Rituximab consolidation after high-dose chemotherapy and autologous blood stem cell transplantation in follicular and mantle cell lymphoma: a prospective, multicenter phase II study

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Background: Patients with follicular (FL) or mantle cell lymphoma (MCL) are incurable with conventional therapy. We investigated the safety and efficacy of rituximab consolidation after autologous stem cell transplantation (ASCT) in order to prevent relapse by clearance of minimal residual disease (MRD).

Methods: Rituximab was given ~8 weeks after CD34+ cell enriched ASCT at 375 mg/m², weekly for 4 weeks. Monitoring of MRD was performed by repetitive PCR analyses.

Results: Thirty-one patients were included; one died early after ASCT before rituximab administration. Thirty patients (20 FL, 10 MCL) were evaluable after rituximab consolidation, and 27 of these were assessable for MRD detection. Rituximab consolidation post-ASCT was safe, the most common toxicity being infection. At a median follow-up of 42 months (range 13–96) after ASCT, 25 patients were censored with an actuarial event-free survival (EFS) of 81% at 4 and 5 years. Four patients (two FL, two MCL) relapsed, and one additional MCL patient died unexpectedly in complete remission. PCR-negativity was observed in 22% of the patients before ASCT, 53% post-ASCT (P = 0.0547), 72% after rituximab (P = 0.0018) and 100% at 6 months post-transplant (P < 0.001).

Conclusions: One single course of rituximab consolidation given after ASCT is safe, may help to eliminate MRD and may translate into improved EFS in both FL and MCL patients.

Key words: autologous transplantation, follicular lymphoma, mantle cell lymphoma, rituximab consolidation

Introduction

Patients with advanced follicular (FL) and mantle cell lymphoma (MCL) usually have widespread disease and are currently incurable by conventional chemotherapy [1–5]. The search for improved treatments includes high-dose chemotherapy (HDT) with autologous stem cell transplantation (ASCT) [6–9]. Initially, ASCT has been performed in progressing or relapsing FL patients. These studies yielded encouraging results, with prolonged progression-free and overall survival (OS) [6, 7]. More recently, phase II trials of HDT and ASCT after maximum response to conventional chemotherapy have been reported as front-line treatment in FL patients [6, 10, 11], and several phase III trials are currently under way to investigate the potential benefits of front-line ASCT in FL patients compared with conventional therapy [12, 13]. Similarly, ASCT has been used in patients with MCL with varying degrees of success [14–17].

Relapse after HDT and ASCT is caused by re-growth of residual malignant cells, arising either as a result of contamination of the transplant, or from cells remaining in the patient. This has led to the implementation of treatments to improve ASCT. One approach is the use of in vivo purging with rituximab, a chimeric monoclonal antibody that is specific for the CD20 B-cell surface antigen [18]. As a single agent, rituximab has demonstrated good efficacy in indolent and aggressive
non-Hodgkin’s lymphoma patients, and may induce remission in patients with MCL [19–22]. Combination of rituximab with CHOP chemotherapy improves efficacy in patients with indolent lymphoma [23]. Whilst in vivo purging may be able to remove malignant cells from the harvest, it is likely that the HDT per se will not eradicate all tumor cells remaining in the patient. Eradicating minimal residual disease (MRD) after HDT, however, may reduce the probability of relapse. Here we describe the safety and efficacy of ASCT followed by four doses of post-transplant rituximab consolidation in patients with advanced FL or MCL. This approach is safe and may help to eradicate MRD, as indicated by the induction of long-lasting clinical and molecular complete remissions in both FL and MCL patients.

Patients and methods

The study was an open label, multicenter, single arm, phase II study aimed at assessing the safety and efficacy of rituximab consolidation after ASCT in order to prevent relapse by clearance of MRD. The protocol (M39005) was approved by the local ethics committees and all patients gave written informed consent before entering the trial. The study was conducted according to the principles of the Declaration of Helsinki. The study was monitored externally by a professional clinical research organization (Algora, Munich, Germany).

