Conventional chemotherapy has failed to substantially prolong survival for patients with advanced follicular lymphoma. To improve outcomes, the German Low-Grade Lymphoma Study Group (GLSG) initiated a randomized trial to compare the effect of potentially curative myeloablative radiochemotherapy followed by autologous stem cell transplantation (ASCT) with interferon-α (IFN-α) maintenance therapy in first remission. Three hundred seven patients (younger than 60 years) with follicular lymphoma were recruited into the trial from 130 institutions. After 2 cycles of cyclophosphamide-doxorubicin-vincristine-prednisone (CHOP) or mitoxantrone-chlorambucil-prednisone (MCP) induction chemotherapy, patients were randomly assigned to either the ASCT or the IFN-α group. The respective therapy was started when patients achieved complete or partial remission after induction chemotherapy. Two hundred forty patients with follicular lymphoma were evaluable for the comparison of ASCT and IFN-α. In patients who underwent ASCT, the 5-year progression-free survival (PFS) rate was 64.7%, and in the IFN-α arm it was 33.3% (P < .0001). As expected, acute toxicity was higher in the ASCT group, but early mortality was below 2.5% in both study arms. In this randomized, multicenter trial, high-dose radiochemotherapy followed by ASCT significantly improved PFS compared with IFN-α in patients with follicular lymphoma when applied as consolidation in first remission. Longer follow-up is necessary to determine the effect of ASCT on overall survival. (Blood. 2004;104:2667-2674)

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Introduction

Indolent lymphomas are B-cell malignancies characterized by a slowly progressive clinical course and a median survival of 7 to 10 years. Morphologically, most cases represent follicular lymphoma grades I and II, whereas only few show marginal zone, lymphoplasmacytic, or small lymphocytic histology. In stages I and II, the disease may be cured by radiotherapy. However, in more than 80% of patients, follicular lymphoma is diagnosed during advanced Ann Arbor stages III and IV disease, at initial presentation. Given that conventional chemotherapy is not curative and does not substantially prolong overall survival (OS), wait-and-watch strategies are frequently pursued, and chemotherapy is given only to symptomatic patients.

To improve the outcomes for patients with indolent lymphoma subtypes, interferon-α (IFN-α) maintenance therapy was introduced in various studies. In a recent meta-analysis, IFN-α significantly prolonged OS compared with observation alone in patients with follicular lymphoma. Monoclonal antibodies targeting B cell-specific antigens may be another promising approach. In follicular lymphoma, the anti-CD20 antibody rituximab as single agent achieved overall response rates of approximately 50% to 60%. Because in vitro data suggest a synergistic effect of combined immunochemotherapy, various phase 2 studies investigated the efficacy of a combined approach and reported encouraging results. In a recent trial of the German Low-Grade Lymphoma Study Group (GLSG), significant improvements in the overall response rate and in progression-free survival (PFS) could be demonstrated in follicular lymphoma.

Recently, the potentially curative concept of high-dose therapy followed by autologous stem cell transplantation (ASCT) was introduced to eliminate residual lymphoma cells after conventional induction chemotherapy. In several phase 2 studies, promising results were achieved. To assess the role of myeloablative...
radiochemotherapy followed by ASCT in follicular lymphoma as consolidation therapy during first remission, the GLSG embarked in 1996 a randomized comparison of this approach compared with IFN-\(\alpha\) maintenance therapy in patients younger than 60 years of age.

Patients, materials, and methods

Inclusion criteria

Inclusion criteria comprised previously untreated patients between 18 to 59 years of age with advanced Ann Arbor stage III and IV follicular lymphoma, mantle cell lymphoma, or lymphoplasmacytic lymphoma according to the current World Health Organization (WHO) classification.\(^{13}\) Histologic diagnosis was confirmed by central pathology review. Similar to the criteria of the British National Lymphoma Investigation (BNLI), patients had to be in need of therapy as defined by one of the following: B symptoms, hematopoietic insufficiency (granulocyte count less than 1500\(\mu\)L, hemoglobin level less than 10 g/dL, platelet count less than 100,000/\(\mu\)L, or bilirubin level 2.0 mg/dL or higher), or renal function (creatinine greater than 2.0 mg/dL) were not enrolled. Local ethics committees of the participating centers approved the study protocol, and all patients gave informed consent in accordance with the Declaration of Helsinki.

