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 (GLSG)

Georg Lenz, M.D. a, Martin Dreyling, M.D., Ph.D. a, Eva Schiegnitz, M.Sc. a,b, Roswitha Forstpointner, M.D. a, Hannes Wandt, M.D., Ph.D. c, Mathias Freund, M.D., Ph.D. d, Georg Hess, M.D. e, Lorenz Truemper, M.D., Ph.D. f, Volker Diehl, M.D. Ph.D. g, Martin Kropff, M.D. h, Michael Kneba, M.D., Ph.D. i, Norbert Schmitz, M.D., Ph.D. j, Bernd Metzner, M.D, Ph.D. k, Markus Pfirrmann, M.Sc. b, Michael Unterhalt, M.D., Ph.D. a and Wolfgang Hiddemann, M.D., Ph.D. a

a Department of Internal Medicine III, Ludwig-Maximilians University, Munich Grosshadern, Germany
b Department of Medical Informatics, Biometrics and Epidemiology (IBE), Ludwig-Maximilians University, Munich Grosshadern, Germany
c Department of Hematology and Oncology, Klinikum Nord, Nuernberg, Germany
d Department of Hematology and Oncology, University of Rostock, Rostock, Germany
e Department of Internal Medicine III, University Hospital Mainz, Mainz, Germany
f Department of Hematology and Oncology, Georg August University, Goettingen, Germany
g Department of Internal Medicine I, University of Cologne, Cologne, Germany
h Department of Medicine, University of Muenster, Muenster, Germany
i Department of Internal Medicine II, University of Kiel, Kiel, Germany
j Department of Hematology, Allgemeines Krankenhaus St. Georg, Hamburg, Germany
k Department of Internal Medicine II, Klinikum Oldenburg, Oldenburg, Germany

Short title: Prolonged PFS following ASCT in follicular lymphoma
Category: Clinical observation, interventions, and therapeutic trials
Word count: 4204 words; abstract count: 200 words
This work was supported in part by a grant of the Deutsche Krebshilfe (project number: 70-2208-Hi 2)

Correspondence:
Wolfgang Hiddemann, M.D., Ph.D.
Department of Internal Medicine III, University Hospital Grosshadern, Ludwig-Maximilians-University
Marchioninistrasse 15
81377 Munich
Germany
Tel.: +49-89-7095-0
Fax.: +49-89-7095-5550
e-mail: wolfgang.hiddemann@med.uni-muenchen.de

Copyright (c) 2004 American Society of Hematology
Abstract

In advanced follicular lymphoma conventional chemotherapy has failed to substantially prolong survival. To improve the outcome, the German Low-Grade Lymphoma Study Group (GLSG) initiated a randomized trial, comparing the effect of a potentially curative myeloablative radiochemotherapy followed by autologous stem cell transplantation (ASCT) to \( \alpha \)-interferon maintenance (IFN\( \alpha \)) in first remission. 307 patients (younger than 60 years) with follicular lymphoma from 130 institutions were recruited into this trial. After two cycles of a CHOP-like induction chemotherapy, patients were randomly assigned to either ASCT or IFN\( \alpha \). The respective therapy was started when patients achieved a complete or partial remission after induction chemotherapy. 240 patients with follicular lymphoma are evaluable for the comparison of ASCT vs. IFN\( \alpha \). In patients receiving ASCT, the five-year progression-free survival (PFS) was 64.7% as compared to 33.3% in the IFN\( \alpha \) arm (\( p < 0.0001 \)). As expected, acute toxicity was higher in the ASCT group, however early mortality was below 2.5% in both study arms. In this randomized multicenter trial, high-dose radiochemotherapy followed by ASCT significantly improved the PFS in comparison to IFN\( \alpha \) in patients with follicular lymphoma when applied as consolidation in first remission. Longer follow-up is necessary to determine the effect of ASCT on the overall survival.
Introduction

Indolent lymphomas are B-cell malignancies which are characterized by a slowly progressive clinical course and a median survival of 7 to 10 years\textsuperscript{1,2}. Morphologically, the vast majority of cases represent follicular lymphoma grade I and II, whereas only few cases show a marginal zone, lymphoplasmacytic or small lymphocytic histology. Only in limited stages I or II, the disease may potentially be cured by radiotherapy. However, more than 80\% of follicular lymphoma cases are diagnosed in advanced Ann Arbor stages III and IV at initial presentation. As conventional chemotherapy is not curative nor substantially prolongs overall survival (OS), wait & watch strategies are frequently pursued and chemotherapy is applied only in symptomatic patients\textsuperscript{1,3}.

To improve the outcome in indolent lymphoma subtypes, $\alpha$-interferon maintenance (IFN$\alpha$) was introduced in various studies. In a recent meta-analysis, IFN$\alpha$ significantly prolonged the OS in comparison to observation alone in follicular lymphoma\textsuperscript{4}. Monoclonal antibodies targeting B cell specific antigens represent another promising approach. In follicular lymphoma the anti-CD20 antibody rituximab as single agent achieved overall response rates of approximately 50 to 60\%\textsuperscript{5-7}. As \textit{in vitro} data suggest a synergistic effect of a combined immuno-chemotherapy, various phase II studies investigated the efficacy of a combined approach and reported encouraging results\textsuperscript{8-10}. In a recent trial of the German Low-Grade Lymphoma Study Group (GLSG) a significant improvement in the overall response rate as well as the progression-free survival (PFS) could be demonstrated in follicular lymphoma\textsuperscript{11}.

