Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial

Mathias J Rummel, Norbert Niederle, Georg Maschmeyer, G Andre Banat, Ulrich von Grünhagen, Christoph Losem, Dorothea Kofahl-Krause, Gerhard Heil, Manfred Welslau, Christina Balser, Ulrich Kaiser, Eckhart Weidmann, Heinz Dürk, Harald Ballo, Martina Stauch, Fritz Roller, Juergen Barth, Dieter Hoelzer, Axel Hinke, Wolfram Brugger, on behalf of the Study group indolent Lymphomas (StiL)

Summary

Background Rituximab plus chemotherapy, most often CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), is the first-line standard of care for patients with advanced indolent lymphoma, and for elderly patients with mantle-cell lymphoma. Bendamustine plus rituximab is effective for relapsed or refractory disease. We compared bendamustine plus rituximab with CHOP plus rituximab (R-CHOP) as first-line treatment for patients with indolent and mantle-cell lymphomas.

Methods We did a prospective, multicentre, randomised, open-label, non-inferiority trial at 81 centres in Germany between Sept 1, 2003, and Aug 31, 2008. Patients aged 18 years or older with a WHO performance status of 2 or less were eligible if they had newly diagnosed stage III or IV indolent or mantle-cell lymphoma. Patients were stratified by histological lymphoma subtype, then randomly assigned according to a prespecified randomisation list to receive either intravenous bendamustine (90 mg/m² on days 1 and 2 of a 4-week cycle) or CHOP (cycles every 3 weeks of cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and vincristine 1·4 mg/m² on day 1, and prednisone 100 mg/day for 5 days) for a maximum of six cycles. Patients in both groups received rituximab 375 mg/m² on day 1 of each cycle. Patients and treating physicians were not masked to treatment allocation. The primary endpoint was progression-free survival, with a non-inferiority margin of 10%. Analysis was per protocol. This study is registered with ClinicalTrials.gov, number NCT00991211, and the Federal Institute for Drugs and Medical Devices of Germany, BfArM 4021335.

Findings 274 patients were assigned to bendamustine plus rituximab (261 assessed) and 275 to R-CHOP (253 assessed). At median follow-up of 45 months (IQR 25–57), median progression-free survival was significantly longer in the bendamustine plus rituximab group than in the R-CHOP group (69·5 months [26·1 to not yet reached] *vs* 31·2 months [15·2–65·7]; hazard ratio 0·58, 95% CI 0·44–0·74; p<0·0001). Bendamustine plus rituximab was better tolerated than R-CHOP, with lower rates of alopecia (0 patients *vs* 245 (100%) of 245 patients who recieved ≥3 cycles; p<0·0001), haematological toxicity (77 [30%] *vs* 173 [68%]; p<0·0001), infections (96 [37%] *vs* 127 [50%]); p=0·0025), peripheral neuropathy (18 [7%] *vs* 73 [29%]; p<0·0001), and stomatitis (16 [6%] *vs* 47 [19%]; p<0·0001). Erythematous skin reactions were more common in patients in the bendamustine plus rituximab group than in those in the R-CHOP group (42 [16%] *vs* 23 [9%]; p=0·024).

Interpretation In patients with previously untreated indolent lymphoma, bendamustine plus rituximab can be considered as a preferred first-line treatment approach to R-CHOP because of increased progression-free survival and fewer toxic effects.

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See Comment page 1163

Medizinische Klinik IV (Prof M J Rummel MD, G A Banat MD, J Barth Pharm), **Department of Radiology** (F Roller MD), **Hospital of the Justus-Liebig-University, Giessen, Germany; Klinikum Leverkusen, Leverkusen, Germany** (Prof N Niederle MD); **Ernst von Bergmann Klinikum, Potsdam, Germany** (Prof G Maschmeyer MD); **Onkologische Praxis, Cottbus, Germany** (U von Grünhagen MD); **Onkologische Praxis, Neuss, Germany** (C Losem MD); **Medizinische Hochschule Hannover, Germany** (D Kofahl-Krause MD); **Klinikum Lüdenscheid, Lüdenscheid, Germany** (Prof G Heil MD); **Onkologische Praxis, Aschaffenburg, Germany** (M Welslau MD); **Onkologische Praxis, Marburg, Germany** (C Balser MD); **St Bernward Krankenhaus, Hildesheim, Germany** (Prof U Kaiser MD); **Krankenhaus Nordwest, Frankfurt am Main, Germany** (Prof E Weidmann MD); **St Marien-Hospital, Hamm, Germany** (H A Duerk MD, PhD); **Onkologische Praxis, Offenbach, Germany** (H Balló MD); **Onkologische Praxis, Kronach, Germany** (M Stauch MD); **Hospital of the Johann Wolfgang Goethe-University, Frankfurt, Germany** (Prof D Hoelzer MD); **Wissenschaftlicher Service**

Introduction

Non-Hodgkin lymphoma is the sixth most common cancer in the USA, with 66 000 new cases diagnosed every year.[1] Indolent or low-grade lymphomas represent 40% of all subtypes of non-Hodgkin lymphoma, of which follicular lymphoma is the most frequent.[2] Indolent lymphomas are characterised by a chronic relapsing-remitting disease course, with patients usually exposed to several successive treatment courses. Mantle-cell lymphoma, which accounts for about 3–10% of all non-Hodgkin lymphomas, has a poorer prognosis than other types of non-Hodgkin lymphoma.

