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European Mantle Cell Lymphoma Network; Zoellner, Anna-Katharina; Unterhalt, Michael; Stilgenbauer, Stephan; Hübel, Kai; Thieblemont, Catherine; Metzner, Bernd; Topp, Max; Truemper, Lorenz; Schmidt, Christian

Published in:
Lancet Haematology

DOI:
10.1016/S2352-3026(21)00195-2

Long-term survival of patients with mantle cell lymphoma after autologous haematopoietic stem-cell transplantation in first remission: a post-hoc analysis of an open-label, multicentre, randomised, phase 3 trial

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Lancet Haematol 2021; 8: e648–57

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Summary

Background Autologous haematopoietic stem-cell transplantation (HSCT) in first remission is the current standard treatment in fit patients with mantle cell lymphoma. In this long-term follow-up study, we aimed to evaluate the efficacy of autologous HSCT versus interferon alfa maintenance after chemotherapy without or with rituximab in patients with primary advanced-stage mantle cell lymphoma.

Methods We did a post-hoc, long-term analysis of an open-label, multicentre, randomised, phase 3 trial done in 121 participating hospitals or practices across six European countries. Patients who were aged 18–65 years with previously untreated stage III–IV mantle cell lymphoma and an ECOG performance score of 0–2 were eligible for participation. Patients were randomly assigned (1:1) to receive either myeloablative radiochemotherapy (fractionated total body irradiation with 12 Gy/day 6–4 days before autologous HSCT and cyclophosphamide 60 mg/kg per day intravenously 3–2 days before autologous HSCT) followed by autologous HSCT (the autologous HSCT group) or interferon alfa maintenance (the interferon alfa maintenance group; 6×10^6 IU three times a week subcutaneously until progression) after completion of CHOP-like induction therapy (cyclophosphamide 750 mg/m² intravenously on day 1, doxorubicin 50 mg/m² intravenously on day 1, vincristine 1·4 mg/m² [maximum 2 mg] intravenously on day 1, and prednisone 100 mg/m² orally on days 1–5; repeated every 21 days for up to 6 cycles) without or with rituximab (375 mg/m² intravenously on day 0 or 1 of each cycle; R-CHOP). The primary outcome was progression-free survival from end of induction until progression or death among patients who had a remission and the secondary outcome was overall survival from the end of induction until death from any cause. We did comparisons of progression-free survival and overall survival according to the intention-to-treat principle between both groups among responding patients and explored efficacy in subgroups according to induction treatment without or with rituximab. Hazard ratios (HRs) were adjusted for the mantle cell lymphoma international prognostic index (MIPI) numerical score, and in the total group also for rituximab use (adjusted HR [aHR]). This trial was started before preregistration was implemented and is therefore not registered, recruitment is closed, and this is the final evaluation.

Findings Between Sept 30, 1996, and July 1, 2004, 269 patients were randomly assigned to receive either autologous HSCT or interferon alfa maintenance therapy. The median follow-up was 14 years (IQR 10–16), with the intention-to-treat population consisting of 174 patients (93 [53%] in the autologous HSCT group and 81 [47%] in the interferon alfa maintenance group) who responded to induction therapy. The median age was 55 years (IQR 47–60), and R-CHOP was used in 68 (39%) of 174 patients. The median progression-free survival was 3·3 years (95% CI 2·5–4·3) in the autologous HSCT group versus 1·5 years (1·2–2·0) in the interferon alfa maintenance group (log-rank p<0·0001; aHR 0·50 [95% CI 0·36–0·69]). The median overall survival was 7·5 years (95% CI 5·7–12·0) in the autologous HSCT group versus 4·8 years (4·0–6·6) in the interferon alfa maintenance group (log-rank p=0·019; aHR 0·66 [95% CI 0·46–0·95]). For patients treated without rituximab, the progression-free survival adjusted HR for autologous HSCT versus interferon alfa was 0·40 (0·26–0·61), in comparison to 0·72 (0·42–1·24) for patients treated with rituximab. For overall survival, the adjusted hazard ratio for HSCT versus interferon alfa was 0·52 (0·33–0·82) without rituximab and 1·05 (0·55–1·99) for patients who received rituximab.