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 II studies promising results were achieved\textsuperscript{12-16}. In order to assess the role of myeloablative radiochemotherapy followed by ASCT in follicular lymphoma as consolidation in first remission, the GLSG embarked in 1996 a randomized comparison of this approach versus IFN$\alpha$ maintenance in patients younger than 60 years of age.
Patients 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 WHO classification. The histological diagnosis was confirmed by a central pathology review. Similar to the BNLI (British National Lymphoma Investigation) criteria, patients had to be in need of therapy as defined by (1) the presence of B-symptoms and/or (2) hematopoietic insufficiency (granulocytopenia < 1,500/µl, anemia < 10 g/dl, thrombocytopenia < 100,000/µl) and/or (3) progressive disease as defined by 50% progression in the past six months and/or (4) bulky disease (largest diameter > 5 cm). Patients with the potential of curative radiation therapy, as well as patients with a poor performance status (ECOG > 2) were excluded. In addition, patients with seriously impaired cardiac, pulmonary, hepatic (GOT/GPT ≥ three times of upper limits and/or bilirubin ≥ 2.0 mg/dl) or renal function (creatinine > 2.0 mg/dl) were not enrolled. The study protocol was approved by the local ethics committees of the participating centers and all patients gave informed consent in accordance with the Declaration of Helsinki.

Treatment schedule

Initially, patients were randomized for cytoreductive therapy either to CHOP (cyclophosphamide 750 mg/m² i.v., day 1, doxorubicin 50 mg/m² i.v., day 1, vincristine 1.4 mg/m² (maximum 2 mg) i.v., day 1 and prednisone 100 mg/m² p.o., days 1-5) or MCP (mitoxantrone 8 mg/m² i.v., days 1 + 2, chlorambucil 3 x 3 mg/m² p.o., days 1-5 and prednisone 25 mg/m² p.o., days 1-5). Since July 1998 all patients received CHOP, as the randomized comparison of CHOP versus MCP showed that MCP was associated with a significant impairment of hematopoietic stem cell mobilization. After two cycles of therapy, patients were randomized either to myeloablative radiochemotherapy followed by ASCT or to IFNα maintenance after the completion of induction therapy (Figure 1). Patients achieving a complete remission (CR) after 4 cycles of initial cytoreductive chemotherapy immediately proceeded to consolidation therapy. All other patients received six cycles of induction therapy. Patients showing progressive disease during induction therapy or patients who did
not achieve at least a partial remission after completion of induction therapy were taken off study.

Patients in the ASCT arm received intensified mobilization chemotherapy with Dexa-BEAM (dexamethasone 3 x 8 mg p.o., days 1-10, BCNU 60 mg/m² i.v., day 2, melphalan 20 mg/m² i.v., day 3, etoposide 75 mg/m² i.v., days 4-7, cytarabine 2 x 100 mg/m² i.v., days 4-7, G-CSF initiated day 11). Peripheral stem cells were harvested and subsequently cryopreserved without any purging procedure. A minimum of 2.0 x 10⁶/kg bw CD34⁺ cells (and 2.0 x 10⁶/kg bw CD34⁺ cells as backup) was 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 to –4; pulmonary dosage was limited to 8 Gy) and cyclophosphamide (60 mg/kg bw i.v., days –3 and –2) regimen. The previously harvested peripheral blood stem cells were reinfused on day 0. G-CSF was initiated on day +1 (Figure 1).

Patients randomized to the IFNα maintenance study arm received two additional courses of conventional chemotherapy to balance the mobilization scheme (Dexa-BEAM). Subsequently α-interferon was applied at a dose of 5 x 10⁶ U s.c. 3 times weekly until progression¹⁸ (Figure 1).

Response criteria and evaluation

Response was defined according to the following criteria: complete remission (CR) was defined as complete absence of disease manifestations for at least four weeks. Partial remission (PR) was defined as at least a 50% reduction of all evaluable lymphoma manifestations, without appearance of new lesions for at least four weeks. Cases with 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; progression (PD) was defined as increase in lymphoma associated symptoms, the appearance of new lymphoma manifestations or an increase in the volume of lymphoma of more than 25%.

Staging procedures included clinical examination, complete blood count, serum biochemistry profile, chest X-ray, abdominal ultrasound, CT scans of the neck, chest and abdomen and a
bone marrow biopsy. Staging was performed prior to therapy, after every second cycle of induction therapy and prior and after ASCT. In addition, follow-up was performed every three months in both study arms.

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

**Randomization and statistical analysis**

Randomization was carried out after 2 cycles of induction therapy, to allow smaller study centers in which the autologous stem cell transplantation 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) (≤2 vs. ≥3), response after two cycles of chemotherapy (CR, PR vs. MR, SD) and initial cytoreductive therapy (CHOP vs. MCP).

The primary trial end point was defined as the PFS after completion of induction therapy. This parameter was monitored continuously and analyzed by means of a sequential procedure in order to allow to stop randomization, as soon as a significant difference or no difference between the two study arms was detected. The logrank test statistic Z and its variance V were calculated after each event and plotted as sample path in the Z-V plane. As soon as the sample path crosses the upper boundary of the triangular continuation region, a significant advantage of ASCT is revealed. If the sample path crosses the lower boundary of the triangle, the statistical test indicates no significant difference between ASCT and IFNα maintenance.

Based on a significance level \(\alpha = 0.05\) and an expected hazard ratio \(\lambda = 0.5\), the one-sided triangular test for the logrank statistic was designed to detect the superiority of ASCT with a probability of 95%. Based on the estimated PFS after IFNα maintenance and the recruiting rates from the previous GLSG trial, a maximum of 65 events and a trial duration of approximately 5 years was estimated. The maximal 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% on a significance level of 5%.

Randomized patients were evaluable for PFS analysis if their documented histological diagnosis and Ann Arbor stage met the inclusion criteria. In addition, induction therapy had to be completed with at least a PR and either the 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. The intention-to-treat analysis included all patients who achieved at least a PR after induction therapy.

Kaplan-Meier estimates were calculated for all time-to-event variables. Two-year and five-year event-free survival probabilities were given with 95% confidence intervals. The p-value for the main parameter was calculated with respect to the sequential design. The two-sided logrank test was used for all other time-to-event variables. All statistical calculations were based on the patients evaluable at the time of the final analysis (“overrun” analysis for the sequential test). A multiple Cox regression analysis with forward stepwise selection applying the Wald statistic was performed for the PFS. Categorical baseline variables and safety data were compared with the two-sided exact Fisher test, continuous baseline variables with the two-sided Mann-Whitney-U-Test. The significance level was set to $\alpha = 0.05$.