Rituximab—an anti-CD20 monoclonal antibody—is established for the treatment of non-Hodgkin lymphoma.[3] Chemoimmunotherapy with rituximab is a standard of care for the first-line treatment of patients with advanced follicular and mantle-cell lymphomas in view of it being more effective than chemotherapy alone.[4–9] Guidelines from the National Comprehensive Cancer Network (NCCN) and European Society for

Pharma GmbH, Langenfeld, Germany (A Hinke PhD); **Schwarzwald-Baar Klinikum Villingen-Schwenningen, Academic Teaching Hospital University of Freiburg, Freiburg im Breisgau, Germany** (Prof W Brugger MD)

Correspondence to: Prof Dr Mathias J Rummel, Medizinische Klinik IV, University Hospital, 35392 Giessen, Germany
mathias.rummel@innere.med.uni-giessen.de

Medical Oncology (ESMO) recommend that in patients with follicular lymphoma, rituximab should be used in combination with one of several chemotherapy regimens, including CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), CVP (cyclophosphamide, vincristine, and prednisolone), fludarabine and cyclophosphamide (with or without mitoxantrone), and single-agent fludarabine.[10,11] Although CHOP plus rituximab (R-CHOP) is the most widely used of these regimens,[12] there are no randomised comparative study data to show that one regimen is better than another. Treatment choices are usually made on the basis of the patient's ability to tolerate chemotherapy, which is generally guided by age, performance status, and co-morbidities. The long-term cardiotoxic potential of anthracyclines can also detract from regimens incorporating doxorubicin.

Although bendamustine is used and has been approved for more than 20 years in Germany, it only gained approval for the management of lymphoid malignancies in the USA in 2008, and the European Union in 2010. As a cytotoxic alkylating drug, bendamustine has a favourable tolerability profile and is highly effective as monotherapy or combined with rituximab for patients with relapsed or refractory lymphoid malignancies.[13–17] On the basis of the longstanding experience with bendamustine in Germany, we postulated that bendamustine plus rituximab would be non-inferior to R-CHOP in terms of efficacy, and would be better tolerated. We therefore assessed the efficacy and safety of bendamustine plus rituximab versus R-CHOP as first-line treatment for patients with indolent or mantle-cell lymphoma.

For the **study protocol** see http://www.stil-info.de/index.php?id=230

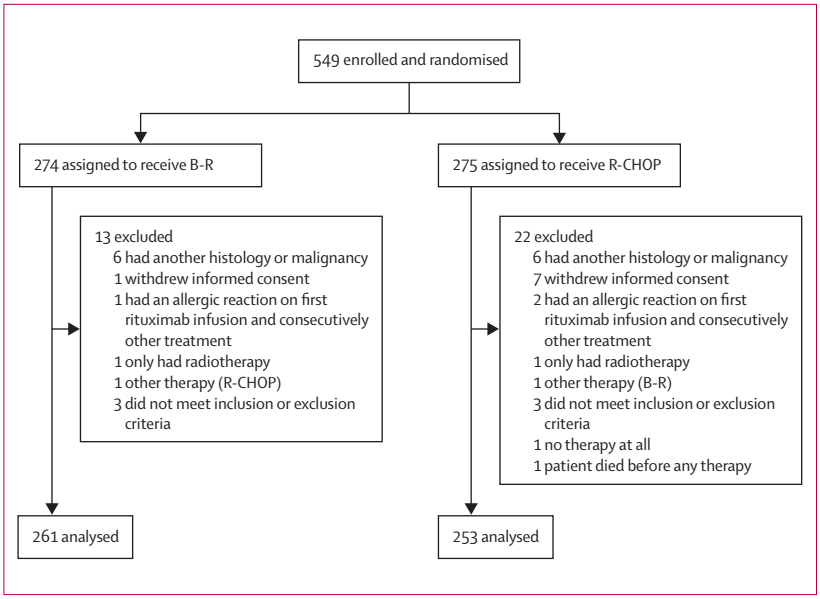

Figure 1: **Trial profile**
B-R=bendamustine plus rituximab. R-CHOP=CHOP plus rituximab.

Methods

Study design and patients

We undertook this multicentre, randomised, non-inferiority, open-label, phase 3 study at 81 centres in Germany between Sept 1, 2003, and Aug 31, 2008. Patients aged 18 years and older with a WHO performance status of 2 or less were eligible for inclusion if they had a histologically confirmed diagnosis of mantle-cell lymphoma or indolent non-Hodgkin lymphoma, including the following CD20-positive subtypes:[2] follicular (grade 1 and 2), lymphoplasmacytic (Waldenström's macroglobulinaemia), small lymphocytic, and marginal-zone lymphoma. Staff at a referral centre reviewed all lymph node, bone marrow, and other specimen biopsies for haematopathological changes.