Study design and treatment schema

The treatment consisted of three active steps: (i) an intensive induction chemotherapy (which was not part of the study); (ii) an autologous CD34+ cell selected stem cell transplant after total-body irradiation (TBI)/cyclophosphamide conditioning; and (iii) a 4-week course of a post-transplant rituximab consolidation (Figure 1). The recommended initial treatment consisted of 6 weeks of VACOP-B (etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin) [24] chemotherapy, followed by two cycles of VP16 (500 mg/m²), ifosfamide (4 g/m²), cisplatin (50 mg/m²) (VIP) chemotherapy [25], with or without etoposide (E) (50 mg/m²). Peripheral blood stem cells (PBSC) were collected after granulocyte colony-stimulating factor (G-CSF)-supported VIP-(E) (50 mg/m²). Peripheral blood stem cells (PBSC) were collected after granulocyte colony-stimulating factor (G-CSF)-supported VIP-(E) chemotherapy. Alternatively, equivalent induction therapy (e.g. CHOP [23]) and stem cell mobilization (e.g. DexaBEAM [26]) were allowed. As an in vitro purging strategy, CD34+ cells were positively selected from the harvest [27] using the CliniMACS (Miltenyi, Bergisch-Gladbach, Germany) or the Isolex 300 (Baxter, Munich, Germany) device. Study onset began immediately before transplantation. ASCT (day 0) was performed after fractionated TBI (6 × 2 Gy, days −6 through −4) and high-dose cyclophosphamide (2× 60 mg per kg bodyweight, days −3 through −2). Concomitant medication consisted of G-CSF, as well as fluconazole and ofloxacin post-transplant until neutrophil recovery. Trimethoprim–sulfamethoxazole prophylaxis for Pneumocystis carinii pneumonia was performed according to the guidelines of each participating center.

Eight weeks after transplantation, rituximab was scheduled at weekly intervals for 4 weeks at 375 mg/m². No further treatment was given thereafter. Rituximab was administered by slow intravenous infusion following standard guidelines, as recommended by the manufacturer (Hoffmann-La Roche AG, Basle, Switzerland). Rituximab was usually administered in an outpatient setting.

**Eligibility and study objectives**

Five German centres participated in this phase II study. Eligibility included patients being aged between 18 and 60 years with newly diagnosed CD20+ FL or newly diagnosed or relapsed CD20+ MCL according to the REAL classification. All patients were to be rituximab-naive. Patients were to be included with advanced clinical stage III or IV disease, a Karnovsky performance status of ≥70% and normal organ function. Only patients with a partial (PR) or complete response (CR) to the induction therapy were considered, and all patients needed to have a PCR-detectable t(14;18) bcl2/IgH rearrangement, a t(11;14) translocation or a monoclonal immunoglobulin rearrangement for the detection of MRD. The study objectives were to determine: (i) the safety of rituximab after ASCT; (ii) the clearance of MRD; and (iii) the event-free (EFS) and OS at a median follow-up time of at least 2 years after transplantation.

**Initial staging and response evaluation**

All patients underwent initial staging procedures including physical examination, complete blood counts, chemistry profile, computed tomography (CT) of the chest and abdomen, and bone marrow (BM) aspiration/biopsy. All areas of lymphoma involvement were documented. Target lesions were measured bidimensionally and followed serially to determine response to therapy. Toxicity was evaluated according to the National Cancer Institute of Canada Common Toxicity Criteria. The diagnosis of MCL was confirmed by t(11;14) translocation or cyclin D1 expression.

Patients’ BM and/or peripheral blood (PB) samples were monitored serially for MRD testing by PCR. PCR and follow-up examinations were performed prior to HDT, prior to rituximab consolidation, after the end of rituximab consolidation, at 6, 9, 12, 18 and 24 months post-transplant, and subsequently at 6 month intervals. Responses were evaluated by CT scan, and the Cheson criteria were used for response definition [28]. Radiology reports gave objective measurement of indicator lesions at each participating site. Patients with bone marrow involvement at study entry had to repeat bone marrow aspiration and biopsy to confirm CR.

EFS or time to treatment-failure (TTF) was defined as the interval from the date of transplantation to the date of documented tumor progression or the date of death if the patient died prior to documentation of disease progression, or to the last date the patient was documented to be in remission.

**PCR for the detection of MRD**

The molecular analyses were centrally performed by F.G. (University of Tübingen). Semi-nested PCR assay for clonal rearrangements of IgH genes was performed in the Department of Molecular Pathology at the University of Tübingen (by R. Kandolf and E. Kaiserling). A PCR-negative status was defined if all results from PB and/or BM were negative.
A PCR-positive status was defined if a positive signal was obtained in PB and/or BM.

