A comparison between sequential administration and simultaneous treatment indicated superior results in those patients who received rituximab together with fludarabine [73]. Combination chemoinmunotherapy with fludarabine, cyclophosphamide and rituximab also achieved high responses in previously untreated (n = 79; ORR 95%, CR 66%) [74] as well as in pretreated patients (n = 102; ORR 72%, CR 23%) [75]. Upfront treatment with rituximab might lead to higher response rates [76], particularly in early stages [77].

Our group has performed a multicenter phase II trial in which four cycles of fludarabine were given together with four cycles of rituximab [72]. Of 31 eligible B-CLL patients enrolled, 20 were previously untreated and 11 relapsed. Side-effects such as fever, chills and exanthema were mild and mainly associated with the

### Table 5. Clinical studies using rituximab in patients with aggressive NHL

<table>
<thead>
<tr>
<th>No. of pts. (evaluable)</th>
<th>Prior therapy</th>
<th>Schedule</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>33 (33)</td>
<td>No</td>
<td>6 cycles: day 1 375 mg/m² R; day 3 CHOP</td>
<td>ORR 94%; CR 61%; median DR: 26+ m</td>
<td>Vose et al. [53]</td>
</tr>
<tr>
<td>399 (398)</td>
<td>No</td>
<td>Two arms: (A) 8 cycles CHOP; day 1 375 mg/m² R; (B) 8 cycles CHOP alone</td>
<td>Median follow-up 24 m: (A) CR 76%, EFS 57%; OS 70%; (B) CR 63%, EFS 38%, OS 57%</td>
<td>Coiffier et al. [54] (GELA)</td>
</tr>
<tr>
<td>54 (52)</td>
<td>Yes or &gt;60 years old</td>
<td>Two arms: (A) 8x 375 mg/m² R; (B) 1x 375 mg/m²; 7x 500 mg/m² R</td>
<td>Pooled A + B: ORR 31%; Median TTP: 8+ m</td>
<td>Coiffier et al. [55]</td>
</tr>
<tr>
<td>31</td>
<td>Yes</td>
<td>3 cycles ICE; day 1 375 mg/m² R</td>
<td>ORR 81%; CR 55%</td>
<td>Kewlaramani et al. [56]</td>
</tr>
<tr>
<td>35 (29)</td>
<td>Yes</td>
<td>Standard dose a after transplant</td>
<td>Median follow-up 24 m: PFS 86%; OS 85%</td>
<td>Horwitz et al. [57]</td>
</tr>
<tr>
<td>20 (18)</td>
<td>No</td>
<td>6–8 cycles EPOCH; day 1 375 mg/m² R</td>
<td>CR 89%; PR 11%; median follow-up 9.3 m: PFS 89%; OS 75%</td>
<td>Wilson et al. [58]</td>
</tr>
<tr>
<td>39 (39) (50)</td>
<td>Yes</td>
<td>4–6 cycles EPOCH; day 1 375 mg/m² R</td>
<td>CR 23%; PR 46%; [CR 28%; PR 36%; median OS 29.3 m]</td>
<td>Stahel et al. (presented at the rituximab meeting in Montreux, 2001)</td>
</tr>
<tr>
<td>22 (22)</td>
<td>Yes</td>
<td>Standard dose a</td>
<td>ORR 36.5%; CR 4.5%</td>
<td>Reiser et al. (presented at the rituximab meeting in Montreux, 2001)</td>
</tr>
<tr>
<td>7 (7)</td>
<td>Yes (CHOP)</td>
<td>Standard dose a after PSCT</td>
<td>CR 43%; PR 57%; median PFS: 6 m</td>
<td>Tsai et al. [59]</td>
</tr>
</tbody>
</table>

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*aFour weekly doses of rituximab 375 mg/m².*

R, rituximab; PFS, progression-free survival; EFS, event-free survival; OS, overall survival; PSCT, autologous peripheral stem cell transplantation; EPOCH, etoposide, doxorubicin, vincristine, cyclophosphamide, prednisone; ICE, ifosfamide, carboplatin, etoposide; m, months.
first rituximab infusion. There were a total of 32 infections in 16 patients, none of which was fatal. The overall response rate was 87% with no difference between pretreated and untreated patients.