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

Results

Between July 1996 and September 2000, 375 patients from 130 clinical institutions were randomized to either ASCT or IFN$\alpha$ maintenance. In April 1999, the sequential procedure showed a significant prolongation of the PFS after ASCT as compared to IFN$\alpha$ maintenance (Figure 2). However, the GLSG decided to continue randomization in order to prospectively evaluate the effect of ASCT on overall survival and the incidence of late onset toxicities. 307 (81.9%) patients were diagnosed with follicular lymphoma, 15 (4.0%) had a mantle cell
lymphoma and 42 (11.2%) a lymphoplasmacytic lymphoma. 11 (3.0%) patients were excluded as the central pathology review did not confirm the initial diagnosis (4 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 following ASCT was 60.7% at five years (95% confidence interval 50.5% to 70.8%) as compared to 32.7% (95% confidence interval 24.3% to 41.2%) in patients receiving IFNα maintenance (p = 0.00174; sequential log-rank test). Similar findings of a prolonged PFS after ASCT were detected in the intention-to-treat analysis.

In patients with mantle cell lymphoma (n = 12) the two-year PFS following ASCT (n = 4) was 75.0% (95% confidence interval 32.6% to 100.0%) as compared to 37.5% (95% confidence interval 4.0% to 71.0%; p = 0.46) following IFNα maintenance (n = 8). The five-year PFS could not be calculated due to the short follow-up of patients with mantle cell lymphoma.

In patients with lymphoplasmacytic lymphoma (n = 27) the two-year PFS following ASCT (n = 16) was 64.9% (95% confidence interval 40.0% to 89.8%) as compared to 72.7% (95% confidence interval 46.4% to 99.0%; p = 0.98) following IFNα maintenance (n = 11). The five-year PFS following ASCT was 36.1% (95% confidence interval 1.6% to 70.6%) as compared to 49.9% (95% confidence interval 17.8% to 82.0%) in the IFNα maintenance group.

As the biological behavior as well as the response to therapy varies strongly in the different lymphoma subtypes included in our trial and the vast majority of patients were diagnosed with follicular lymphoma, the emphasis of this analysis is put on the results obtained from patients with follicular lymphoma.

**Characteristics of patients**

240 patients with follicular lymphoma were evaluable for the comparison of ASCT vs. IFNα. The trial profile is shown in Figure 3. In this subgroup, 74.2% were diagnosed with stage IV disease, 27.9% had an elevated LDH serum level and 36.3% presented with B-symptoms. In
addition, of the 217 patients evaluable for the IPI, 58.5% had a low-risk IPI, 33.2% a low-intermediate risk IPI and 8.3% a high-intermediate IPI. Patients’ characteristics in the two study arms were comparable and are summarized in Table 1.

Response to therapy

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

In the IFN$\alpha$ group, 20 of 126 patients achieved a CR (15.9%), and 106 a PR (84.1%) after induction therapy. After two additional cycles of consolidating chemotherapy 21.4% (n = 27) of the patients achieved a CR and 77.8% (n = 98) a PR. Subsequently IFN$\alpha$ maintenance $5 \times 10^6$ U s.c. three times weekly was initiated.

Progression-free survival

After a median follow-up of 4.2 years (4.1 years in the ASCT study arm and 4.4 years in patients receiving IFN$\alpha$ maintenance), 31 relapses (27.2%) were observed in the ASCT group and 76 (60.3%) relapses in the IFN arm. In addition, five deaths occurred in remission (four patients in the ASCT study arm and one in the IFN group): one patient died shortly after ASCT due to cardiac failure, two patients developed infectious complications following ASCT or Dexa-BEAM mobilization and one patient committed suicide after Dexa-BEAM. The patient in the IFN study group died of pneumonia after therapy of a secondary rectum carcinoma. Accordingly, the PFS was significantly different in the two study arms. In patients receiving ASCT, the PFS was 79.1% after two years (95% confidence interval 71.4% to
86.9%) and 64.7% after five years (95% confidence interval 54.6% to 74.8%) in comparison to only 52.7% (95% confidence interval 43.8% to 61.7%) after two years and 33.3% (95% confidence interval 24.3% to 42.3%) after five years in the IFNα study arm respectively (p < 0.0001; 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 = 140) the five year PFS was 62.0% (95% confidence interval 52.7% to 71.4%) compared to 36.2% (95% confidence interval 27.6% to 44.8%) in the IFNα group (n = 143; p < 0.0001).

Additionally, analysis of the PFS was performed according to the response to initial induction chemotherapy. CR patients had a five year PFS of 72.3% (95% confidence interval 50.6% to 93.9%) in the ASCT group (n = 22) in comparison to a PFS of 42.0% (95% confidence interval 19.3% to 64.7%) in the interferon subgroup (n = 20; p = 0.0861). PFS was significantly different in PR patients. In the ASCT arm (n = 92) the five year PFS was 63.0% (95% confidence interval 51.8% to 74.3%) in comparison to 32.0% (95% confidence interval 22.4% to 41.6%) in the IFNα group (n = 106; p < 0.0001).

The analysis of the PFS according to the IPI demonstrated a similar advantage of ASCT in both subgroups. In the low-risk group (n = 127) the five year PFS in patients receiving ASCT (n = 53) was 66.7% (95% confidence interval 51.4% to 82.1%) compared to 39.4% (95% confidence interval 27.0% to 51.8 %) in the IFNα arm (n = 74; p = 0.0053; Figure 5A). Similar results were obtained in the intermediate IPI subgroup (n = 90). The five year PFS was 67.3% (95% confidence interval 52.4% to 82.2%) in the ASCT arm (n = 45) and only 25.6% (95% confidence interval 12.1% to 39.0%) in patients receiving IFNα (n = 45; p = 0.0002; Figure 5B).