**Semi-nested PCR for the (14;18) translocation**

Genomic DNA was isolated from PBMC using the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany). In the first stage of semi-nested PCR, a touchdown PCR was applied on 1–2 μg genomic DNA in a 50 μl reaction with 50 pmol of a primer specific for the BCL2-MBR (5’-GGTG-GTTTGGCCTTTAGAGA-3’) and a JH consensus primer (5’-ACCTGAGGAGACGGTGACCAGGGT-3’) [29]. For semi-nested reamplification, a 2 μl aliquot of stage 1 product was used in the same reaction mix containing the same BCL2-MBR primer and a JH4 primer (5’-ACCAGGGTTCCTGGCCACCCA-3’). The temperature profile was: 5 min at 94°C initial denaturation and 35 cycles at 94°C for 15 s, 60°C for 15 s and 72°C for 45 s. A final step at 72°C for 7 min was added.

Ten microliters of the PCRs were electrophoresed through a 3% agarose gel and stained with ethidium bromide.

**Semi-nested PCR for the (11;14) translocation**

In the first stage, a hot-start touchdown PCR was applied on 1–2 μg genomic DNA in a 50 μl reaction with 50 pmol of a primer specific for the BCL1-MTC (5’-TCCGTAGACCTGTTAGTTCAG-3’) and a JH consensus primer (5’-ACCTGAGGAGACGGTGACCAGGGT-3’) [30]. For semi-nested reamplification, a 2 μl aliquot of stage 1 product was used in a 50 μl hot-start PCR containing the same primer for the BCL1-MTC, a JH4 primer (5’-ACCAGGGTTCCTGGCCACCCA-3’) and additionally 20 μl Q-solution (Qiagen). The temperature profile was: initial denaturation at 95°C for 15 min followed by 35 cycles at 94°C for 15 s, 60°C annealing for 15 s and 45 s at 72°C. A final elongation at 72°C for 7 min was added.

Ten microliters of the PCRs were electrophoresed through a 3% agarose gel and stained with ethidium bromide.

**Statistical analysis**

Data for 30 patients were considered sufficient to allow meaningful descriptive analyses in order to determine the study objectives. If a patient had received at least one rituximab infusion, this patient was considered eligible for the intention-to-treat analysis.

Statistics were performed using the SAS system for Windows, release 8.02. Response rates were analysed by frequency tables. EFS and OS were analyzed by the Kaplan–Meier method. Patients without progression or death were censored at the last information available showing that the patient had not yet progressed. Adverse events (AEs) were analysed by frequency tables and on a per patient basis. If appropriate, 95% exact confidence intervals (95% CI) were given and P values only were calculated for descriptive purposes. The analysis was performed on a database, which was closed on 14 December 2003.

**Results**

**Patient characteristics**

Between October 1997 and July 2001, 31 patients <60 years of age with a histologically proven FL or MCL were treated. One FL patient (patient 27) died early after transplant before rituximab therapy, and was not evaluable for safety and efficacy of rituximab consolidation. Three other patients with FL did not have a PCR-detectable molecular marker and were excluded. On an intention-to-treat basis, however, all 30 patients were assessed for safety and efficacy of rituximab after ASCT.

The response and survival evaluation was performed separately for both the entire group of 30 patients, and for the 27 molecularly evaluable patients as treated per protocol. Since no differences were observed, safety and efficacy results were combined and are not illustrated separately.

The clinical characteristics of the 30 patients are listed in Table 1. The median time from initial diagnosis to autologous transplantation for all patients was 6.2 months (range 3.2–33.7). Three patients with MCL were treated in first or second relapse.

**Clinical response before rituximab consolidation**

After induction therapy, four CRs (13%) and 26 PRs (87%) were observed. All patients proceeded to ASCT. After transplantation, CR was observed in 13 patients (43%) while 17 patients (57%) were in PR (Table 2).
Clinical efficacy of rituximab consolidation after HDT and ASCT

Rituximab was started a median of 61.5 days (range 38–108) after transplantation. The CR rates continuously increased over time, from 43% after ASCT to 89% after rituximab consolidation (Table 2). Maximum response rates (100% CR; 95% CI 83.2% to 100%) were observed in all 20 FL patients and in nine of the 10 MCL patients (90% CR; 95% CI 55.5% to 99.8%), resulting in an overall CR rate of 97% (95% CI 82.8% to 99.9%). Interestingly, maximum responses by CT scanning were observed at 18 months post-ASCT and rituximab consolidation (Table 2).