All patients had to have previously untreated stage III or IV disease, and patients with indolent lymphoma subtypes had to meet at least one of the following criteria: impaired haemopoiesis (haemoglobin <100 g/L, granulocyte count $<1{\cdot}5\times10^9$ per L, or platelet count $<100\times10^9$ per L); presence of B-symptoms; large tumour burden (three areas >5 cm or one area >7·5 cm); bulky disease with impingement on internal organs; progressive disease, defined as a more than 50% increase of tumour mass within 6 months; or a hyperviscosity syndrome. Patients were ineligible if they had a history of severe cardiac disease or previous malignancy; inadequate hepatic, renal, or cardiac function; or infection with HIV or hepatitis B. We recommended patients younger than 65 years with mantle-cell lymphoma for alternative clinical trials incorporating autologous stem-cell transplantation, as was proposed in the subsequently published ESMO current treatment standards.[18]

All patients gave written informed consent and the protocol was approved by the local ethics committee and institutional review boards at each participating centre. This study complied with the Declaration of Helsinki and its amendments, and was done in accordance with Good Clinical Practice guidelines.

Randomisation and masking

Patients were centrally randomly assigned (1:1) by the Study group indolent Lymphomas (StiL) Head Office according to a prespecified randomisation list to receive bendamustine plus rituximab or R-CHOP. Randomisation was stratified by subtype of histological lymphoma. Patients, treating physicians, and individuals assessing outcomes and analysing data were not masked to treatment allocation.

Procedures

All treatments were approved in Germany for the specific disease indication. Intravenous bendamustine 90 mg/m² was given over 30–60 min on days 1 and 2 of a 4-week cycle for up to six cycles. CHOP consisted of cycles every 3 weeks of cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and vincristine 1·4 mg/m² (up to a maximum

dose of 2 mg) on day 1, and prednisone 100 mg per day for 5 days, for a maximum of six cycles. Patients in both groups received rituximab 375 mg/m² on day 1 of each cycle, according to standard procedure. No maintenance or consolidation treatment was given.

All patients received standard antiemetic prophylaxis, but no prophylactic antibiotic treatment. Prophylactic use of granulocyte-colony stimulating factors (G-CSF) was allowed, according to guidelines from the American Society of Clinical Oncology. We delayed treatment cycles for 1 week if the leucocyte count was less than 2×10^9 per L or the platelet count less than 100×10^9 per L before a scheduled cycle. If we noted a leucocyte count less than 1×10^9 per L or a platelet count less than 5×10^9 per L on 2 consecutive days between cycles, the dose of bendamustine was decreased to 70 mg/m², and for R-CHOP, the doses of cyclophosphamide and doxorubicin to 600 mg/m² and 40 mg/m², respectively. Vincristine was discontinued in the case of grade 2 or higher neurological toxic effects.

All patients underwent standard pretreatment screening, including a physical examination; complete blood count; assessment of serum chemistry; serum immunoelectrophoresis; measurement of immunoglobulin concentrations; chest radiograph; CT scan of the chest, abdomen, and pelvis; sonography of the abdomen; and bone marrow aspiration and biopsy. If clinically relevant, endoscopy of the gastrointestinal tract was done. Tumour responses were assessed after cycles three and six or at the end of treatment, and were classified as complete response, partial response, stable disease, or progressive disease, with standard WHO response criteria.

We used WHO's toxicity criteria to assess treatment-related toxic effects. Blood counts, including differential counts, were done once a week. Duration of remission was assessed with clinical assessment and CT scan or sonographic examination every 3 months for the first 2 years. Patients had a CT scan at least every 6 months.

Statistical analysis

The primary endpoint was progression-free survival, defined as the time between first treatment and one of the following events: progressive disease, relapse after response, or death from any cause. Secondary endpoints were rates of overall and complete response; acute and late toxic effects; overall survival; time to next anti-lymphoma treatment; and event-free survival, with an event defined as progression of disease, death from any cause, patients not achieving at least a partial response after three treatment cycles, or start of subsequent salvage treatment. Start of subsequent treatment not specified in the protocol, such as a rituximab maintenance therapy in ongoing remission, was not counted as an event for event-free survival, but was censored at the time of treatment. We counted all subsequent treatments as events in the analysis of time to next antilymphoma treatment, irrespective of the reason for their initiation.

	B-R (n=261)	CHOP-R (n=253)
Age (years)	64 (34–83)	63 (31–82)
<60	94 (36%)	90 (36%)
61–70	107 (41%)	105 (42%)
>70	60 (23%)	58 (23%)
Stage		
II	9 (3%)	9 (4%)
III	50 (19%)	47 (19%)
IV	202 (77%)	197 (78%)
Histology		
Follicular	139 (53%)	140 (55%)
Mantle cell	46 (18%)	48 (19%)
Marginal zone	37 (14%)	30 (12%)
Lymphoplasmacytic*	22 (8%)	19 (8%)
Small lymphocytic	10 (4%)	11 (4%)
Low grade, unclassifiable	7 (3%)	5 (2%)
B symptoms	100 (38%)	74 (29%)
Bone marrow involved	177 (68%)	170 (67%)
Extranodal involved sites ≥1	212 (81%)	193 (76%)
LDH >240 U/L	100 (38%)	84 (33%)
Median β-2 microglobulin (mg/L)	2·6 (0·7-17·8)	2·4 (1·1-23·2)
Prognostic groups for all patients (IPI)		
>2 risk factors	96 (37%)	89 (35%)
Prognostic groups according to FLIPI		
Low risk (0–1 risk factor)	16/139 (12%)	26/140 (19%)
Intermediate risk (2 risk factors)	57/139 (41%)	44/140 (31%)
Poor risk (3–5 risk factors)	63/136 (46%)	64/134 (48%)

Data are median (range), n (%), or n/N (%). B-R=bendamustine plus rituximab. R-CHOP=CHOP plus rituximab. LDH=lactate dehydrogenase. IPI=Intentional Prognostic Index. FLIPI=Follicular Lymphoma International Prognostic Index. *Waldenström's macroglobulinaemia.