Taken together, these data, as summarized in Table 7, indicate that rituximab has efficacy in CLL but might require combination with chemotherapy. Thus, further information including the optimal schedule and best combination partner has to be established. The German CLL Study group is currently preparing such a study in which a fludarabine–cyclophosphamide (FC) combination will be compared with FC plus rituximab in a prospectively randomized fashion.

**Multiple myeloma**

CD20 is present on the malignant cells of 20% of patients with multiple myeloma (MM) [6]. In addition, CD20 is expressed on clonotopic B-cells, which may be relevant precursors in MM. Since CD20+ MM patients have a shorter survival compared with CD20− patients [78], the expression of this antigen might be associated with a more aggressive phenotype. A phase II clinical trial with single-agent rituximab has been reported [79]. Although the response rates were low (1/19 PR, 5/19 SD), five of six responders had CD20+ bone marrow plasma cells upon study entry. Median time to treatment failure was 5.5 months. In another trial, rituximab was used in combination with a melphalan/prednisone regimen in newly diagnosed MM patients [80]. Rituximab seemed to improve the ORR, but the impact on PFS is yet to be determined.

The combination of rituximab and IFN-γ might be particularly attractive in MM, since IFN-γ is a potent inducer of CD20 on plasma cell lines and clinical studies using this combination in MM are currently underway.

**Waldenström’s macroglobulinemia**

CD20 is expressed on malignant lymphoplasmacytic cells in most patients with Waldenström’s macroglobulinemia (WM). Several retrospective analyses have indicated activity of rituximab in these patients with high response rates even in refractory cases [81, 82]. Interestingly, disease-associated polyneuropathy improved after rituximab treatment [83]. In a recent report, mean

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<table>
<thead>
<tr>
<th>Table 6. Clinical studies using rituximab in patients with mantle cell lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of pts (evaluable)</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>74 (67)</td>
</tr>
<tr>
<td>10 (10)</td>
</tr>
<tr>
<td>42 (39)</td>
</tr>
<tr>
<td>40 (39)</td>
</tr>
<tr>
<td>(37)</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7 (7)</td>
</tr>
<tr>
<td>13 (12)</td>
</tr>
<tr>
<td>35 (35)</td>
</tr>
<tr>
<td>77 (75)</td>
</tr>
</tbody>
</table>

*Four weekly doses of rituximab 375 mg/m².

R, rituximab; PSCT, peripheral stem cell transplantation; pts, patients; FCM, fludarabine, cyclophosphamide, mitoxantrone; HDCT, high-dose chemotherapy; OS, overall survival; PFS, progression-free survival; HCVAD, HyperCAVD-Methotrexate/Ara-C.
IgM levels for all 30 patients were reduced from 2.4 to 1.5 mg/dl after single-agent rituximab, with 87% of the patients showing a decline of IgM levels of >25% [84]. Moreover, median bone marrow involvement was reduced from 60% to 15%. In addition, 63% of the patients had an increase in their hematocrit and platelet counts. Prospective studies are currently ongoing that seem to confirm the activity of rituximab in Waldenström’s disease [85].

Other B-cell malignancies

Several attempts have been made to evaluate rituximab in patients with primary cutaneous B-cell lymphomas (pCBCL), either intravenously or intralesionally [86, 87]. Therapy with rituximab appears to be effective, in particular for patients with primary cutaneous large B-cell lymphomas of the leg, who have a poorer prognosis using conventional therapies than patients with other subtypes of pCBCL. There are some reports on rituximab in other B-cell malignancies such as B-acute lymphoblastic leukemia (B-ALL), Burkitt’s lymphoma, AIDS-related lymphoma and primary CNS lymphoma. Responses have been documented, but more studies are warranted to determine the impact of rituximab in these disorders.