Event-free survival

This analysis was carried out on an intention-to-treat basis. With a median follow-up of 42 months (range 13–96) after transplantation, the median actuarial TTF has not yet been reached. Twenty-five patients (83%) were censored; four patients relapsed (patients 10, 13, 14 and 23) and one MCL patient (patient 29) died unexpectedly in CR at 18 months post-transplant in a community hospital, due to respiratory failure. The two patients with FL (patients 10 and 13) relapsed 24 and 33 months after ASCT. Both patients are alive after having received second-line therapy. The two MCL patients (patients 14 and 23) had disease progression 24 and 39 months post-transplant, respectively. Patient 14 died 1 year later due to further lymphoma progression. Patient 23 is alive with disease, and is currently receiving salvage therapy.

At a median follow-up of 42 months post-ASCT, 28 of the 30 patients (93%) are alive and 25 are in CR with an actuarial EFS for the entire group of patients of 81% (95% CI 65% to 96%) at 48 and 60 months post-transplant.

The actuarial EFS for the 20 FL patients is 88% (95% CI 73% to 100%) at 48 and 60 months post-transplant. For the 10 MCL patients, the actuarial EFS is 78% (95% CI 51% to 100%) at 36 months and 64% (95% CI 30% to 97%) at 54 months post-transplant (Figure 2).

Molecular response to ASCT and rituximab consolidation

As mentioned earlier, three of the 20 FL patients did not have a PCR-detectable Bcl2/IgH marker (patients 9, 12 and 13), and were excluded. Thus, 27 patients (17 FL, 10 MCL) were evaluable for molecular remission analysis. A highly sensitive semi-nested PCR assay for the detection of cells carrying the t(14;18) translocation was applied. The sensitivity of the PCR detected at least one t(14;18)-carrying lymphoma cell diluted in 10⁵ normal cells. The sensitivity of the PCR for the detection of cells carrying the t(11;14) translocation was performed similarly. Serial dilutions with the t(11;14)-carrying cell line JVM-2 in normal PBMC were made to detect approximately one t(11;14)-carrying lymphoma cell diluted in 10⁵ normal cells (data not shown).

In 12 patients, harvested cells could be analyzed by PCR before and after CD34+ cell selection. Unfortunately, we could not test all the stem cell samples for MRD because of the limited material obtained after CD34+ cell selection. Only two of 12 (17%) harvests were PCR-negative before CD34+ cell selection. After selection, six of 12 patients were tested PCR-negative, suggesting that circulating tumor cells were present in the majority of patients at the time of stem cell harvest.

The PCR results are summarized in Figure 3. Before HDT, five of 23 (22%) (95% CI 7.5% to 43.7%) of the patients’ PB and/or BM samples were PCR-negative. One month after transplantation, 10 of 19 tested patients (53%) (95% CI 28.9% to 75.6%) were PCR-negative (P = 0.0547 compared with status before HDT). Four weeks after the start of rituximab consolidation, 13 of 18 tested patients (72%) (95% CI 46.5% to 90.3%) (P = 0.0018 compared with status before HDT) were PCR-negative, and at 6 months after ASCT and rituximab treatment, 100% of the tested patients (19/19) (95% CI 82.4% to 100%) were PCR-negative (P < 0.001). A pair-wise testing of the different groups showed no significant changes between the PCR status after HDT and the status immediately at

### Table 2. Clinical response rates and follow-up over time

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<tr>
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<th>Complete response (%)</th>
<th>Partial response (%)</th>
<th>Progressive disease (%)</th>
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<tbody>
<tr>
<td>Before ASCT</td>
<td>30</td>
<td>13</td>
<td>87</td>
<td>0</td>
</tr>
<tr>
<td>After ASCT</td>
<td>30</td>
<td>43</td>
<td>57</td>
<td>0</td>
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<tr>
<td>After rituximab</td>
<td>30</td>
<td>57</td>
<td>43</td>
<td>0</td>
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<tr>
<td>6 months</td>
<td>30</td>
<td>60</td>
<td>40</td>
<td>0</td>
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<tr>
<td>9 months</td>
<td>30</td>
<td>73</td>
<td>27</td>
<td>0</td>
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<tr>
<td>12 months</td>
<td>30</td>
<td>83</td>
<td>17</td>
<td>0</td>
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<tr>
<td>18 months</td>
<td>28</td>
<td>89</td>
<td>11</td>
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<td>24 months</td>
<td>28</td>
<td>89</td>
<td>4</td>
<td>7</td>
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*Response rates were evaluated by computed tomography scanning criteria for all 30 patients who were treated with ASCT and rituximab consolidation.