Treatment schedule

Initially, patients were randomly assigned for cytoreductive therapy with CHOP (cyclophosphamide 750 mg/m\(^2\) intravenously, day 1; doxorubicin 50 mg/m\(^2\) intravenously, day 1; vincristine 1.4 mg/m\(^2\) [maximum, 2 mg] intravenously, day 1; and prednisone 100 mg/m\(^2\) by mouth, days 1-5) or MCP (mitoxantrone 8 mg/m\(^2\) intravenously, days 1-2; chlorambucil 3 \(\times\) 3 mg/m\(^2\) by mouth, days 1-5; and prednisone 25 mg/m\(^2\) by mouth, days 1-5). In Beginning in July 1998, all patients received CHOP because a randomized comparison of CHOP with MCP showed that MCP was associated with a significant impairment of hematopoietic stem cell mobilization. After 2 cycles of therapy, patients were randomly assigned to myeloablative radiochemotherapy followed by ASCT or to IFN-\(\alpha\) maintenance after the completion of induction therapy (Figure 1). Patients achieving complete remission (CR) after 4 cycles of initial cytoreductive chemotherapy immediately proceeded to consolidation therapy. All other patients received 6 cycles of induction therapy. Patients who had progressive disease during induction therapy or who did not achieve at least partial remission after the completion of induction therapy were removed from the study.

Patients in the ASCT arm received intensified mobilization chemotherapy with Dexa-BEAM (dexamethasone 3 \(\times\) 8 mg by mouth, days 1-10; BCU\(\mathrm{N}60 \text{ mg/m}^2\) intravenously, day 2; melphanal 20 mg/m\(^2\) intravenously, day 3; etoposide 75 mg/m\(^2\) intravenously, days 4-7; cytarabine 2 \(\times\) 100 mg/m\(^2\) intravenously, days 4-7; and granulocyte–colony-stimulating factor [G-CSF] initiated on day 11). Peripheral stem cells were harvested and subsequently cryopreserved without any purging procedure. At least 2.0 \(\times\) 10\(^9\)/kg body weight CD34\(^+\) cells (and 2.0 \(\times\) 10\(^9\)/kg body weight CD34\(^+\) cells as backup) were required for ASCT. Myeloablative therapy was performed within 2 months of mobilization and consisted of a combined total body irradiation (TBI) (12 Gy; TBI was fractionated into 6 applications of 2 Gy on days \(-6 \text{ to } -4\); pulmonary dosage was limited to 8 Gy) and cyclophosphamide (60 mg/kg body weight intravenously, days \(-3\) and \(-2\)) regimen. Previously harvested peripheral blood stem cells were reinfused on day 0. G-CSF was initiated on day +1 (Figure 1).

Patients randomly assigned to the IFN-\(\alpha\) maintenance study arm received 2 additional courses of conventional chemotherapy to balance the mobilization scheme (Dexa-BEAM). Subsequently, \(\alpha\)-interferon was applied at a dose of 5 \(\times\) 10\(^6\) units subcutaneously 3 times weekly until progression\(^{14}\) (Figure 1).

Response criteria and evaluation

CR was defined as the complete absence of disease manifestations for at least 4 weeks. PR was defined as at least a 50% reduction of all evaluable lymphoma manifestations, without the appearance of new lesions for at least 4 weeks. Unconfirmed CR (CRu) were evaluated as PR. Minimal response (MR) was defined as a reduction of all evaluable lymphoma manifestations of less than 50%. Stable disease (SD) was defined as no reduction of evaluable lymphoma manifestations. Progressive disease (PD) was defined as an increase in lymphoma-associated symptoms, the appearance of new lymphoma manifestations, or an increase in the volume of lymphoma of more than 25%.

Stage procedures included clinical examination, complete blood count, serum biochemistry profile, chest radiography, abdominal ultrasound, computed tomography of the neck, chest, and abdomen, and bone marrow biopsy. Staging was performed before therapy, after every second cycle of induction therapy, and before and after ASCT. In addition, follow-up was performed every 3 months in both study arms.