Table 1: **Patient characteristics**

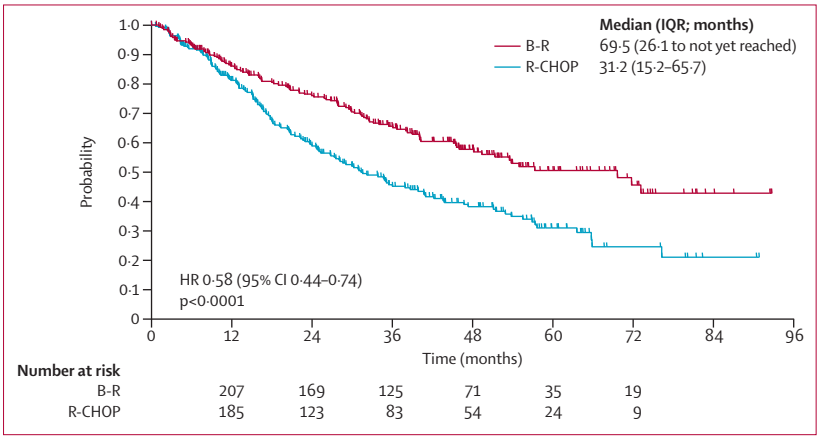

Figure 2: **Progression-free survival**
B-R=bendamustine plus rituximab. R-CHOP=CHOP plus rituximab.

On the cutoff date for this analysis (Oct 31, 2011), we censored data for patients who had no reported events at the most recent assessment. We aimed to show non-inferiority of bendamustine plus rituximab versus

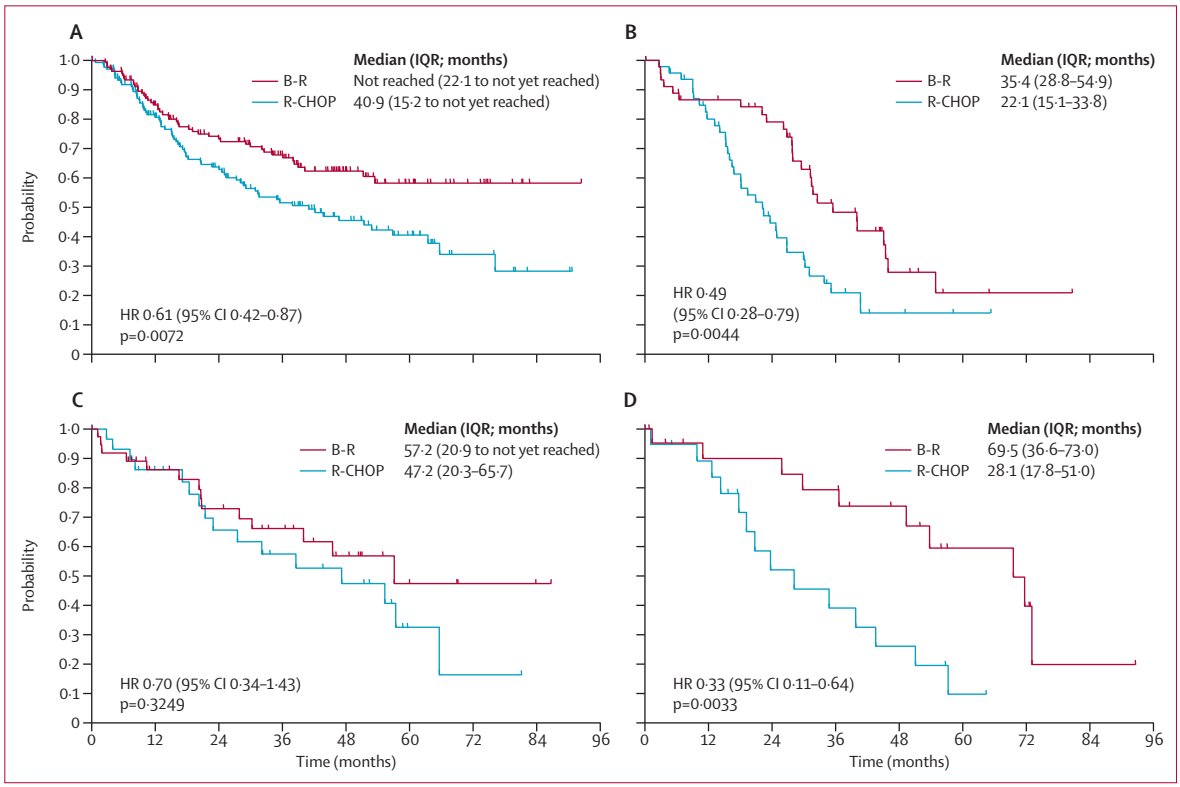

Figure 3: **Progression-free survival in histological subtypes of follicular lymphoma (A), mantle-cell lymphoma (B), marginal-zone lymphoma (C), and Waldenstrom's macroglobulinaemia (D)**
B-R=bendamustine plus rituximab. R-CHOP=CHOP plus rituximab.