Table 7. Clinical studies using rituximab in CLL patients

<table>
<thead>
<tr>
<th>No. of pts (evaluable)</th>
<th>Prior therapy</th>
<th>Schedule</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 (9)</td>
<td>Yes</td>
<td>Standard dose(^e)</td>
<td>0</td>
<td>11</td>
<td>Winkler et al. [68]</td>
</tr>
<tr>
<td>15 (15)</td>
<td>Yes</td>
<td>Standard dose(^e)</td>
<td>0</td>
<td>7</td>
<td>Nguyen et al. [61]</td>
</tr>
<tr>
<td>29 (28)</td>
<td>Yes</td>
<td>Standard dose(^e)</td>
<td>0</td>
<td>14</td>
<td>Foran et al. [60]</td>
</tr>
<tr>
<td>28</td>
<td>Yes</td>
<td>Standard dose(^e)</td>
<td>0</td>
<td>25</td>
<td>Huhn et al. [69]</td>
</tr>
<tr>
<td>33 (29)</td>
<td>Yes</td>
<td>3× 375 mg/m(^2) (R) weekly for 4 weeks</td>
<td>4</td>
<td>48</td>
<td>Byrd et al. [51]</td>
</tr>
<tr>
<td>40 (39)</td>
<td>Yes</td>
<td>First dose: 375 mg/m(^2) (R). Second to fourth dose: fixed for each pt, doses were 500, 650, 825, 1000, 1500, 2250 mg/m(^2); given once a week</td>
<td>0</td>
<td>500–825 mg/m(^2); 22%; 1000–1500 mg/m(^2); 43%; 2250 mg/m(^2); 75%</td>
<td>O’Brien et al. [50]</td>
</tr>
<tr>
<td>22 (22)</td>
<td>Yes</td>
<td>Day 1 375 mg/m(^2) (R); day 2 cyclophos, days 1–7 decadron; every 4 weeks until a maximum response (median of 4 cycles)</td>
<td>36</td>
<td>41</td>
<td>Gupta et al. [71]</td>
</tr>
<tr>
<td>32 (31)</td>
<td>Yes (11 pts); no (20 pts)</td>
<td>Cycles 1 + 2: flu; cycles 3 + 4 flu plus R 375 mg/m(^2) (fractionated first dose), cycles 5 + 6 375 mg/m(^2) (R)</td>
<td>33</td>
<td>55</td>
<td>Schulz et al. [72]</td>
</tr>
<tr>
<td>104 (104)</td>
<td>No</td>
<td>Two arms: (A) 6 × monthly days 1–5 flu, 2 months later R at standard dose(^e); (B) 6 × monthly flu, day 1 of each cycle 375 mg/m(^2) R (+day 4 of the first cycle)</td>
<td>(A) 28; (B) 47</td>
<td>(A) 49; (B) 43</td>
<td>Byrd et al. [73]</td>
</tr>
<tr>
<td>79</td>
<td>No</td>
<td>6 cycles of flu/cyclophos; day 1 of the first cycle 375 mg/m(^2) (R), day 1 of the other cycles 500 mg/m(^2) (R)</td>
<td>66</td>
<td>29</td>
<td>Wierda et al. [74]</td>
</tr>
<tr>
<td>167 (102)</td>
<td>Yes</td>
<td>6 cycles of flu/cyclophos; day 1 of the first cycle 375 mg/m(^2) (R), day 1 of the other cycles 500 mg/m(^2) (R)</td>
<td>23</td>
<td>49</td>
<td>Manero et al. [75]</td>
</tr>
<tr>
<td>70 (57)</td>
<td>No</td>
<td>Standard dose(^e), eventually repeated courses at 6 m intervals</td>
<td>9</td>
<td>35</td>
<td>Hainsworth et al. [76]</td>
</tr>
<tr>
<td>31 (21)</td>
<td>No</td>
<td>8× 375 mg/m(^2) (R) weekly</td>
<td>19</td>
<td>71</td>
<td>Thomas et al. [77]</td>
</tr>
</tbody>
</table>

\(^e\)Four weekly doses of rituximab 375 mg/m\(^2\).

pts, patients; R, rituximab; flu, fludarabine; cyclophos, cyclophosphamide.