Progression-free survival (PFS) was defined from the end of successful induction therapy until documented progression or death. OS was defined as the time between the end of induction therapy and death. The frequency and severity of adverse effects was recorded according to the WHO classification.\(^{19}\)

Randomization and statistical analysis

Randomization was carried out after 2 cycles of induction therapy to allow smaller study centers in which ASCT could not be performed to find an appropriate transplantation center. Randomization was carried out centrally, blocked, and stratified according to histology (follicular lymphoma vs mantle cell lymphoma vs lymphoplasmacytic lymphoma), number of risk factors at baseline according to the International Prognostic Index (IPI)\(^{20}\) (2 or less vs 3 or more), response after 2 cycles of chemotherapy (CR, PR vs MR, SD), and initial cytoreductive therapy (CHOP vs MCP).

The primary trial end point was defined as PFS after the completion of induction therapy. This parameter was monitored continuously and was analyzed by means of a sequential procedure to allow randomization to end as soon as a significant difference or no difference between the 2 study arms was detected. The log-rank test statistic Z and its variance V were calculated after each event and were plotted as a sample path in the Z-V plane. As soon as the sample path crossed the upper boundary of the triangular continuation region, a significant advantage of ASCT was revealed. If the sample path crossed the lower boundary of the triangle, the statistical test indicated no significant difference between ASCT and IFN-\(\alpha\) maintenance therapy.

Based on a significance level of \(\alpha = 0.05\) and an expected hazard ratio of \(\lambda = 0.5\), the one-sided triangular test for the log-rank statistic was designed to detect the superiority of ASCT with a probability of 95%.\(^{21}\) Based on the estimated PFS after IFN-\(\alpha\) maintenance and the recruiting rates from the previous GLSG trial, a maximum of 65 events and a trial duration of approximately 5 years were estimated. The maximum possible
number of events of the sequential test was calculated to 154. The fixed-sample test would have required 91 events to detect a hazard ratio of 50% with a power of 95% at a significance level of 5%.

Randomly assigned patients were evaluable for PFS analysis if their documented histologic diagnosis and Ann Arbor stage met the inclusion criteria. In addition, induction therapy had to be completed with at least PR; stem cell mobilization with Dexa-BEAM or consolidation therapy was initiated according to randomization. In addition, a strict intention-to-treat analysis of PFS was performed to control for a potential selection bias of excluded patients. Intention-to-treat analysis included all patients who achieved at least PR after induction therapy.

Kaplan-Meier estimates were calculated for all time-to-event variables. Two-year- and 5-year-event-free survival probabilities were given with 95% confidence interval (95% CI). Probability for the main parameter was calculated with respect to the sequential design. The 2-sided log-rank test was used for all other time-to-event variables. All statistical calculations were based on data from patients who were evaluable at the time of the final analysis (overrun analysis for the sequential test). Multiple Cox regression analysis with forward stepwise selection applying the Wald statistic was performed for PFS. Categorical baseline variables and safety data were compared with results from the 2-sided exact Fisher test, and continuous baseline variables were compared with results from the 2-sided Mann-Whitney U test. The significance level was set to α = 0.05.

The design of the triangular test, the calculation of the sample size, and the analysis of the main parameter were carried out using the PEST3 software (PEST version 3; Applied Statistics Department, Reading University, United Kingdom). All other statistical analyses were performed using the SAS system (SAS version 8.02; SAS Institute, Cary, NC).

Results

Between July 1996 and September 2000, 375 patients from 130 clinical institutions were randomly assigned to either ASCT or IFN-α maintenance. In April 1999, the sequential procedure showed a significant prolongation of PFS after ASCT compared with IFN-α maintenance therapy (Figure 2). However, the GLSG decided to continue randomization to prospectively evaluate the effect of ASCT on overall survival and the incidence of late-onset toxicities. Follicular lymphoma was diagnosed in 307 (81.9%) of patients, mantle cell lymphoma in 15 (4.0%), and lymphoplasmacytic lymphoma in 42 (11.2%). Eleven (3.0%) patients were excluded because the central pathology review did not confirm the initial diagnosis (4 chronic lymphocytic leukemia [CLL], 4 marginal zone lymphoma and 3 aggressive lymphoma).