	HR (95% CI)	p value
Age (years)		
≤60 (n=199)	0·52 (0·33–0·79)	0·002
>60 (n=315)	0·62 (0·45–0·84)	0·002
LDH concentration		
Normal (n=319)	0·48 (0·34–0·67)	<0·0001
Elevated (n=184)	0·74 (0·50–1·08)	0·118
FLIPI subgroup		
Favourable (0–2 risk factors; n=143)	0·56 (0·31–0·98)	0·043
Unfavourable (3–5 risk factors; n=127)	0·63 (0·38–1·04)	0·068

PFS=progression-free survival. LDH=lactate dehydrogenase. FLIPI=Follicular Lymphoma International Prognostic Index. HR=hazard ratio.

Table 2: **Exploratory subgroup analysis to assess the progression-free survival benefit of bendamustine plus rituximab versus CHOP plus rituximab**

R-CHOP for the primary endpoint. With an assumed equal efficacy of both treatment groups, a hypothetical inferiority of bendamustine plus rituximab with a progression-free survival rate of 40% versus a rate of 50% or more with R-CHOP after 3 years (corresponding to a non-inferiority margin of 10% and a hazard ratio of 1·32) had to be excluded with 95% confidence and a power of 80%. Therefore, 224 patients were needed per group, with a recruitment time of 4 years. We intentionally over-recruited patients because of a delay in primary events compared with original expectations. Analysis was per protocol.

We used the Kaplan-Meier method to estimate survival curves, applied the log-rank test for comparisons, and used the Cox proportional hazards model with a stepwise backward variable selection approach ($p<0·1$) for multivariate analysis and to obtain hazard ratios with confidence intervals. We used Fisher's exact or χ^2 tests to compare toxic effects and rates of G-CSF use. Except for the primary endpoint, all statistical tests that included subgroup and interaction analyses were exploratory and not prospectively defined; we made no adjustments for multiplicity. All tests were two-sided.

This trial is registered with Clinical Trials.gov, number NCT00991211, and with the Federal Institute for Drugs and Medical Devices of Germany, BfArM 4021335.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. 274 patients were assigned to the bendamustine plus rituximab group and 275 to the R-CHOP group. 35 patients were excluded, leaving 514 patients for analysis (figure 1).

Baseline characteristics and numbers of patients in specific histology subgroups were similar between the treatment groups (table 1). More than half the patients had follicular lymphoma and about a fifth had mantle-cell lymphoma (table 1). Within the histological subgroups, the median age of patients was 60 years (IQR 51–67) for those with follicular lymphoma, 70 years (64·5–74) for those with mantle-cell lymphoma, 66 years (61–70) for those with marginal-zone lymphoma, and 64 years (56–69) for those with Waldenström's macroglobulinemia. According to the Follicular Lymphoma International Prognostic Index (FLIPI),[19] about half the patients in both groups were in the poor-risk category (table 1). 1450 cycles of bendamustine plus rituximab and 1425 of R-CHOP were given (mean number of cycles per patient 5·58 [SD 1·05] *vs* 5·63 [1·08]). Full doses of treatment were given in 95·9% of bendamustine plus rituximab cycles and 88·8% of R-CHOP cycles.

Over the course of follow-up, we noted 103 (39%) events in the bendamustine plus rituximab group and 143 (57%) in the R-CHOP group. Bendamustine plus rituximab significantly prolonged progression-free survival compared with R-CHOP (figure 2). The appendix shows results for interaction of histological subgroups on the basis of a stratified log-rank test. Median follow-up for both treatment groups at the time of analysis was 45 months (29–57).

A significant benefit for progression-free survival was shown with bendamustine plus rituximab versus R-CHOP for all histological subtypes, except for marginal-zone lymphoma (figure 3), with no significant treatment-by-subgroup interaction (appendix). The improvement in progression-free survival with bendamustine plus rituximab was independent of age, concentration of lactate dehydrogenase (LDH), and FLIPI score (table 2 and appendix). In multivariate analysis with backward selection, we identified mantle-cell histology (HR 1·84, 95% CI 1·37–2·48; p<0·0001) and LDH concentrations of more than 240 U/L (1·40, 1·08–1·82; p=0·010) as independent negative predictors of poor outcome; whereas treatment with bendamustine plus rituximab showed a very similar benefit to that noted in the unadjusted analysis (HR 0·56, 95% CI 0·43–0·72; p<0·0001). The rate of overall response did not differ between the treatment groups (242 [93%] of 261 patients in the bendamustine plus rituximab group *vs* 231 [91%] of 253 in the R-CHOP group); however, the rate of complete response was significantly increased in patients in the bendamustine plus rituximab group (104 [40%] *vs* 76 [30]; p=0·021).