Interpretation Our results confirm the long-term efficacy of autologous HSCT to treat mantle cell lymphoma established in the pre-rituximab era. The suggested reduced efficacy after immunochemotherapy supports the need for its re-evaluation now that antibody maintenance, high-dose cytarabine, and targeted treatments have changed the standard of care for patients with mantle cell lymphoma.

Funding Deutsche Krebshilfe, the European Community, and the Bundesministerium für Bildung und Forschung, Kompetenznetz Maligne Lymphome.

Introduction

Mantle cell lymphoma accounts for about 6–8% of all non-Hodgkin lymphomas in Europe and North America. This type of lymphoma frequently presents with an aggressive clinical course. Although no curative treatment is available, autologous haematopoietic stem-cell transplantation (HSCT) has been shown to lead to high response and progression-free survival rates in fit patients in several clinical trials[1–4] over the past 20 years, and it is the current standard of care for fit young patients with mantle cell lymphoma in advanced stages.[5]

One of the pivotal trials establishing the role of autologous HSCT was started by the European Mantle Cell Lymphoma Network in 1996.[1] This very first study was an open-label, multicentre, randomised, phase 3 trial designed to assess the efficacy and safety of autologous HSCT versus interferon alfa maintenance therapy after a cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-like induction therapy without or with rituximab (ie, R-CHOP) in patients with advanced-stage mantle cell lymphoma who were younger than 65 years. According to the primary trial publication, patients in the autologous HSCT group had significantly longer progression-free survival than those in the interferon alfa maintenance group. However, overall survival was not significantly different between both groups after a median follow-up of 25 months.[1] At the time of primary evaluation, the statistical power was not sufficient to detect relevant overall survival differences.

In the 15 years since this first report, treatment options for patients with mantle cell lymphoma have progressed. The use of rituximab in induction therapy,[6,7] the alternating induction regimen of three courses of R-CHOP and three courses of rituximab plus dexamethasone, cytarabine, and cisplatin,[2] and rituximab maintenance therapy for 3 years after R-CHOP or rituximab plus cytarabine-containing induction and autologous HSCT in the frontline setting have improved response rates, progression-free survival, and overall survival.[3,8] Insights on molecular drivers of the individual disease have been increasing, as has the availability of effective, targeted drugs. Together, they are changing the treatment options for mantle cell lymphoma.[9]

In 2018, more than 20 years from the trial's start in 1996, we decided to report the final trial results with a focus on efficacy data. We aimed to evaluate the mature results on clinical outcome—especially overall survival—of patients with primary advanced-stage mantle cell lymphoma treated with high-dose radiochemotherapy and autologous HSCT, or interferon alfa maintenance in remission after chemotherapy without or with rituximab. Furthermore, we investigated whether the efficacy of autologous HSCT is modified by the addition of rituximab to first-line induction in this setting.

Methods

Study design and participants

We did a post-hoc, long-term analysis of the open-label, multicentre, randomised, phase 3 trial, which was done at 121 participating hospitals or doctor's practices in Germany, France, Belgium, the Netherlands, Italy, and the UK (appendix pp 30–36). Detailed methods for this international confirmatory European Mantle Cell Lymphoma Network trial have previously been

Research in context

Evidence before this study

We searched PubMed on April 27, 2021, using the following search criteria: "(mantle cell lymphoma)" AND "(transplantation)" AND "(randomized or randomised or phase 3 or phase III)" NOT "(review[Publication Type])"". Out of the 69 publications, none, except for the primary publication of this trial, reported on a randomised trial of autologous haematopoietic stem-cell transplantation (HSCT) versus non-autologous HSCT control for first-line treatment of mantle cell lymphoma. The first publication of this trial had shown an improved progression-free survival after response to induction with autologous HSCT compared with interferon alfa maintenance, but did not have sufficient statistical power to detect differences in overall survival.