In 279 patients, consolidation therapy was initiated and outcome was evaluable according to the study protocol. After a median follow-up of 4.2 years, the PFS rate after ASCT was 60.7% at 5 years (95% CI, 50.5%-70.8%) compared with 32.7% (95% CI, 24.3%-41.2%) in patients receiving IFN-α maintenance (P = .00174; sequential log-rank test). Similar findings of prolonged PFS after ASCT were detected in the intention-to-treat analysis.

In patients with mantle cell lymphoma (n = 12), the 2-year PFS rate after ASCT (n = 4) was 75.0% (95% CI, 32.6%-100.0%) compared with 37.5% (95% CI, 4.0%-71.0%; P = .46) after IFN-α maintenance (n = 8). The 5-year PFS rate could not be calculated because of the short follow-up of patients with mantle cell lymphoma.

In patients with lymphoplasmacytic lymphoma (n = 27), the 2-year PFS rate after ASCT (n = 16) was 64.9% (95% CI, 40.0%-89.8%) compared with 72.7% (95% CI, 46.4%-99.0%; P = .98) after IFN-α maintenance (n = 11). The 5-year PFS rate after ASCT was 36.1% (95% CI, 1.6%-70.6%) compared with 49.9% (95% CI, 17.8%-82.0%) in the IFN-α maintenance group.

Because biologic behavior and response to therapy varied strongly among patients with the different lymphoma subtypes included in our trial and most diagnoses were of follicular lymphoma, the emphasis of this analysis is on the results obtained from patients with follicular lymphoma.

Characteristics of patients

Two hundred forty patients with follicular lymphoma were evaluable for the comparison between ASCT and IFN-α therapy. The trial profile is shown in Figure 3. In this subgroup, 74.2% were diagnosed with stage IV disease, 27.9% had elevated serum lactate dehydrogenase (LDH) levels, and 36.3% had B symptoms. In addition, of the 217 patients evaluable according to IPI, 58.5% had low-risk IPI scores, 33.2% had low-intermediate IPI scores, and 8.3% high-intermediate IPI scores. Characteristics of patients in the 2 study arms were comparable and are summarized in Table 1.

Response to therapy

After cytoreductive therapy with CHOP (n = 86) or MCP (n = 28), 22 (19.3%) patients in the ASCT group achieved CR, and 92 (80.7%) achieved PR. In 31 (27.2%) patients, the assigned number of 4.0 × 10^6/kg body weight CD34+ stem cells (2.0 × 10^6/kg body weight CD34+ stem cells for transplantation and 2.0 × 10^6/kg body weight CD34+ stem cells as backup) could not be separated after Dexa-BEAM mobilization. Nevertheless, 19 of these patients received myeloablative radiochemotherapy followed by ASCT because fewer stem cells were retransfused (n = 15), stem cells were collected after a second course of Dexa-BEAM (n = 1), or steady state mobilization was performed (n = 3). These data were included in the statistical analysis. After consolidation with radiochemotherapy and ASCT, 52.1% of the patients achieved CR and 45.8% achieved PR.

In the IFN-α group, 20 of 126 (15.9%) patients achieved CR, and 106 (84.1%) achieved PR after induction therapy. After 2 additional cycles of consolidation chemotherapy, 21.4% (n = 27) of the patients achieved CR and 77.8% (n = 98) achieved PR. Subsequently, IFN-α maintenance therapy (5 × 10^6 units subcutaneously) 3 times weekly was initiated.
Progression-free survival