Response evaluation after rituximab was performed ~1 week after the last infusion.

ASCT, autologous stem cell transplantation.
the end of rituximab treatment ($P = 0.3133$), while a significant change was observed between rituximab treatment and the status at 6 months post-transplant (i.e. ∼4 months after rituximab) ($P = 0.0197$). Thereafter, no significant changes were observed. These results suggest that clearance of MRD may continuously occur up to 4 months after rituximab treatment. At the 24 months follow-up, 100% (95% CI 81.5% to 100%) (18/18) of the tested patients were PCR-negative ($P < 0.001$ compared with pre-HDT).

Individual PCR data from each patient at various time points are shown in Figure 4. During initial cytoreduction, some of the patients became PCR-negative. After treatment, additional patients became PCR-negative over time. At 6 months after HDT and rituximab consolidation, all patients evaluable for PCR analysis were PCR-negative. Four patients showed transient positive signals in PB and/or BM but were PCR-negative at later time points. One MCL patient (patient 23) became PCR-positive in peripheral blood 3 months before the relapse was documented, but was tested negative in the control test despite histological confirmation of a mediastinal relapse.

**Regeneration of hematopoiesis after ASCT**

Safety of HDT and ASCT was not part of this analysis, but data on the reconstitution of hematopoiesis were analyzed. As mentioned earlier, there was one early death after ASCT due to sepsis and multiorgan failure. Hematopoietic reconstitution after ASCT was rapid and stable. A median number of $7.1 \times 10^6$ (range 2.4–22.7 $\times 10^6$) positively selected CD34+ cells/kg were transplanted. Median time to leucocytes $>1 \times 10^9/l$ was 10 days (range 8–11) and median time to unsupported platelet counts $>20 \times 10^9/l$ was 11 days (range 8–16). CD20+ B cells were absent until 6 months post-transplant and remained in the subnormal range until 9–12 months post-transplant. At 18 months after ASCT and rituximab treatment, the number of circulating B cells returned to normal values in all patients (data not shown). With a maximum follow-up of 96 months post-transplant, none of the patients developed therapy-related myelodysplasia or secondary acute myeloblastic leukemia.

**Safety of rituximab after ASCT**

Adverse events (AEs) were analyzed after ASCT and rituximab consolidation. A total of 170 AEs were reported during the entire treatment procedure, mostly grade 1–2. These events were classified as either unknown with respect to rituximab treatment or as possibly related. The most common AEs were mild infections ($n = 67; 39\%$), which occurred in 25 of 30 patients (83%). Only 28 of the 170 events (16%) were grade 3–4 (Table 3). As expected, infection, leukopenia and lymphocytopenia were the most common AEs, constituting 4.7%, 3.6% and 3.5%, respectively. The number of serious AE (SAEs) was low throughout the study, constituting 16 of a total of 170 AEs (9.4%) observed. Among them, pneumonia was the most common and serious AE. For safety reasons at the beginning of the study, seven patients with pneumonia were re-hospitalized and were therefore classified as SAEs (Table 4). However, none of these infections was life-threatening, and all
patients recovered fully after appropriate antibiotic treatment. One patient with MCL died unexpectedly in CR (see above) 18 months after ASCT and rituximab therapy due to pulmonary failure.

**Discussion**

Given the incurability of advanced FL and MCL with conventional therapy, we initiated a potentially important approach in 1997 by combining two highly active treatment modalities, i.e. HDT with CD34+ enriched ASCT and one course of post-transplant rituximab consolidation in order to prevent relapse by clearance of MRD.

We demonstrate that four doses of rituximab after ASCT are well tolerated; there was no infusional toxicity. During follow-up, we observed mild infections in 83% of our patients, including eight episodes of grade 3 infections, but none of them was life-threatening. The reason for this relatively high rate of mild infections is unexplained, but most likely not related to late occurring cytopenias, since we observed grades 3–4 leukopenias in only 3.6% of our patients. However, the patients in our study were under close surveillance, and there was more opportunity to detect even mild infections. The low rate of neutropenia in our study is in contrast to a recent report by the Stanford group, which observed grades 3–4 neutropenia in 54% of their patients without any serious infections [31]. B-cell recovery was similar in both studies.