A multiple Cox regression analysis was performed to independently evaluate the effect of the parameters included in the IPI (elevated serum LDH level, extranodal involvement (> 1 site), ECOG performance status ≥ 2), the choice of induction therapy (MCP vs. CHOP) and the choice of consolidation therapy (ASCT vs. IFNα maintenance) on the PFS. This analysis identified ASCT with a hazard ratio of 0.388 (95% confidence interval 0.250 to 0.601; p < 0.0001) and low number of involved extranodal sites with a hazard ratio of 0.565 (95% confidence interval 0.354 to 0.901; p = 0.0166) to be independently associated with an improved PFS.
Overall survival

After a median follow-up of 4.2 years, 31 of the 240 evaluable patients with FL have died (12.9%). The survival probability after end of induction therapy was 94.5% (95% confidence interval 91.6% to 97.4%) after two years and 84.3% (95% confidence interval 78.9% to 89.6%) after five years respectively (Figure 6). As the number of evaluable patients as well as the median follow-up is still too short to definitely evaluate the OS in both study arms, these results are still blinded.

Toxicity

As expected acute toxicity was higher in the ASCT study arm. Especially, hematological toxicity was significantly more frequently observed in this group (Table 2a). Anemia (95.2%; 44.8% grade 3 and 4), leukocytopenia (100%; 96.2% grade 3 and 4), granulocytopenia (91.4%; 90.5% grade 3 and 4) and thrombocytopenia (97.1%; 96.2% grade 3 and 4) according to the WHO classification was observed in almost all cases. The median time of thrombocytopenia < 30 x 10⁹/L following myeloablative radiochemotherapy and ASCT was 19 days (range 10-76), whereas the median duration of leukocytopenia < 1000/µl was 16 days (range 11-81). Accordingly, infections occurred in 85.6% (23.1% grade 3 and 4) in the ASCT group in comparison to 31.7% (1.7% grade 3 and 4) in the IFNα study arm. However, mortality due to acute infections was only 1.8% in the ASCT study arm. Other non-hematological toxicity also occurred more frequently in patients receiving stem cell transplantation. The most frequent non-hematological side-effect was mucositis which was observed in 89.5% (53.3% grade 3 and 4). In addition, gastrointestinal side-effects (nausea and vomiting) in 84.8%, pulmonary in 26.9%, renal in 10.6% and liver toxicity in 44.2% of cases was also observed more frequently in patients receiving stem cell transplantation.

In contrast, muscle and bone pain as well as depression occurred more frequently during IFNα maintenance (Table 2b). The starting dose of IFNα maintenance of 5 x 10⁶ U 3 times weekly was given to 75.2% of the patients in the IFNα study arm. 1.8% of patients received more than 15 x 10⁶ U weekly and 19.7% received less than 15 x 10⁶ U weekly but at least 9 x 10⁶ U weekly. The median time until the IFNα dosage had to be reduced was 303 days (95% confidence interval 163 days to 513 days). Accordingly, the median dose of patients in
remission was $9 \times 10^6$ U weekly after one year (range 0 to $18 \times 10^6$ U weekly) and $8.3 \times 10^6$ U weekly after two years (range 0 to $15 \times 10^6$ U weekly).

**Discussion**

In advanced stage III or IV indolent lymphoma, conventional chemotherapy is a non-curative approach\textsuperscript{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 therapy of malignant lymphoma. In contrast to conventional chemotherapy, stem cell transplantation seems to be capable to eliminate effectively residual lymphoma cells which may represent an important prognostic factor\textsuperscript{15,23,24}. Due to its potential curative impact, stem cell transplantation has been accepted as standard therapy in relapsed aggressive non-Hodgkin’s lymphoma\textsuperscript{25}. In follicular lymphoma, encouraging results have been achieved when applied as first-line therapy or in relapsed respectively refractory disease\textsuperscript{13-15}. However, so far no randomized trial confirming the superiority of stem cell transplantation has been published. Consequently, the GLSG embarked a randomized trial comparing myeloablative radiochemotherapy followed by ASCT to an IFN\(\alpha\) maintenance following initial CHOP-like cytoreductive chemotherapy. The primary study endpoint was defined as the PFS after ASCT respectively IFN\(\alpha\) maintenance.

Mobilization chemotherapy with Dexa-BEAM as well as consolidation radiochemotherapy was feasible and well tolerated in the vast majority of patients. As expected, toxicity was significantly higher in the ASCT study group in comparison to IFN\(\alpha\). Hematological toxicity with anemia, thrombocytopenia, granulocytopenia as well as non-hematological side-effects with mainly gastrointestinal, pulmonary and liver toxicity were the main toxic events following ASCT. Depression as well as muscle and bone pain were significantly more frequent in patients receiving IFN\(\alpha\). However, toxicity was acceptable in both study arms. Only two patients (1.8%) in the ASCT arm died due to infectious complications. Consequently, our data are in line with previous studies, which reported safety and feasibility of myeloablative therapy and ASCT in patients with follicular lymphoma\textsuperscript{12,26-29}. In a recent trial of the GELA, ASCT resulted in only 2% premature abort of therapy and no therapy associated mortality was reported\textsuperscript{29}. Similar results were obtained by Apostolidis et al., who reported an “early” treatment-related mortality of 4%\textsuperscript{12}. 
The current trial by the GLSG demonstrates that myeloablative radiochemotherapy with subsequent ASCT is a feasible approach in patients younger than 60 years of age and leads to a significant improvement of the PFS. Hence, within the observation period only 31 patients (27.2%) have relapsed after ASCT as compared to 76 relapses (60.3%) in the IFNα group. The projected five-year PFS after ASCT was 64.7% and only 33.3% in the interferon arm (p < 0.0001). These data confirm previous results of non-randomized phase II studies. Rohatiner and colleagues reported an estimated PFS of 63% after five years, which was significantly better in comparison to a historical control group receiving conventional chemotherapy only12. However, no significant difference in survival was reported in this retrospective study. A similar PFS of 67% at four years was observed by Ladetto et al.30 In another monocentric retrospective study, Horning et al. reported a PFS of 76% after five years31. Two recently published randomized trials suggested an improved OS in patients receiving ASCT28,29. However, in the GELA trial, two different induction regimens were applied (4 cycles of CHOP in the ASCT study group vs. a 18 months 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 hampers the comparison of both study arms. Thus, despite a significantly different OS, no differences in the PFS were observed. The recently published CUP trial suffered from a slow recruitment into three different study arms. Thus, the reported survival differences are based on the analyses of only 89 patients. In contrast to these studies, in the recently presented GOELAMS trial, a significant prolongation of the PFS was observed32. However, due to frequently observed secondary neoplasias, no differences in the OS following ASCT and conventional chemotherapy were detectable. Similarly, a preliminary analysis in our trial identified a significantly increased risk of secondary malignancies following ASCT33. Thus, it is currently unclear, if this increased risk of secondary tumors might counter-weight the benefit of ASCT.