Added value of this study

This study was a post-hoc, long-term analysis that compared autologous HSCT with interferon alfa maintenance in first remission mantle cell lymphoma that showed the translation of the previously seen improvement in progression-free survival into an improvement in the clinically relevant endpoint of overall survival. Furthermore, the hypothesis that the benefit of autologous HSCT was reduced after the addition of rituximab to induction chemotherapy was generated.

Implications of all the available evidence

The results confirm the establishment of autologous HSCT as the standard first-line treatment for mantle cell lymphoma and could serve as a benchmark for novel therapies. However, the efficacy of autologous HSCT needs to be rechallenged by currently available targeted approaches.

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See Online for appendix

described.[1] In summary, patients aged 18–65 years with previously untreated advanced stage III and IV mantle cell lymphoma as defined by the classification from WHO[10] were eligible. The histological diagnosis was confirmed by a central pathology review at one of the designated pathology reference centres (European Mantle Cell Lymphoma Pathology Panel). Exclusion criteria comprised patients with poor performance status (Eastern Cooperative Oncology Group [ECOG] score >2), severe cardiac, pulmonary, hepatic, or renal impairment, and pregnant or lactating women.

The trial was approved by the local ethics committees at the respective participating hospitals or practices. Written informed consent was obtained from all participating patients and the trial was done in accordance to the Declaration of Helsinki. The study protocol is reported in the appendix (pp 5–29).

Randomisation and masking

Patients were randomly assigned (1:1; up-front randomisation), before the start of induction therapy, to receive either myeloablative radiochemotherapy followed by autologous HSCT (the autologous HSCT group) or interferon alfa maintenance (the interferon alfa maintenance group) after completion of induction therapy.[1] Randomisation was done centrally by computer-based random number generation, was stratified for the number of international prognostic index[11] risk factors (except for age and disease stage) and study group, and was blocked with a fixed block size. Investigators contacted the data centre for randomisation by phone or fax. Because of the autologous HSCT treatment modality, the masking of patients and study investigators was not feasible.