After a median follow-up of 4.2 years (4.1 years, ASCT study arm; 4.4 years, IFN-α study arm), 31 relapses (27.2%) were observed in the ASCT group and 76 (60.3%) relapses in the IFN arm. In addition, 5 deaths occurred in remission (4 patients in the ASCT study arm and 1 in the IFN group). One patient died shortly after ASCT because of heart failure, 2 patients had infectious complications after ASCT or Dexa-BEAM mobilization, and 1 patient committed suicide after Dexa-BEAM. The patient in the IFN study group died of pneumonia after therapy for secondary rectum carcinoma. Accordingly, PFS was significantly different in the 2 study arms. In patients who underwent ASCT, the PFS rates were 79.1% after 2 years (95% CI, 71.4%-86.9%) and 64.7% after 5 years (95% CI, 54.6%-74.8%) compared with 52.7% (95% CI, 43.8%-61.7%) after 2 years and 33.3% (95% CI, 24.3%-42.3%) after 5 years in the IFN-α study arm (P < .0001; log-rank test; Figure 4). Similar results were obtained in the intention-to-treat analysis of the 283 patients evaluable for PFS. In the ASCT arm (n = 127), the 5-year PFS rate was 63.0% (95% CI, 51.8%-74.3%) compared with 32.0% (95% CI, 22.4%-41.6%) in the IFN-α group (n = 106; P < .0001).

Additional analysis of PFS was performed according to the response to initial induction chemotherapy. CR patients had a 5-year PFS rate of 72.3% (95% CI, 50.6%-93.9%) in the ASCT group (n = 22) compared with a PFS rate of 42.0% (95% CI, 19.3%-64.7%) in the IFN-α subgroup (n = 20; P = .0861). PFS was significantly different in patients who achieved PR. In the ASCT arm (n = 92), the 5-year PFS rate was 63.0% (95% CI, 51.8%-74.3%) compared with 32.0% (95% CI, 22.4%-41.6%) in the IFN-α group (n = 106; P < .0001).

Analyses of PFS according to IPI scores demonstrated a similar advantage of ASCT in both subgroups. In the low-risk group (n = 127), the 5-year PFS rate in patients who underwent ASCT (n = 53) was 66.7% (95% CI, 51.4%-82.1%) compared to 39.4% (95% CI, 27.0%-51.8%) in the IFN-α arm (n = 74; P = .0053; Figure 5A). Similar results were obtained in the intermediate IPI subgroup (n = 90). The 5-year PFS rate was 67.3% (95% CI, 52.4%-82.2%) in the ASCT arm (n = 45) and only 25.6% (95% CI, 12.1%-39.0%) in the IFN-α arm (n = 45; P = .0002; Figure 5B).

Multiple Cox regression analysis was performed to independently evaluate the effect of the parameters included in the IPI (elevated serum LDH level, extranodal involvement (more than 1 site), ECOG performance status 2 or greater), the choice of induction therapy (MCP vs CHOP), and the choice of consolidation therapy (ASCT vs IFN-α maintenance) on PFS. This analysis identified ASCT with a hazard ratio of 0.388 (95% CI, 0.250-0.601; P < .0001) and low number of involved extranodal sites with a hazard ratio of 0.565 (95% CI, 0.354-0.901; P = .0166) to be independently associated with an improved PFS rate.

Overall survival

After a median follow-up of 4.2 years, 31 of the 240 (12.9%) evaluable patients with follicular lymphoma have died. The survival probability after the end of induction therapy was 94.5% (95% CI, 91.6%-97.4%) after 2 years and 84.3% (95% CI, 78.9%-89.6%) after 5 years (Figure 6). Given that the number of evaluable patients and the median follow-up is still too short to definitively evaluate OS in both study arms, these results are still blinded.

Toxicity

As expected, acute toxicity was higher in the ASCT study arm. Hematologic toxicity was significantly more frequently observed in
Anemia (95.2%; 44.8% grades 3 and 4), leukocytopenia (100%; 96.2% grades 3 and 4), granulocytopenia (91.4%; 90.5% grades 3 and 4), and thrombocytopenia (97.1%; 96.2% grades 3 and 4) according to the WHO classification were observed in almost all patients. The median time of thrombocytopenia less than 30,000/μL after myeloablative radiochemotherapy and ASCT was 19 days (range, 10-76 days), whereas the median duration of leukocytopenia less than 1000/μL was 16 days (range, 11-81 days). Accordingly, infections occurred in 85.6% (23.1% grades 3 and 4) in the ASCT group in comparison with 31.7% (1.7% grades 3 and 4) in the IFN-α study arm. However, the mortality rate from acute infections was only 1.8% in the ASCT study arm. Other types of nonhematologic toxicity also occurred more frequently in patients who underwent stem cell transplantation. The most frequent nonhematologic adverse effect was mucositis, which was observed in 89.5% (53.3% grades 3 and 4) of patients. In addition, gastrointestinal adverse effects (nausea and vomiting) in 84.8% of patients, pulmonary in 26.9%, renal in 10.6%, and liver toxicity in 44.2% were also observed more frequently in patients who underwent stem cell transplantation.