In spite of the substantially improved PFS following ASCT, it is not yet proven whether relapses are definitely prevented in a subgroup of patients or only postponed in their occurrence. 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 currently being applied to eliminate these contaminations. They comprise either conventional purging procedures34 or "in vivo" purging with monoclonal anti-CD20 antibodies as rituximab27,35-38. Especially antibody based purging seems to be very
efficient in killing residual lymphoma cells as encouraging results concerning the OS have been reported in various phase II studies.

Another promising approach is the application of a combined immuno-chemotherapy instead of high-dose consolidation. The GLSG recently completed a randomized trial comparing initial cytoreductive chemotherapy with CHOP to a combination of rituximab and CHOP (R-CHOP). This resulted in a significant improvement of initial response but more importantly, a significant improvement in the PFS could be demonstrated\textsuperscript{11}. The benefit was comparable to the effect of ASCT following an induction containing only CHOP. Thus, it is tempting to speculate whether R-CHOP as alternative approach may substitute the high-dose consolidation which bears potential long-term side-effects. These questions are currently addressed in several clinical trials comparing the effect of high-dose chemotherapy to a combined immuno-chemotherapy.
Acknowledgment

The following persons and institutions participated in this study: M Hahn, S Müller, Praxis für Hämatologie/Onkologie, Ansbach; J Gensicke, P Dravoj, Stadtkrankenhaus Arolsen, Arolsen; G Schlimok, M Sandherr, Zentralklinikum Augsburg, Augsburg; G Unverferth, W Langer, F Püschel, Kreiskrankenhaus Aurich, Aurich; R Paliege, P Majunke, Kreiskrankenhaus Bad Hersfeld, Bad Hersfeld; W Schultz, H Fuss, P Frenzel, Humaine Klinikum Bad Saarow, Bad Saarow; WD Ludwig, H Harder, Robert Rössle Klinik, Berlin; B Dörken, G Massenkeil, Charité/Virchow-Klinikum Berlin, Berlin; K Possinger, O Sezer, Universitätsklinikum Charité/Campus Mitte Berlin, Berlin; HJ Weh, B Angrick, Franziskus Hospital, Bielefeld; W Schmieg, U Graeven, Medizinische Universitätsklinik und Knappschafts-Krankenhaus Bochum, Bochum; WE Schmidt, JE Baier, St.-Josef-Hospital, Bochum; H Vetter, Y Ko, S Fronhoffs, Universitätsklinikum Bonn, Bonn; E Musch, H Röhl, G Mann, Marien-Hospital Bottrop, Bottrop; B Wörmann, G Jordan, A Pies, Städtisches Klinikum Braunschweig, Braunschweig; M Adler, Praxis für Hämatologie, Braunschweig; FJ Riedhammer, A Pronath, Krankenhaus Burglengenfeld, Burglengenfeld; J Hotz, F Marquard, Allgemeines Krankenhaus Celle, Celle; F Fiedler, A Hänel, Klinikum Chemnitz, Chemnitz; M Löhner, Carl-Thiem-Klinikum Cottbus, Cottbus; U v Grünhagen, Onkologische Schwerpunktpraxis, Cottbus; FW Kleinsorge, Internistische Praxis, Detmold; TU Hausamen, W Freund, Städtisches Krankenhaus Dortmund, Dortmund; M Schäfers, K Quabeck, Internistische Praxis, Duisburg; W Lange, Johanniter-Krankenhaus Rheinhausen, Duisburg; R Haas, Universitätsklinikum Düsseldorf, Düsseldorf; WD Schoppe, B Günther, Städtische Kliniken Düsseldorf/Benrath, Düsseldorf; M Gramatzki, Universitätsklinikum Erlangen, Erlangen; R Fuchs, S Wehle-Ika, J Wiegand, St.-Antonius-Hospital, Eschweiler; U Dührsen, Universitätsklinikum Essen, Essen; S Seeber, MR Nowrousian, Westdeutsches Tumorzentrum, Essen; U v Verschuer, R Rudolph, Praxis für Hämatologie, Essen; JG Saal, D Hartwigsen, U Strack, St.-Franziskus-Hospital, Flensburg; A Machraoui, T Koch, Diakonissenkrankenhaus Flensburg, Flensburg; A Knuth, J Orth, Krankenhaus Nordwest, Frankfurt; T Reiber, D Semsek, Praxis für Innere Medizin, Freiburg; R Mertelsmann, J Finke, Universitätsklinikum Freiburg, Freiburg im Breisgau; A Ochs, U Brand, Evangelisches Diakoniekrankenhaus, Freiburg im Breisgau.; J Brücher, B Ullmann, Robert-Koch-Krankenhaus, Gehrden; G Heil, E Stelzer, Klinikum Gera, Gera; B Glaß, Universitätsklinikum Göttingen, Göttingen; Th Scholten, RD Hanrath, S Schlotzhauer, Allgemeines Krankenhaus Hagen, Hagen; H Eimermacher, Katholisches Krankenhaus,