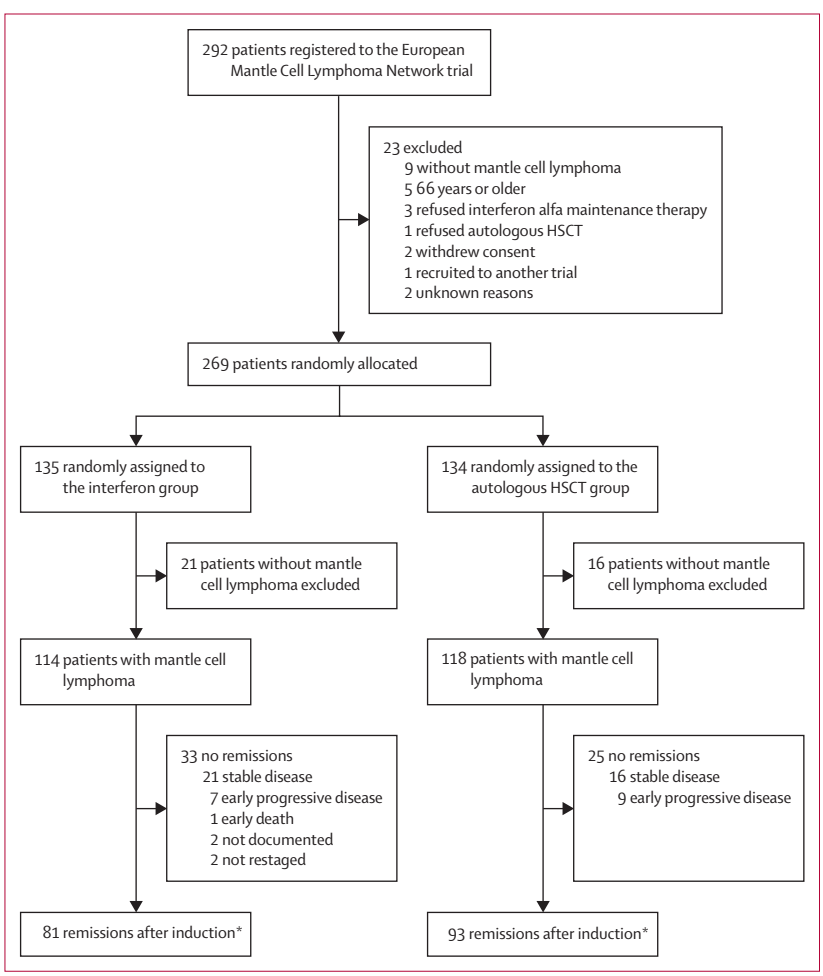

Figure 1: **Study profile**
HSCT=haematopoietic stem-cell transplantation. *Included in the intention-to-treat analyses.

Procedures

Induction therapy consisted of four cycles (ie, for those who achieved complete remission after four cycles) or six cycles (all others) of CHOP (cyclophosphamide 750 mg/m² intravenously on day 1, doxorubicin 50 mg/m² intravenously on day 1, vincristine 1·4 mg/m² [maximum 2 mg] intravenously on day 1, and prednisone 100 mg/m² orally on days 1–5; repeated every 21 days), CHOP-like regimens, or a combination of rituximab (375 mg/m² intravenously on day 0 or 1 of each cycle) plus CHOP. As per protocol, for patients not having a partial remission after six cycles of induction therapy, further treatment was up to the discretion of the treating physician.

Patients allocated to the autologous HSCT group received intensified stem-cell mobilisation chemotherapy with Dexa-BEAM (dexamethasone 8 mg orally three times per day on days 1–10, 1,3-bis[2-chloroethyl]-1-nitrosourea 60 mg/m² intravenously on day 2, melphalan 20 mg/m² intravenously on day 3, etoposide 75 mg/m² intravenously on days 4–7, cytarabine 100 mg/m² intravenously every 12 h on days 4–7, and granulocyte colony-stimulating factor [G-CSF] initiated on day 11). Myeloablative therapy was done within 2 months of mobilisation and consisted of a total body irradiation (12 Gy/day; fractionated 6–4 days before autologous HSCT; pulmonary dosage was limited to 8 Gy) and high-dose cyclophosphamide (60 mg/kg per day intravenously 3–2 days before autologous HSCT) regimen. The previously harvested peripheral blood stem cells were reinfused on day 0 and G-CSF was initiated on day 1.

Patients assigned to the interferon alfa maintenance group received two additional courses of conventional chemotherapy to balance the mobilisation scheme. Subsequently, interferon alfa was applied at a starting dose of 6×10^6 IU subcutaneously three times per week until progression of lymphoma. In case of intolerable toxicity, the dosage was adapted as follows:[1] any side-effects of WHO grades 2 or worse, except for fever, resulted in a dose reduction to 3×10^6 IU; persistence or recurrence of side-effects of WHO grades 2 or worse resulted in a further dose reduction to $1{\cdot}5\times10^6$ IU; and persistence or recurrence of side-effects of WHO grades 2 or worse had their treatment terminated.

Patients were followed-up until disease progression by assessing history and doing a physical examination, ultrasound examination of the abdomen, and a complete laboratory investigation every 3 months; as well as a chest radiography every 6 months. Survival follow-up until death was planned.

Outcomes

The primary outcome for this post-hoc, long-term analysis was progression-free survival from the end of induction until progression or death among patients who had a remission, named in accordance with current consensus response criteria. The primary outcome evaluated in this study is identical to the primary outcome defined in the trial protocol. However, the trial protocol synonymously used disease-free survival, event-free interval, and relapse-free survival for the primary outcome, all defined exactly as progression-free survival from the end of induction among patients who had a remission. Of note, at the time of protocol development, international consensus criteria for lymphoma outcomes were not yet available. To update the wording to current nomenclature and for clarity and consistency with the primary trial publication, we now strictly termed this primary outcome as progression-free survival. The secondary outcome was overall survival from the end of induction until death. In the absence of consensus criteria, response was evaluated as described in the trial protocol (appendix pp 18,19). The applied criteria are in principle consistent with the 1999 International Working Group response criteria.[12] Unmasked central medical review of efficacy outcomes was done at the European Mantle Cell Lymphoma Network study centre. Except secondary malignancies, adverse events were not reported in this long-term follow-up.