Post-transplant lymphoproliferative disorder

Rituximab was investigated in the treatment of post-transplant lymphoproliferative disorder (PTLD), which is mostly composed of CD20+ B-cells. The ORR ranged from 62% to 75% in solid organ recipients [88–90]. ORR of 92% (CR 46%) was reached in combination with 2-chlorodeoxyadenosine and granulocyte–
macrophage colony-stimulating factor [91]. Rituximab also appears to have an impact on the Epstein–Barr virus (EBV) infection that underlies PTLD after hematopoietic stem cell transplantation [92]. Pre-emptive therapy with the antibody appears to prevent EBV-associated PTLD [93]. Longer follow-up is required to assess the durability of the responses.

Hodgkin’s disease

The CD20 antigen is expressed on roughly 20% of Hodgkin–Reed–Sternberg (HRS) cells in classical Hodgkin’s disease (HD) [94]. In contrast, the malignant cell population in lymphocyte predominant HD (LPHD) express the CD20 antigen in high density (Figure 4).

Rehwald et al. [95] have treated 14 patients with relapsed LPHD or other CD20+ classical HD. The ORR was 86% with 8/14 CRs (57%) and 4/14 PRs (29%), with 10/12 responders in continuous remission at a median follow-up of 12 months. The median DR has not been reached at 20+ months. Encouraging results were also reported from another phase II study including only patients with LPHD [96], in which six of nine evaluable patients (67%) achieved a CR and three a PR (33%).

Based on the hypothesis that normal B-lymphocytes in patients with HD might promote HRS cell survival, Younes et al. [97] treated 24 patients with relapsed HD irrespective of CD20 expression on their HRS cells in order to deprive HRS cells from important growth signals. The patients received rituximab once a week for six doses. In the evaluable 22 patients the ORR was 23%. CD20 was expressed on HRS cells only in two cases of the responding patients.

Longer follow-up as well as larger number of patients are needed for a final judgement on rituximab in CD20+ HD. Possible new studies to be conducted include a combination of radiotherapy and rituximab in the early stages of LPHD, as well as chemotherapy and rituximab in the advanced stages.

Rituximab in autoimmune diseases

Autoimmune disorders are mediated at least in part by B-cells. Elimination of autoreactive B-cell clones is the rationale for the use of rituximab in these diseases. Currently, most information is available on the treatment of idiopathic thrombocytopenic purpura (ITP). A dose-escalation trial was reported in ITP patients with platelet counts of <75,000/µl who failed corticosteroid therapy [98]. Twenty-five per cent of the 20 patients who received four weekly doses of rituximab 375 mg/m² showed objective clinical responses. Other studies involving a total of 47 patients were conducted in cases resistant to standard therapy including splenectomy [99–101]. The attained ORRs ranged from 40% to 75%, and sustained responses for more than 6 months were reported. In responders, the rise in platelet count was usually observed 1 week after the first infusion of rituximab. Thus, mechanisms other than the reduction of circulating antiplatelet antibodies might explain the effect of rituximab in this disease. In fact, median serum IgG, IgM and IgA levels remained within normal limits throughout the study [101]. One might speculate that opsonized B-cells can inhibit macrophage Fc receptor function and clearance of IgG-coated platelets. The suppression of autoreactive B-cell clones might account for the sustained remissions observed in some patients.

Interest in the treatment of autoimmune hemolytic anemia (AIHA) with rituximab has grown after initial encouraging case reports. A small prospective study was recently reported [102]: five patients with chronic cold agglutinin disease were treated with a standard dose of rituximab with four of five patients responding (one CR, three PRs). Two further trials also documented high response rates with CRs between 83% and 100%, and DRs ranging from 4 months to 2.7 years [103, 104]. Eight of eight CLL patients with AIHA achieved a remission after treatment with a rituximab/cyclophosphamide/dexamethasone combination [105].

Others have applied rituximab in the prevention of acute graft-versus-host disease (aGVHD). B-lymphocytes may act as antigen-presenting cells capable of triggering T-cell activation. Though the clinical relevance of the elimination of B-cells in this context remains to be more precisely defined, the incidence of severe aGVHD in patients with NHL after allogeneic stem cell
transplantation was lower in those who had previously received rituximab (18% versus 51%) [106].