Hagen; HJ Schmoll, HH Wolf, Klinikum der Universität Halle, Halle (Saale); HJ Hurtz, R Rohrberg, R Behrends, Onkologische Schwerpunktpraxis, Halle (Saale); C Spohn, Praxis für Hämatologie/Onkologie, Halle (Saale); P Dreger, Allgemeines Krankenhaus St. Georg, Hamburg; DK Hossfeld, J Dierlamm, AR Zander, N Kröger, H Renges, Universitätsklinikum Eppendorf, Hamburg; G Habel, C Gerigk, J Kurzbach, Marienkrankenhaus Hamburg, Hamburg; K Verpoort, W Zeller, Onkologische Schwerpunktpraxis, Hamburg; A Ganser, D Peest, Medizinische Hochschule Hannover, Hannover; H Kirchner, M Hosada, Klinikum Hannover, Hannover; R Mao, Hämatologische Praxis, Hannover; R Voigtmann, E Schilling, Marienhospital Herne, Herne; H Dietzfelbinger, Privatklinik Dr. R. Schindlbeck, Herrsching; M Prisch, M Bach, St.-Elisabeth-Hospital, Herten; D Urbanitz, TF Heide, U Kaiser, St. Bernward-Krankenhaus, Hildesheim; M Pfreundschuh, Universitätsklinik des Saarlandes, Homburg (Saar); AA Fauser, M Kiehl, Klinik für KMT, Hämatologie/Onkologie, Idar-Oberstein; K Höffken, HJ Fricke, Universitätsklinikum Jena, Jena; S Hahnfeld, B Krombholz, Gemeinschaftspraxis für Innere Medizin, Jena; J Fischer, S Wilhelm, R Ehrhardt, Städtisches Klinikum Karlsruhe, Karlsruhe; J Mezger, G Göckel, Vincentius Krankenhaus, Karlsruhe; WD Hirschmann, EU Steinhauer, Städtisches Klinikum Kassel, Kassel; S Siehl, U Söling, Gemeinschaftspraxis für Hämatologie/Internistische Onkologie, Kassel; C Pott, Universitätsklinikum Kiel, Kiel; A Engert, M Reiser, Universitätsklinikum Köln, Köln; S Schmitz, T Steinmetz, Internistische Praxis, Köln; I Meuthen, G Kunzmann, H Spangenberg, Krankenhaus Holweide, Köln; M Planker, M Busch, M Hipp, Klinikum Krefeld, Krefeld; B Tschechne, Praxis für Hämatologie/Onkologie, Lehrte; D Niederwieser, W Pönisch, Universitätsklinikum Leipzig, Leipzig; HP Lohrmann, H Middeke, Klinikum Lippe-Lemgo, Lemgo; L Heidenreich, KA Jost, Dreifaltigkeitshospital, Lippstadt; F Bergmann, Evangelisches Krankenhaus Lippstadt, Lippstadt; S Fetscher, Städtisches Krankenhaus Süd, Lübeck; T Wagner, S Peters, Medizinische Universität Lübeck, Lübeck; G Heil, Klinikum Lüdenscheid, Lüdenscheid; M Uppenkamp, M Hoffmann, Klinikum der Stadt, Ludwigshafen; U Apel, Universitätsklinikum Magdeburg, Magdeburg; T Fischer, C Huber, Universitätsklinikum Mainz, Mainz; M Jung, U Bauermann, St.-Hildegardis-Krankenhaus, Mainz; R Hehlmann, E Lengfelder, I Kottke, Universitätsklinikum Mannheim, Mannheim; A Neubauer, N Schwella, Klinikum der Phillipps Universität Marburg, Marburg; M Schwonzen, H Spangenger, St.-Walburga-Krankenhaus, Meschede; H Bodenstein, HH Wöltjen, Klinikum Minden, Minden; M Becker, C Kreisel-Büstgens, Gemeinschaftspraxis für Hämatologie/Internistische Onkologie, Minden; HE Reis, D Kohl, D Berkovic, Klinikum Maria Hilf, Mönchengladbach; C Peschel, C v Schilling, Klinikum Rechts der Isar der
Technischen Universität München, München; PC Scriba, B Emmerich, Medizinische Klinik Innenstadt der Universität München, München; R Hartenstein, N Brack, Städtisches Krankenhaus München-Harlaching, München; WE Berdel, Universitätsklinikum Münster, Münster; R Kriebel-Schmitt, V Burstedde, B Berning, Schwerpunktpрактик für Hämatologie/Onkologie, Münster; H Rühle, N Grobe, F Jungmichel, Klinikum Neubrandenburg, Neubrandenburg; B Krämer, W Linke, Kreiskrankenhaus Nordhorn, Nordhorn; S Fries, Klinikum Nord, Nürnberg; HJ Illiger, Klinikum Oldenburg, Oldenburg; H Keller, H Leber, D Nöcker, Brüderkrankenshaus St. Josef, Paderborn; L Theilmann, B Sandritter, Städtisches Klinikum Pforzheim, Pforzheim; R Pasold, F Rothmann, A Haas, Ernst-von-Bergmann-Klinik, Potsdam; R Andreesen, S Krause, S Mayer, Universitätsklinikum Regensburg, Regensburg; ED Kreuser, Krankenhaus Barmherzige Brüder, Regensburg; W Bootsveld, Jakobi-Krankenhaus, Rheine; M Freund, Universitätsklinikum Rostock, Rostock; P Ketterer, O Anders, Klinikum Südoststadt, Rostock; J Preiß, P Schmidt, Caritas Klinik St. Theresia, Saarbrücken; J Schimke, G Jacobs, Praxis für Hämatologie/Onkologie, Saarbrücken; H Schönborn, Nordwest Krankenhaus Sanderbusch, Saarbrücken; R Subert, D Häling, C Schult, Medizinisches Zentrum der Landeshauptstadt, Schwerin; E Jähde, Evangelisches Jung-Stilling Krankenhaus, Siegen; W Gassmann, T Gaska, St.-Marien-Krankenhaus Siegen, Siegen; HR Ochs, G Schütte, Marienkrankenhaus Soest, Soest; W Aulitzky, S Martin, Robert-Bosch-Krankenhaus, Stuttgart; Bürgerhospital, Stuttgart; HG Mergenthaler, J Schleicher, Katharinenhospital, Stuttgart; E Höring, M v Ehr, M Respondek, Praxis für Hämatologie/Onkologie, Stuttgart; HG Biedermann, W Larisch, Kreiskrankenhaus Traunstein, Traunstein; MR Clemens, Mutterhaus der Borromäerinnen, Trier; CB Köbel, KJ Weber, H Kirchen, Krankenhaus der Barmherzigen Brüder, Trier; B Rendenbach, Onkologische Praxis, Trier; H Döhner, M Bentz, Universitätsklinikum Ulm, Ulm; L Labedzki, HJ Bias, Kreiskrankenhaus Waldbrohl, Waldbrohl; KM Josten, S Schneider, Deutsche Klinik für Diagnostik, Wiesbaden; N Frickhofen, HG Fuhr, G Müller, Dr. H. Schmidt-Kliniken Wiesbaden, Wiesbaden; W Augener, St.-Willehad-Hospital, Wilhelmshaven; Th Bock, Praxis für Hämatologie/Onkologie, Wittenberge; U Rasenack, A Körfer, Stadtkrankenhaus Wolfsburg, Wolfsburg; K Wilms, H Rückle-Lanz, M Wilhelm, U Gunzer, Universitätsklinikum Würzburg, Würzburg; G Schott, Heinrich-Braun-Krankenhaus Zwickau, Zwickau.
References