In contrast, muscle and bone pain and depression occurred more frequently during IFN-α maintenance therapy (Table 3). The toxicity was evaluated using the World Health Organization (WHO) classification system. The median time of thrombocytopenia less than 30,000/μL after myeloablative radiochemotherapy and ASCT was 19 days (range, 10-76 days), whereas the median duration of leukocytopenia less than 1000/μL was 16 days (range, 11-81 days). Accordingly, infections occurred in 85.6% (23.1% grades 3 and 4) in the ASCT group in comparison with 31.7% (1.7% grades 3 and 4) in the IFN-α study arm. However, the mortality rate from acute infections was only 1.8% in the ASCT study arm. Other types of nonhematologic toxicity also occurred more frequently in patients who underwent stem cell transplantation. The most frequent nonhematologic adverse effect was mucositis, which was observed in 89.5% (53.3% grades 3 and 4) of patients. In addition, gastrointestinal adverse effects (nausea and vomiting) in 84.8% of patients, pulmonary in 26.9%, renal in 10.6%, and liver toxicity in 44.2% were also observed more frequently in patients who underwent stem cell transplantation.

In contrast, muscle and bone pain and depression occurred more frequently during IFN-α maintenance therapy (Table 3).
starting dose of IFN-α maintenance therapy of 5 × 10⁶ units 3 times weekly was given to 75.2% of the patients in the IFN-α study arm; 1.8% of patients received more than 15 × 10⁶ units weekly, and 19.7% received less than 15 × 10⁶ units weekly but at least 9 × 10⁶ units weekly. The median time until the IFN-α dosage had to be reduced was 303 days (95% CI, 163–513 days). Accordingly, the median dose of patients in remission was 9 × 10⁶ units weekly after 1 year (range, 0.18–10⁶ units weekly) and 8.3 × 10⁶ units weekly after 2 years (range, 0.15 × 10⁶ units weekly).

Discussion

In advanced stage III or IV indolent lymphoma, conventional chemotherapy is a noncurative approach.1,22 Consequently, new therapeutic strategies are urgently warranted. Intensive consolidation with high-dose therapy followed by ASCT represents one of the recently established approaches in the treatment of malignant lymphoma. In contrast to conventional chemotherapy, stem cell transplantation seems capable of effectively eliminating residual lymphoma cells, which may represent an important prognostic factor.15,23,24 Because of its potential curative impact, stem cell transplantation has been accepted as standard therapy for relapsed aggressive non-Hodgkin lymphoma.25 In follicular lymphoma, encouraging results have been achieved when applied as first-line therapy or in relapsed refractory disease.13,15 Thus far, no results of a randomized trial confirming the superiority of stem cell transplantation have been published. Consequently, the GLSG embarked on a randomized trial comparing myeloablative radiochemotherapy followed by ASCT with IFN-α maintenance after initial CHOP-like cytoreductive chemotherapy. The primary study end point was defined as PFS after the completion of induction therapy. Mobilization chemotherapy with Dexa-BEAM and consolidation radiochemotherapy was feasible and well tolerated in most patients. As expected, toxicity was significantly higher in the ASCT study group than in the IFN-α group. Hematologic toxicity with anemia, thrombocytopenia, and granulocytopenia and nonhematologic adverse effects primarily with gastrointestinal, pulmonary, and liver toxicity were the main toxic events after ASCT. Depression and muscle and bone pain were significantly more frequent in patients receiving IFN-α. However, toxicity rates were acceptable in both study arms. Only 2 (1.8%) patients in the ASCT arm died of infectious complications. Consequently, our data are in line with previous studies reporting the safety and feasibility of myeloablative therapy and ASCT in patients with follicular lymphoma.12,26-29 In a recent trial of the Groupe d’Etude des Lymphomes de l’Adulte (GELA), ASCT resulted in only 2% discontinuations of therapy, and no therapy-associated mortality was reported.29 Similar results were obtained by Apostolidis et al,12 who reported an “early” treatment-related mortality rate of 4%.