Statistical analysis

Patients without an event were censored at the latest event-free contact date. The analysis was done according to the intention-to-treat principle with the modification that patients without confirmed mantle cell lymphoma or without response to induction therapy were excluded. The primary endpoint had been monitored with regular interim analyses in a sequential procedure for the log-rank test. The trial was powered to detect a hazard ratio (HR) of 0·35 with a probability of 95% and a maximum number of 67 events (one-sided significance level of 5%, evaluation per protocol).

The statistical monitoring of the primary comparison by planned interim analyses using the triangular test had stopped previously by deciding for a superiority of the autologous HSCT group compared with the interferon alfa maintenance group in terms of progression-free survival (p=0·0108).[1,13] With long-term follow-up, we report the confirmatory overrunning analysis for the primary hypothesis, correcting for interim analyses, with an exploratory intention-to-treat comparison of progression-free survival, a confirmatory intention-to-treat evaluation of overall survival, and results of the exploratory subgroup analyses with respect to the quality of remission at end of induction or the type of induction treatment (without or with rituximab). The analysis of overall survival is considered confirmatory, because no previous overall survival evaluation has been done with the intention to stop recruitment or observation, and no future analysis is planned. At the time of this analysis, the number of observed deaths warrants a statistical power of 90% to detect an overall survival HR of 0·56 in a two-sided log-rank-test with a significance level of 5% and a one-to-one allocation ratio. Time-to-event outcomes were described by Kaplan-Meier estimates and compared using the log-rank test. Analyses adjusting for the mantle cell lymphoma international prognostic index (MIPI)[14] numerical score and rituximab use (adjusted HRs), and exploratory subgroup analyses were done using Cox regression including the formal interaction term between the subgrouping and the treatment variables. Adjusting for main prognostic factors was planned before the analysis to account for potential imbalances due to the up-front randomisation and selection of responding

	Total (n=174)	Interferon alfa maintenance group (n=81)	Autologous HSCT group (n=93)
Age (years)	55 (47–60)	54 (49–60)	55 (47–60)
Sex			
Male	135 (78%)	60 (74%)	75 (81%)
Female	39 (22%)	21 (26%)	18 (19%)
Stage			
II	1 (1%)	0	1 (1%)
III	30 (17%)	14 (17%)	16 (17%)
IV	143 (82%)	67 (83%)	76 (82%)
Elevated serum LDH concentration*	51 (29%)	25 (31%)	26 (28%)
B symptoms present†	70/173 (40%)	36/81 (44%)	34/92 (37%)
Eastern Cooperative Oncology Group performance status			
0	72 (41%)	34 (42%)	38 (41%)
1	93 (53%)	41 (51%)	52 (56%)
2	9 (5%)	6 (7%)	3 (3%)
Mantle cell lymphoma international prognostic index			
Low risk	127 (73%)	55 (68%)	72 (77%)
Intermediate risk	35 (20%)	20 (25%)	15 (16%)
High risk	12 (7%)	6 (7%)	6 (6%)
Induction treatment			
CHOP	88 (51%)	43 (53%)	45 (48%)
R-CHOP	68 (39%)	27 (33%)	41 (44%)
CHOP-like chemotherapy regimen	18 (10%)	11 (14%)	7 (8%)
Quality of remission at end of induction			
Complete remission	51 (29%)	19 (23%)	32 (34%)
Partial remission	123 (71%)	62 (77%)	61 (66%)

Data are median (IQR), n (%), or n/N (%). HSCT=haematopoietic stem-cell transplantation. LDH=lactate dehydrogenase. CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone. R-CHOP=rituximab plus CHOP. *Greater than the upper limit of normal. †Information on B symptoms is missing in one patient because source data were not available.

Table 1: **Patient characteristics**

patients with mantle cell lymphoma for outcome comparisons. For secondary haematological and non-haematological malignancies, cumulative incidence rates were estimated by subdistribution functions, treating death without haematological or non-haematological malignancy, respectively, as competing events.