Tables

Table 1: Characteristics of patients with follicular lymphoma.

<table>
<thead>
<tr>
<th></th>
<th>IFN</th>
<th>ASCT</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients evaluable</td>
<td>126 (100.0%)</td>
<td>114 (100.0%)</td>
<td>240 (100.0%)</td>
</tr>
<tr>
<td>Median age of evaluable patients in years (range)</td>
<td>49.1 (29-59)</td>
<td>49.1 (29-59)</td>
<td>49.1 (29-59)</td>
</tr>
<tr>
<td>IPI (n = 217)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>74 (62.2%)</td>
<td>53 (54.1%)</td>
<td>127 (58.5%)</td>
</tr>
<tr>
<td>Low-intermediate risk</td>
<td>34 (28.6%)</td>
<td>38 (38.8%)</td>
<td>72 (33.2%)</td>
</tr>
<tr>
<td>High-intermediate risk</td>
<td>11 (9.2%)</td>
<td>7 (7.1%)</td>
<td>18 (8.3%)</td>
</tr>
<tr>
<td>Male gender</td>
<td>56 (44.4%)</td>
<td>62 (54.4%)</td>
<td>118 (49.2%)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>93 (73.8%)</td>
<td>85 (74.6%)</td>
<td>178 (74.2%)</td>
</tr>
<tr>
<td>Elevated serum LDH (n = 219)</td>
<td>27 (22.5%)</td>
<td>34 (34.3%)</td>
<td>61 (27.9%)</td>
</tr>
<tr>
<td>ECOG &gt; 1 (n = 236)</td>
<td>10 (8.0%)</td>
<td>3 (2.7%)</td>
<td>13 (5.5%)</td>
</tr>
<tr>
<td>B-symptoms</td>
<td>49 (38.9%)</td>
<td>38 (33.3%)</td>
<td>87 (36.3%)</td>
</tr>
<tr>
<td>Induction therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCP</td>
<td>31 (24.6%)</td>
<td>28 (24.6%)</td>
<td>59 (24.6%)</td>
</tr>
<tr>
<td>CHOP</td>
<td>95 (75.4%)</td>
<td>86 (75.4%)</td>
<td>181 (75.4%)</td>
</tr>
</tbody>
</table>

Abbreviations: IFN: α-interferon maintenance; ASCT: autologous stem cell transplantation; n: number of patients. IPI: International Prognostic Index; ECOG: Eastern Cooperative Oncology Group.
Table 2a: Hematological toxicity according to the WHO classification\textsuperscript{19} following autologous stem cell transplantation (ASCT) and α-interferon maintenance respectively.

<table>
<thead>
<tr>
<th>WHO toxicity</th>
<th>Grade</th>
<th>IFN (n = 122)</th>
<th>ASCT (n = 105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>I/II</td>
<td>27.7%</td>
<td>50.5%</td>
</tr>
<tr>
<td></td>
<td>II/IV</td>
<td>0.8%</td>
<td>44.8%</td>
</tr>
<tr>
<td>Leukocytopenia</td>
<td>I/II</td>
<td>33.6%</td>
<td>3.8%</td>
</tr>
<tr>
<td></td>
<td>II/IV</td>
<td>51.3%</td>
<td>96.2%</td>
</tr>
<tr>
<td>Granulocytopenia</td>
<td>I/II</td>
<td>34.2%</td>
<td>1.0%</td>
</tr>
<tr>
<td></td>
<td>II/IV</td>
<td>37.8%</td>
<td>90.5%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>I/II</td>
<td>18.6%</td>
<td>1.0%</td>
</tr>
<tr>
<td></td>
<td>II/IV</td>
<td>4.2%</td>
<td>96.2%</td>
</tr>
</tbody>
</table>

Abbreviations: IFN: α-interferon maintenance; ASCT: autologous stem cell transplantation.
Table 2b: Non-hematological toxicity according to the WHO classification\textsuperscript{19} following autologous stem cell transplantation (ASCT) and α-interferon maintenance respectively.