At the time of analysis, 74 salvage treatments had been started in the bendamustine plus rituximab group compared with 116 in the R-CHOP group. Time to next antilymphoma treatment was significantly longer with bendamustine plus rituximab than with R-CHOP (HR 0·52, 95% CI 0·39–0·69; p<0·0001); median time to next antilymphoma treatment was not reached for bendamustine plus rituximab (IQR 35·1 to not yet reached), versus 42·3 months (18·2 to not yeat reached) for R-CHOP. Overall survival did not differ between the treatment groups (appendix); 43 patients died in the bendamustine plus rituximab group compared with 45 in the R-CHOP group. Median overall survival was not reached in either group (appendix).

Patients in the bendamustine plus rituximab group had fewer toxic effects than did those in the R-CHOP group, with serious adverse events occurring in 49 (19%) and 74 (29%) patients (appendix). We noted significantly fewer haematological toxic effects in patients in the bendamustine plus rituximab group than in those in the R-CHOP group, with lower frequencies of grade 3–4 leucocytopenia (p<0·0001) and neutropenia (p<0·0001; table 3). We noted no relevant cases of thrombocytopenia or anaemia in either group, but G-CSF use was significantly reduced in the bendamustine plus rituximab group compared with R-CHOP group (58 cycles [4%] *vs* 282 cycles [20%]; p<0·0001). Infections of any grade were significantly less frequent in patients in the bendamustine plus rituximab group than in those in the R-CHOP group (table 4). Severe infectious complications with a fatal outcome were less frequent in the bendamustine plus rituximab group: one patient died from sepsis compared with five in the R-CHOP group. No

See Online for appendix

	Grade 1		Grade 2		Grade 3		Grade 4		Grade 3–4	
	R-CHOP	B-R	R-CHOP	B-R	R-CHOP	B-R	R-CHOP	B-R	R-CHOP	B-R
Leucocytopenia	13 (5%)	52 (19%)	39 (15%)	80 (30%)	110 (44%)	85 (32%)	71 (28%)	13 (5%)	181 (72%)*	98 (37%)*
Neutropenia	6 (2%)	30 (11%)	19 (8%)	61 (23%)	70 (28%)	53 (20%)	103 (41%)	24 (9%)	173 (69%)*	77 (29%)*
Lymphocytopenia	12 (5%)	14 (5%)	72 (29%)	38 (14%)	87 (35%)	122 (46%)	19 (8%)	74 (28%)	106 (43%)	196 (74%)
Anaemia	115 (46%)	102 (38%)	84 (33%)	44 (16%)	10 (4%)	6 (2%)	2 (<1%)	2 (<1%)	12 (5%)	8 (3%)
Thrombocytopenia	89 (35%)	104 (39%)	20 (8%)	19 (7%)	11 (4%)	15 (6%)	5 (2%)	2 (<1%)	16 (6%)	13 (5%)

B-R=bendamustine plus rituximab. R-CHOP=CHOP plus rituximab. *p<0·0001 between groups.

Table 3: **Haematological toxic events in patients receiving at least one dose of study treatment**

	B-R (n=261)	R-CHOP (n=253)	p value
Alopecia	0	245 (100%)*	<0·0001
Paresthesia	18 (7%)	73 (29%)	<0·0001
Stomatitis	16 (6%)	47 (19%)	<0·0001
Skin (erythema)	42 (16%)	23 (9%)	0·024
Skin (allergic reaction)	40 (15%)	15 (6%)	0·0006
Infectious episodes	96 (37%)	127 (50%)	0·0025
Sepsis	1 (<1%)	8 (3%)	0·019

B-R=bendamustine plus rituximab. R-CHOP=CHOP plus rituximab. *Includes only patients who received three or more cycles.

Table 4: **All grades of non-haematological toxic events in patients receiving at least one dose of study treatment**

patients had alopecia in the bendamustine plus rituximab group, but this occurred in all patients who received three or more cycles of R-CHOP (table 4). Neurotoxic effects, specifically peripheral neuropathy, were significantly less common in the bendamustine plus rituximab group (table 4). By contrast, drug-associated erythematous skin reaction (urticaria, rash) was more common in patients given bendamustine plus rituximab than in those given R-CHOP (table 4). Skin irritations, which arose in combination with fever, were assessed as allergic reactions in more patients in the bendamustine group than in the R-CHOP group (table 4). We noted no Stevens-Johnson Syndrome or toxic epidermal necrolysis in either group.

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We recorded 20 secondary malignancies in the bendamustine plus rituximab group compared with 23 in the R-CHOP group, with one haematological malignancy in each group (one case of myelodysplastic syndrome in the bendamustine plus rituximab group and one of acute myeloid leukemia in the R-CHOP group).

Discussion

Our findings show that bendamustine and rituximab significantly improved progression-free survival compared with R-CHOP. Furthermore, bendamustine plus rituximab significantly increased rate of complete response and time to next lymphoma treatment. Notably, progression-free survival significantly improved with bendamustine and rituximab in three of four histological subgroups. This improvement is particularly notable for mantle-cell lymphoma, which has a more aggressive disease course than other lymphomas.

Our results for the R-CHOP regimen seem to be inferior compared to those noted by Czuczman and colleagues[20] and Hiddemann and colleagues,[5] but this finding could be because of differences in patient population and trial design. Our study included patients with several histologies and a greater proportion of high-risk patients (including a higher median age, poor FLIPI score, and increased concentrations of LDH). In the Czuczman study, the median patient age was 48·5 years (range 29–77), and many patients did not need treatment.