We did the statistical analyses using SAS (version 9.4) and ggsurvplot from the package survminer to generate the Kaplan-Meier plots under R (version 4.0.4). Overrunning analysis correcting for interim analyses were done using Planning and Evaluation of Sequential Trials (PEST) version 3 (Reading University, Reading, UK) This trial was started before preregistration was implemented and is therefore not registered.

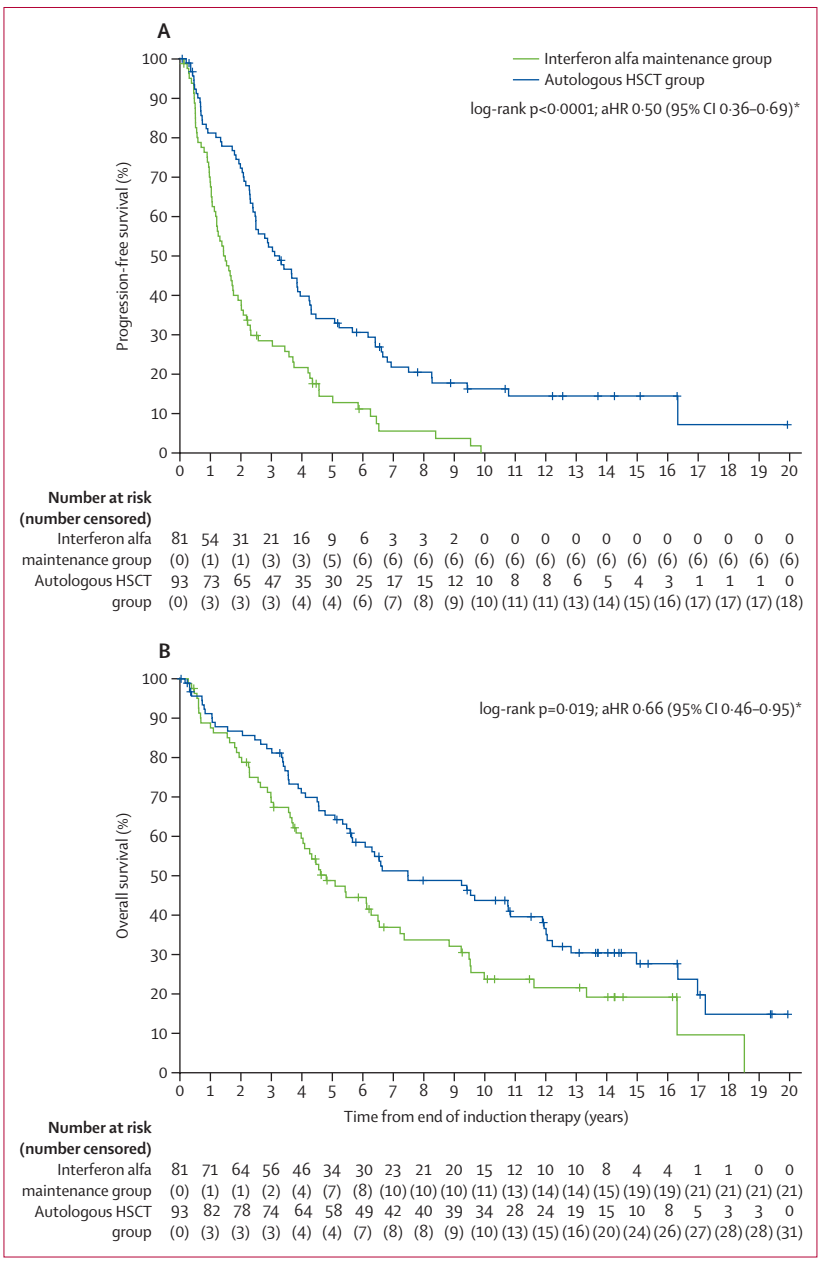

Figure 2: **Progression-free survival (A) and overall survival (B) of responding patients**
aHR=adjusted hazard ratio. HSCT=haematopoietic stem-cell transplantation. MIPI=mantle cell lymphoma international prognostic index. *The HR has been adjusted for MIPI score and rituximab use.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Sept 30, 1996, and July 1, 2004, 269 patients were randomly allocated to receive either autologous HSCT (n=134) or interferon alfa maintenance therapy (n=135). After randomisation, 37 patients were excluded because they had an unconfirmed diagnosis of mantle cell lymphoma by the reference pathologist panel. Out of the 21 patients excluded in the interferon alfa maintenance group, ten (48%) had received R-CHOP, as compared with only two (13%) of 16 patients excluded in the autologous HSCT group. 54 (23%) of 232 patients with mantle cell lymphoma did not reach partial remission or complete remission after induction therapy, two (1%) patients were not restaged, and two (1%) patients had no response documented after induction therapy (figure 1). The intention-to-treat population comprised 174 patients (81 [47%] in the interferon alfa group and 93 [53%] in the autologous HSCT group) in remission after induction treatment (table 1). Median follow-up was 14 years (IQR 10–16) and the median age of the patients was 55 years (IQR 47–60). 88 (51%) of 174 patients were given CHOP and 68 (39%) were given R-CHOP as induction therapy; only 18 (10%) patients received CHOP-like chemotherapy regimens such as mitoxantrone, chlorambucil, and prednisolone. In total, 51 (29%) of 174 patients had a complete remission after the induction therapy. Overall, the patient characteristics in the two treatment groups were comparable, with slightly more frequent low-risk MIPI, R-containing treatment regimens, and a complete remission in the autologous HSCT group than in the interferon alfa maintenance group (table 1).