<table>
<thead>
<tr>
<th>WHO toxicity</th>
<th>Grade</th>
<th>IFN (n = 122)</th>
<th>ASCT (n = 105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucositis</td>
<td>I/II</td>
<td>15.0%</td>
<td>36.2%</td>
</tr>
<tr>
<td></td>
<td>III/IV</td>
<td>0.0%</td>
<td>53.3%</td>
</tr>
<tr>
<td>Infections</td>
<td>I/II</td>
<td>30.0%</td>
<td>62.5%</td>
</tr>
<tr>
<td></td>
<td>III/IV</td>
<td>1.7%</td>
<td>23.1%</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>I/II</td>
<td>35.5%</td>
<td>52.4%</td>
</tr>
<tr>
<td></td>
<td>III/IV</td>
<td>1.7%</td>
<td>32.4%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>I/II</td>
<td>8.3%</td>
<td>48.1%</td>
</tr>
<tr>
<td></td>
<td>III/IV</td>
<td>1.7%</td>
<td>13.5%</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>I/II</td>
<td>10.4%</td>
<td>22.1%</td>
</tr>
<tr>
<td></td>
<td>III/IV</td>
<td>0.9%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Liver</td>
<td>I/II</td>
<td>20.6%</td>
<td>40.4%</td>
</tr>
<tr>
<td></td>
<td>III/IV</td>
<td>0.9%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Renal</td>
<td>I/II</td>
<td>0.9%</td>
<td>9.6%</td>
</tr>
<tr>
<td></td>
<td>III/IV</td>
<td>0.0%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Muscle/bone pain</td>
<td>I/II</td>
<td>42.2%</td>
<td>22.1%</td>
</tr>
<tr>
<td></td>
<td>III/IV</td>
<td>11.0%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Depression</td>
<td>I/II</td>
<td>19.6%</td>
<td>8.7%</td>
</tr>
<tr>
<td></td>
<td>III/IV</td>
<td>4.9%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

Abbreviations: IFN: α-interferon maintenance; ASCT: autologous stem cell transplantation.
Figure legends

Figure 1:
Design of the trial.

Figure 2:
Time course of the sequential triangular test for statistical analysis of the progression-free survival until statistical significance in April 1999. $Z$ is the logrank-statistic and indicates the deviation of the observed number from the expected number of events in the IFNα group under the null hypothesis of no difference. $V$ is the variance of $Z$ and is approximately equal to a quarter of the observed number of events in both groups. The sample path crossed the upper line and thus, a significant advantage of ASCT could be detected. At the time of the final analysis, the value for $Z$ was 26.6 and the value for $V$ was 32.9.

Figure 3:
Trial profile for patients with follicular lymphoma (* not evaluable for the intention-to-treat analysis as no remission was achieved after induction therapy).

Figure 4:
Progression-free survival after high-dose radiochemotherapy followed by autologous stem cell transplantation and interferon-α maintenance in follicular lymphoma. Patients assigned to stem cell transplantation experience significantly longer progression-free survival (logrank-test).

Figure 5A:
Progression-free survival after high-dose radiochemotherapy followed by autologous stem cell transplantation and interferon-α maintenance in the subgroup of patients with low-risk IPI. Patients assigned to stem cell transplantation experience significantly longer progression-free survival (logrank-test).

Figure 5B:
Progression-free survival after high-dose radiochemotherapy followed by autologous stem cell transplantation and interferon-α maintenance in the subgroup of patients with
intermediate-risk IPI. Patients assigned to stem cell transplantation experience significantly longer progression-free survival (logrank-test).

Figure 6:
Overall survival of patients with follicular lymphoma following autologous stem cell transplantation and interferon-α maintenance respectively.
Figures

Figure 1:
Figure 2:
Figure 3:

- 332 enrolled
- 25 not randomized
  - 13 refused IFNo
  - 8 refused ASCT
  - 4 age over 60
- 307 randomized
- 153 randomized to ASCT
  - 35 did not receive assigned therapy
    - 11 no remission
    - 8 refused ASCT
    - 5 other treatment
    - 4 lost to follow-up
    - 3 inadequate documentation
    - 1 secondary disease
    - 1 age over 60
    - 2 other reasons
  - 4 excluded from analysis
    - 4 abort of induction in remission
- 114 analyzed
- 154 randomized to IFNo.
  - 20 did not receive assigned therapy
    - 10 no remission
    - 7 other treatment
    - 2 inadequate documentation
    - 1 refused therapy
  - 8 excluded from analysis
    - 4 CNS I-II stage or II
    - 3 abort of induction in remission
    - 1 radiation in remission
- 126 analyzed
Figure 4:

![Survival probability graph](image)

- **ASCT**
- **IFN**

Values: $p < 0.0001$

<table>
<thead>
<tr>
<th>years after end of induction therapy</th>
<th>numbers of patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ASCT</td>
</tr>
<tr>
<td>0</td>
<td>114</td>
</tr>
<tr>
<td>1</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>38</td>
</tr>
<tr>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>
Figure 5:

A

```
<table>
<thead>
<tr>
<th>Years after end of induction therapy</th>
<th>ASCT</th>
<th>IFN</th>
<th>p = 0.0053</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>35</td>
<td>32</td>
<td>0.0053</td>
</tr>
<tr>
<td>6</td>
<td>29</td>
<td>21</td>
<td>0.0053</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>8</td>
<td>0.0053</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>6</td>
<td>0.0053</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>5</td>
<td>0.0053</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>4</td>
<td>0.0053</td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>3</td>
<td>0.0053</td>
</tr>
<tr>
<td>0</td>
<td>8</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>
```

B

```
<table>
<thead>
<tr>
<th>Years after end of induction therapy</th>
<th>ASCT</th>
<th>IFN</th>
<th>p = 0.0002</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>16</td>
<td>12</td>
<td>0.0002</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>8</td>
<td>0.0002</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>5</td>
<td>0.0002</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>3</td>
<td>0.0002</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>2</td>
<td>0.0002</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>1</td>
<td>0.0002</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>0</td>
<td>0.0002</td>
</tr>
<tr>
<td>0</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>
```
Figure 6:
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 (GLSG)

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