In terms of efficacy, the combined treatment approach may indeed help to eliminate MRD in peripheral blood and/or bone marrow. With a median follow-up of 42 months after ASCT, high rates of long-lasting clinical and molecular remissions were observed. These data are encouraging and may translate into improved EFS and possibly OS in this group of younger patients. However, long-term follow-up will have to be awaited.

Interestingly, no differences in clinical and molecular response rates or TTF rates were apparent between FL and MCL patients, suggesting that this approach may also translate into prolonged EFS and OS in MCL patients. However, the small number of patients in this study has to be considered. Our observation is in line with data from two studies performed by Hiddemann et al. [12] and Molina et al. [32], who showed an improved disease-free and possibly OS in MCL patients transplanted in first CR. Late relapses, however, were observed in these studies, suggesting that ASCT alone may not be curative in MCL patients. Similarly, conventional CHOP chemotherapy when given with rituximab does not lead to a prolonged progression-free survival in MCL patients as demonstrated in a single arm, non-comparative trial [33]. Although preliminary data from a randomized trial by Hiddemann et al. [34] do suggest that the addition of rituximab to chemotherapy improves the outcome in low-grade, including MCL, lymphomas, a significant number of patients relapse, indicating that the optimal treatment for long-term control of FL and MCL patients still needs to be determined.

In the future, however, therapeutic strategies may change, particularly by combining rituximab with various conventional chemotherapy regimens, such as CVP (cyclophosphamide, vincristine and prednisone) or CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone). Therefore, the clinical activity of rituximab and its relevance in the setting of HDT and post-transplant rituximab consolidation may be overstated, and not applicable to future patients who will all have received rituximab–CVP or rituximab–CHOP [23] prior to HDT.

The presence of bcl1 in MCL and bcl2/IgH gene rearrangements in FL can be detected by highly sensitive PCR and may be used as molecular markers of MRD. Clearance from the BM of cells carrying the bcl2 rearrangement has been
associated with a lower risk of relapse, and the clearance of bcl2-positive cells can be viewed as a possible early indicator of treatment efficacy [35–37]. In our study, sequential PCR analyses of PB and/or BM have shown impressive rates of molecular remissions in both FL and MCL patients (see Figures 3 and 4) with a long-lasting follow-up of nearly 70 months. Being aware that the follow-up is somewhat short for FL, these early data are encouraging, with an actuarial 48- and 60-month EFS of 81%.

Our results are in line with those from Magni et al. [38], who showed successful in vivo purging of CD34+ PBSC harvests by the combined use of both sequential HDT and rituximab-purged stem cell autografting in a pilot study in 15 patients with MCL and FL. Recently, these data have been updated in 28 MCL patients, demonstrating an EFS and OS at 54 months of 79% and 89%, respectively [39]. In this particular study, rituximab was infused for a total of six doses (four before stem cell harvest and two after the final myeloablative step), whereas in our study, rituximab was given only four times post-transplant. The results of our study show that in some patients the molecular conversion was transient, and in others a clinical relapse of the disease was documented despite the molecular negativity. This observation supports the finding of Howard et al. [33] in MCL, that molecular remissions are not predictive of progression-free survival. In addition, conversion of PCR-positivity to PCR-negativity in follow-up after ASCT for FL has been observed previously where further therapy for MRD was not administered [40]. Moreover, the relevance of molecular response following rituximab has not been validated, as many patients may have residual disease and yet be PCR-negative, as demonstrated also in the present study. Nevertheless, although a contribution of a delayed effect of HDT with ex vivo purged ASCT cannot be excluded in our patients, we favor the notion that the clearance of MRD might be due to the efficacy of rituximab, supported by the significant improvement of PCR-negativity over time.

However, based on the design of our study, it is impossible to evaluate the only effects of rituximab in the chain of various treatment modalities, i.e. induction chemotherapy, HDT with purged CD34+ selected ASCT, and rituximab post-transplant. Only a randomized study would ultimately be capable of differentiating the effects of the various treatment components.

Currently, it is not known from randomized studies whether ASCT with or without rituximab can achieve longer OS in patients with FL or MCL when compared with conventional chemotherapy plus rituximab. In this respect it is noteworthy that molecular responses have also been observed with rituximab alone or in combination with conventional chemotherapy [22, 41–43]. However, even among molecularly responding patients, no convincing plateau of the freedom from recurrence curve has been observed, either in FL or in MCL. Longer follow-up of current studies as well as phase III randomized studies will ultimately determine whether clearance of MRD post-transplant with rituximab may translate into improved outcomes.

References