The formal overrunning analysis of the primary comparison correcting for the sequential design confirmed the statistically significant progression-free survival advantage for patients assigned to the autologous HSCT group (corrected p-value 0.0088, corrected maximum-likelihood estimate for HR 0·50). In the exploratory intention-to-treat analysis, the median progression-free survival for patients receiving autologous HSCT was 3·3 years (95% CI 2·5–4·3) compared with 1·5 years (1·2–2·0) for those receiving interferon alfa (p<0·0001). The adjusted HR for the autologous HSCT group versus the interferon alfa maintenance group was 0·50 (95% CI 0·36–0·69; figure 2A; table 2).

The median overall survival for patients in partial remission or complete remission after induction therapy

	Autologous HSCT group		Interferon alfa maintenance group		Adjusted hazard ratio (95% CI)*	log-rank p value
	Median (years)	Number of events	Median (years)	Number of events		
All patients						
Progression-free survival	3·3 (2·5–4·3)	75/93 (81%)	1·5 (1·2–2·0)	75/81 (93%)	0·50† (0·36–0·69)	<0·0001
Overall survival	7·5 (5·7–12·0)	62/93 (67%)	4·8 (4·0–6·6)	60/81 (74%)	0·66† (0·46–0·95)	0·019
Patients receiving induction therapy without rituximab						
Progression-free survival	3·1 (2·5–4·3)	42/52 (81%)	1·2 (1·0–1·9)	51/54 (94%)	0·40‡ (0·26–0·61)	<0·0001
Overall survival	6·7 (5·4–12·9)	36/52 (69%)	4·3 (3·6–6·6)	44/54 (81%)	0·52‡ (0·33–0·82)	0·016
Patients receiving induction therapy with rituximab						
Progression-free survival	3·4 (2·4–6·8)	33/41 (80%)	1·7 (1·4–5·9)	24/27 (89%)	0·72‡ (0·42–1·24)	0·087
Overall survival	9·6 (5·5–12·2)	26/41 (63%)	5·5 (4·6–NR)	16/27 (59%)	1·05‡ (0·55–1·99)	0·68

Data are median (95% CIs) or n/N (%), unless otherwise specified. HSCT=haematopoietic stem-cell transplantation. MIPI=mantle cell lymphoma international prognostic index. NR=not reached. *Adjusted hazard ratios were estimated by Cox regression. †Adjusted for MIPI score and the use of rituximab as part of induction therapy. ‡Adjusted for MIPI score.