Additional autoimmune diseases in which rituximab is currently being evaluated include IgM polyneuropathy, dermatomyositis, myasthenia gravis, thrombotic thrombocytopenic purpura, acquired factor VIII deficiency, rheumatoid arthritis, pemphigus vulgaris and systemic lupus erythematosus.

Toxicity

Rituximab is generally well tolerated, in patients with both malignant and non-malignant disease, including children and pregnant women [104, 107]. Severe adverse events develop only in a small number of patients. The most common adverse events are infusion-related and occur most frequently during or shortly after the first infusion. This syndrome consists of chills, fever, headache, rhinitis, pruritus, vasodilation, asthenia and angioedema. Less often reported are hypotension, rash, bronchospasm, rash and pain at tumor sites. About 95% of these adverse reactions are mild or moderate and resolve completely after temporary interruption of the infusion. Symptomatic treatment with antipyretics, antihistamines, and, if necessary, steroids readily controls severe unwanted reactions in most cases.

Importantly, the increasing use of rituximab in entities other than follicular NHL has revealed no other side-effects than those previously described. Infusion-related side-effects are mediated by inflammatory cytokines such as TNF-α, interleukin (IL)-8 and IFN-γ [51]. This cytokine-release syndrome is more frequently observed in patients with higher numbers (>50 × 10⁹/l) of tumor cells in their peripheral blood [68]. Winkler et al. [68] found a correlation of clinical symptoms and increased serum levels of TNF-α and IL-6 90 min after the first application of rituximab (Figure 5A and B). Postmarketing surveillance database includes reports of very few cases with fatal outcome who were related to severe forms of the cytokine-release syndrome in patients with high peripheral tumor load and other comorbidities. In most fatal cases, patients had prior pulmonary or cardiovascular disease, pulmonary infiltrates or had been treated with cardiotoxic drugs. Thus, patients with a high number of circulating cells should only be treated with fractionated doses of rituximab initially, and should be closely monitored. In addition, only patients with <50 × 10⁹/l cell count peripherally should be treated. When the infusion of the antibody has to be interrupted due to adverse reactions, complete resolution of clinical symptoms has to be awaited before restarting the application.

Rituximab induces a rapid depletion of CD20+ B-cells in the peripheral blood. B-cells remain at low levels for at least 2–6 months with recovery to pretreatment values within 12 months [47]. Other hematological toxicity is generally mild and rare. About 10% of patients experience temporary reduction of platelets or neutrophils, and occasionally reduced immunoglobulin levels. Some case reports showed reactivation of hepatitis B following rituximab administration [108]. In contrast, a recently published Japanese study suggests that the risk for a reactivation might be lower than expected [109]. Most importantly, the incidence of other infections does not seem to be increased in patients treated with rituximab alone. This observation has been confirmed in the few available prospectively randomized studies. Combination with chemotherapy was also not associated with more toxicity than expected, although a higher rate of neutropenia has been described [26].

Human anti-chimeric antibodies (HACA) were rarely observed with no impact on toxicity and on clinical outcome [9, 110]. However, the detection of HACAs is difficult and has been neglected in most studies. Thus, further studies should aim at a more comprehensive investigation of auto-antibody development.

Single serious late effects have been documented, occurring weeks to months after treatment with rituximab, including arthralgia, vasculitis, serum sickness, acute agranulocytosis, uveitis and bullous cutaneous reaction possibly related to other yet to be clarified immune phenomena [111, 112].

Conclusions and prospects

Since rituximab has been widely documented as effective treatment associated with few serious side-effects, most patients with indolent lymphoma receive this chimeric monoclonal antibody during the course of their disease. In the USA and in Europe rituximab was also approved for patients with DLCL when com-
bined with standard chemotherapy (CHOP). Other entities currently under investigation include CLL, MCL, plasmocytoma, HD and autoimmune diseases. Although the use of rituximab in most of these entities has become standard praxis particularly in the US, carefully designed randomized studies are warranted to further define the optimal treatment strategies with this new exciting component.

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112. Rituximab 1999 package insert.