Panel: Research in context

Systematic review

Bendamustine is a cytotoxic drug that has been explored for indolent non-Hodgkin lymphoma and chronic lymphocytic leukaemia after being first investigated for these disorders more than 30 years ago. In our phase 3 randomised trial, we compared bendamustine plus rituximab with R-CHOP, a standard treatment for newly diagnosed indolent lymphoma. Immunochemotherapy with rituximab is regarded as a standard treatment for newly diagnosed advanced indolent lymphomas on the basis of results of several randomised phase 3 trials, which have shown a significant benefit in outcome compared with chemotherapy alone.[4-9] We searched Pubmed from 2005, with no inclusion criteria or restrictions. Findings from a Cochrane systematic review,[24] which included seven randomised trials, showed improved overall survival for patients with indolent lymphoma (particularly those with the follicular and mantle-cell lymphomas) when treated with rituximab plus chemotherapy compared with chemotherapy alone.[24] CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) plus rituximab is, along with CVP (cyclophosphamide, vincristine, and prednisolone) plus rituximab, one of the most widely used immunochemotherapy regimens and is a National Comprehensive Cancer Network (NCCN) recommended treatment.

Interpretation

Bendamustine plus rituximab was more effective and less toxic than was R-CHOP. On the basis of these favourable results, therapy with bendamustine plus rituximab now constitutes a backbone regimen in ongoing Study group indolent Lymphomas (StiL) studies. Of note, the NCCN guidelines have been updated to include this regimen as a first-line treatment option for follicular lymphoma, and bendamustine with or without rituximab as a less aggressive induction treatment option for mantle-cell lymphoma. Similarly, clinical practice guidelines from the European Society for Medical Oncology recommend the bendamustine plus rituximab regimen for newly diagnosed follicular lymphoma.[25] Therefore, this regimen can be considered as a preferred first-line treatment approach. Future studies will establish whether the addition of rituximab maintenance, which significantly improved results after immunochemotherapy in the PRIMA study,[21] will further improve the outcomes achieved with the bendamustine plus rituximab regimen.

Furthermore, unlike the Hiddemann study, patients in our study did not receive any consolidation therapy after either regimen. Similarly, because of substantial differences in trial designs, we cannot compare our findings to those of the FL2000 study, which included 18 months of interferon-alfa consolidation therapy,[9] or the PRIMA study, in which responding patients were randomly assigned to rituximab maintenance therapy after immunochemotherapy.[21] Furthermore, differences in the

definition of response could explain discrepant results between our findings and those of other trials. For example, some trials used a combined rate of complete response plus unconfirmed complete response, making cross-trial comparisons difficult.

Our comparison of two distinct treatment strategies meant that timings and treatment durations differed between the two groups. We based the timings of disease assessment on clinical practice. Nevertheless, despite a potential effect on the results, the large difference in progression-free survival between the two groups precludes a substantial effect on outcome owing to differences in treatment duration. The incidence of non-Hodgkin lymphoma increases with age, with a median age at diagnosis of 67 years.[22] In our study, the median age of patients was 64 years in the total patient group, and extended up to a median of 70 years in patients with mantle-cell lymphoma, which shows that this patient group was broadly representative of patients with non-Hodgkin lymphoma in routine practice.

Because indolent non-Hodgkin lymphoma is regarded as incurable and mostly affects elderly individuals, the toxic effects of treatment regimens are a particular concern because existing comorbidities or decreased organ function can compromise the ability to tolerate cytotoxic chemotherapy. In our study, grade 3–4 neutropenia was 2·25 times less frequent with bendamustine and rituximab than with R-CHOP; consistent with this finding, the use of haemopoietic growth factors and the occurrence of infectious episodes were increased with R-CHOP. In particular, five people died from sepsis in the R-CHOP group compared with one in the bendamustine and rituximab group. Neurotoxic effects were also four times less frequent with bendamustine and rituximab than with R-CHOP. Furthermore, the long-term effects of chemotherapy were similar for both groups with secondary primary malignancies occurring in similar numbers of patients. However, whether bendamustine increases the risk for late-stage secondary malignancies, particularly myelodysplastic syndromes or acute myeloid leukaemia, cannot be idenified from this study because of the short observation time and the small number of patients. No patients had alopecia in the bendamustine and rituximab group compared with those who received three or more cycles of R-CHOP. Although chemotherapy-induced alopecia is not a life-threatening adverse event, it can have profound psychosocial and quality-of-life consequences, resulting in anxiety, depression, negative body image, lowered self-esteem, and a reduced sense of wellbeing.[23] The absence of alopecia with bendamustine and rituximab therefore represents a substantial potential benefit for patients undergoing first-line treatment for indolent and mantle-cell lymphomas (panel).

These phase-3 data clearly show that bendamustine and rituximab is more effective and less toxic than R-CHOP for patients who need treatment for indolent and mantle-cell lymphoma. Findings from the phase-3 PRIMA study showed that 2 years of rituximab maintenance after immunochemotherapy as first-line treatment for follicular lymphoma significantly improved progression-free survival.[21] On the basis of these results, the ongoing StiL Study MAINTAIN (ClinicalTrials.gov, number NCT00877214) aims to assess the addition of rituximab maintenance after bendamustine and rituximab induction for 2 years versus 4 years, which could further improve the efficacy of the bendamustine plus rituximab induction regimen.