The current trial by the GLSG demonstrates that myeloablative radiochemotherapy with subsequent ASCT is a feasible approach for patients younger than 60 and leads to significant improvement in PFS. Hence, within the observation period, only 31 (27.2%) patients had relapses after ASCT compared with 76 (60.3%) in the IFN-α group. The projected 5-year PFS after ASCT was 64.7%, and it was only 33.3% in the IFN-α arm (P < .0001). These data confirm previous results of nonrandomized phase 2 studies. Apostolidis et al12 reported an estimated PFS rate of 63% after 5 years, which was significantly better than that of a historical control group receiving conventional chemotherapy only.12 However, no significant difference in survival was reported in this retrospective study. A similar PFS rate of 67% at 4 years was observed by Ladetto et al.30 In another monocentric retrospective study, Horning et al31 reported a PFS rate of 76% after 5 years. Two recently published randomized trials suggested improved OS rates in patients who underwent ASCT.28,29 However, in the GELA trial, 2 different induction regimens were applied (4 cycles of CHOP in the ASCT study group vs 18-month induction regimen of 6 cycles CHVP followed by 6 bimonthly courses combined with IFN in the conventional therapy arm). This led to imbalances of intensity and duration of induction therapy, and it hampers the comparison of both study arms. Thus, despite significantly different OS rates, no differences in the PFS rates were observed. The recently published CUP trial suffered from a slow recruitment into 3 different study arms. Reported survival differences are based on analyses of only 89 patients. In contrast to these studies, in the recently presented Groupe Ouest Est des Leucemies et des Autres Maladies du Sang (GOELAMS) trial, a significant prolongation of the PFS was observed.32 However, because of frequently observed secondary neoplasias, no differences in the OS after ASCT and conventional chemotherapy were detectable. Similarly, a preliminary analysis in our trial identified a significantly increased risk for secondary malignancies after ASCT.33 Thus, it is unclear whether this increased risk for secondary tumors might counteract the benefit of ASCT.

In spite of the substantially improved PFS rate after ASCT, it is not yet proven whether relapses are prevented or postponed in a subgroup of patients. Hence, further long-term follow-up is necessary. One major caveat of ASCT is the potential contamination of the harvested stem cells with circulating lymphoma cells. Different approaches are being applied to eliminate these contaminations. They consist of conventional purging procedures34 or in vivo purging with monoclonal anti-CD20 antibodies such as rituximab.35-38 Antibody-based purging seems especially efficient in killing residual lymphoma cells given the encouraging results concerning OS reported in various phase 2 studies.

Another promising approach is the application of combined immunochemotherapy rather than high-dose consolidation. The GLSG recently completed a randomized trial comparing initial cytoreduction chemotherapy and CHOP with a combination of rituximab and CHOP (R-CHOP). Results have shown a significant improvement in initial response and, more important, a significant improvement in PFS.11 The benefit was comparable to the effect of ASCT after induction therapy containing only CHOP. It is tempting to speculate whether R-CHOP as an alternative approach may substitute for high-dose consolidation therapy, which bears potential long-term adverse effects. These questions are currently addressed in several clinical trials comparing the effects of high-dose chemotherapy with combined immunochemotherapy.

Appendix

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Myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission prolongs progression-free survival in follicular lymphoma: results of a prospective, randomized trial of the German Low-Grade Lymphoma Study Group

Georg Lenz, Martin Dreyling, Eva Schiegnitz, Roswitha Forstpointner, Hannes Wandt, Mathias Freund, Georg Hess, Lorenz Truemper, Volker Diehl, Martin Kropff, Michael Kneba, Norbert Schmitz, Bernd Metzner, Markus Pfirrmann, Michael Unterhalt and Wolfgang Hiddemann