Contributors

MJR conceptualised the study. The StiL steering committee designed the study. The StiL head office collected data. AH and MJR did the statistical analysis. MJR developed an early draft, and all investigators reviewed and approved the submitted report.

Members of the StiL steering committee

Mathias Rummel, Hospital of the Justus-Liebig University, Gießen, Germany; Ulrich Kaiser, St Bernward Krankenhaus, Hildesheim, Germany; Norbert Niederle, Städtisches Klinikum, Leverkusen, Germany; Hartmut Link, Westpfalz Klinikum, Kaiserslautern, Germany; Wolfram Brugger, Schwarzwald-Baar Klinikum, Villingen-Schwenningen, Academic Teaching Hospital University of Freiburg, Germany; Jürgen Barth, Justus-Liebig University, Gießen, Germany; Manfred Welslau, Onkologische Schwerpunktpraxis, Aschaffenburg, Germany; André Banat, Hospital of the Justus-Liebig University, Gießen, Germany; Axel Hinke, WISP, Langenfeld, Germany; Wolfgang Knauf, Onkologische Schwerpunktpraxis, Frankfurt, Germany; Dorothea Kofahl-Krause, Medizinische Hochschule, Hannover, Germany; Eckhart Weidmann, Krankenhaus Nordwest, Frankfurt, Germany; Markus Klein, Onkologische Schwerpunktpraxis, Wiesbaden, Germany; Michael Baldus, Onkologische Schwerpunktpraxis, Rüsselsheim, Germany; Michael Sandherr, Onkologische Schwerpunktpraxis, Weilheim, Germany.

Study investigators

C Aulmann, G Schlimok, Augsburg; M Baldus, Rüsselsheim; H-P Böck, H Balló, Offenbach; C Balser, F Weidenbach, Marburg; D Behringer, Bochum; S Krüger, P S Mitrou, Frankfurt; P Bojko, W Abenhardt, München; F Breuer, Frechen; O Brudler, Augsburg; W Brugger, Villingen-Schwenningen; A Burchardt, W Blau, A Banat, Gießen; K Chow, H-J Cordes, Frankfurt; M Clemens, R Mahlberg, Trier; H Dürk, Hamm; M Eckart, Erlangen; J Eggert, Moers; H Fiechtner, Stuttgart; S Fuxius, Heidelberg; M Görner, M Just, E Schäfer, Bielefeld; M Graubner, Schotten; G Günther, Potsdam; L Hahn, Herne; R Hecker, Groß Gerau; G Heil, Lüdenscheid; O Herrmann, Offenburg; S Hochdörfer, Rehling; T Hoffmann, Weimar; K Hünermund, Ludwigshafen; P Immenschuh, M Burk, Hanau; K Josten, Wiesbaden; U Kaiser, T Heide, Hildesheim; F Katz, Wiesbaden; S Klein, Bayreuth-Mannheim; W Knauf, H Tesch, Frankfurt; G Kobbe, F Zohren, R Haas, Düsseldorf; M Koch, J Rauh, Witten; G Köchling, Villingen-Schwenningen; D Kofahl-Krause, A Ganser, Hannover; G Kojouharoff, G Dingeldey, Darmstadt; S Koniczek, Heilbronn; H Link, J Kirsch, Kaiserslautern; C Losem, Neuss; G Maschmeyer, F Rothmann, Potsdam; A Matzdorff, Saarbrücken; J Mittermüller, Germering; S Müller, M Hahn, Ansbach; L Müller, Leer; S Müller-Hagen, Hamburg; M Neise, Krefeld; K Schalk, T Neuhaus, K Hens, Limburg; N Niederle, A Heider, G Kloster, H Nowak, Leverkusen; O Prümmer, Kempten; M Reeb, R Hansen, Kaiserslautern; R Rohrberg, H-J Hurtz, Halle; D Fritze, A Rost, A Brecht, R Kayser, H Bernhard, Darmstadt; M Sandherr, M Perker, Weilheim; M Schauer, Nürnberg; R Schlag, Würzburg, G Schließer, A Käbisch, C Weber, Gießen; U-M Schmidt, Berlin; I Schmidt-Wolf, P Brossart, Bonn; J Schneider, Oberhausen, J Schröder, Mülheim an der Ruhr; M Schroeder, Duisburg; H-J Schütte, K-D Artmann, Düsseldorf; I Schwaner, Berlin; G Seipelt, U Koch, Bad Soden; J Selbach, J Anhuf, Duisburg; U Söling, Kassel, M Stauch, Kronach; E Thiel, W-K Hofmann, Mannheim; L Fischer, Berlin; K Tischbirek, Wiesbaden; U von Grünhagen, Cottbus; H Wagner, J Wilke, Fürth; M Wattad, P Reimer, Essen; R Weide, J Heymanns, Koblenz; E Weidmann, E Jäger, Frankfurt; J Weiß, Weiden; M Welslau, M Klausmann, Aschaffenburg; G Wittmann, Eltville; J Zimber, Nürnberg.

Conflicts of interest
MJR has received honoraria and research grants from Roche and Mundipharma. WB has received honoraria from Roche and Mundipharma. All other authors declare that they have no conflicts of interest.

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