Table 2: **Summary of outcome comparisons in the intention-to-treat population**

receiving autologous HSCT was 7·5 years (95% CI 5·7–12·0) compared with 4·8 years (4·0–6·6) for those receiving interferon alfa (p=0·019). The adjusted HR for the autologous HSCT group versus the interferon alfa maintenance group was 0·66 (95% CI 0·46–0·95; figure 2B; table 2).

Exploratory analysis of secondary malignancies, not prespecified in the protocol, showed no clear effect of autologous HSCT versus interferon alfa maintenance on the risk of secondary myelodysplastic syndrome or leukaemia (HR 1·6, 95% CI 0·31–8·3; p=0·58). In the autologous HSCT group, the 5-year cumulative incidence rate was 2·2% (n=2) and the 10-year cumulative incidence rate was 5·9% (n=5); whereas in the interferon alfa maintenance group, the 5-year cumulative incidence rate was 1·3% (n=1) and the 10-year cumulative incidence rate was 2·7% (n=2). By contrast, a tendency for an increased risk of secondary non-haematological tumours was observed in the interferon alfa maintenance group compared with the autologous HSCT group (HR 0·34, 95% CI 0·11–1·1; p=0·049). In the autologous HSCT group, the 5-year cumulative incidence rate was 1·1% (n=1) and the 10-year cumulative incidence rate was 3·5% (n=3); whereas in the interferon alfa maintenance group, the 5-year cumulative incidence rate was 3·9% (n=3) and the 10-year cumulative incidence rate was 11·8% (n=8).

In an exploratory subgroup analysis, not prespecified in the protocol, patients receiving autologous HSCT had significantly longer progression-free survival regardless of complete remission or partial remission status (appendix pp 1–2). Patients in complete remission after induction therapy had a median progression-free survival of 3·9 years (95% CI 3·0–7·5; 24 events among 32 patients) in the autologous HSCT group versus 1·9 years (1·06–3·0; 18 events among 19 patients) in the interferon alfa maintenance group (p=0·0003). Patients in partial remission after induction therapy reached a median progression-free survival of 2·5 years (95% CI 2·3–4·3; 51 events among 61 patients) in the autologous HSCT group versus 1·4 years (1·1–2·0; 57 events among 62 patients) in the interferon alfa maintenance group (p=0·0026). In the Cox regression analysis adjusted for MIPI score and the addition of rituximab, the adjusted HR for the autologous HSCT group versus the interferon alfa maintenance group was 0·41 (95% CI 0·22–0·76) for patients with complete remission and 0·54 (0·37–0·80) for those with partial remission ($p_{interaction}$=0·45; differences in adjusted HR consistent with chance; appendix pp 1–2).

Patients in complete remission after induction therapy reached a median overall survival of 9·7 years (95% CI 6·7 to not reached; 21 events among 32 patients) in the autologous HSCT group versus 6·5 years (4·0–18·5; 15 events among 19 patients) in the interferon alfa maintenance group (p=0·15). In comparison, patients with partial remission reached a median overall survival of 6·3 years (95% CI 5·1–12; 41 events among 61 patients) in the autologous HSCT group versus 4·6 years (3·7–7·4; 45 events among 62 patients) in the interferon alfa maintenance group (p=0·10; appendix pp 3–4). In the Cox regression analysis adjusted for MIPI score and the use of rituximab, the adjusted HR for the autologous HSCT group versus the interferon alfa maintenance group was 0·65 (95% CI 0·33–1·26) for patients with complete remission and 0·68 (0·44–1·04) for those with partial remission ($p_{interaction}$=0·91; differences in adjusted HR consistent with chance).

In the further exploratory subgroup analyses, not prespecified in the protocol, patients with a rituximab-free induction regimen had a significantly increased progression-free survival and overall survival after receiving autologous HSCT in comparison with those receiving interferon alfa maintenance therapy. The median progression-free survival was 3·1 years (95% CI 2·5–4·3) in the autologous HSCT group versus

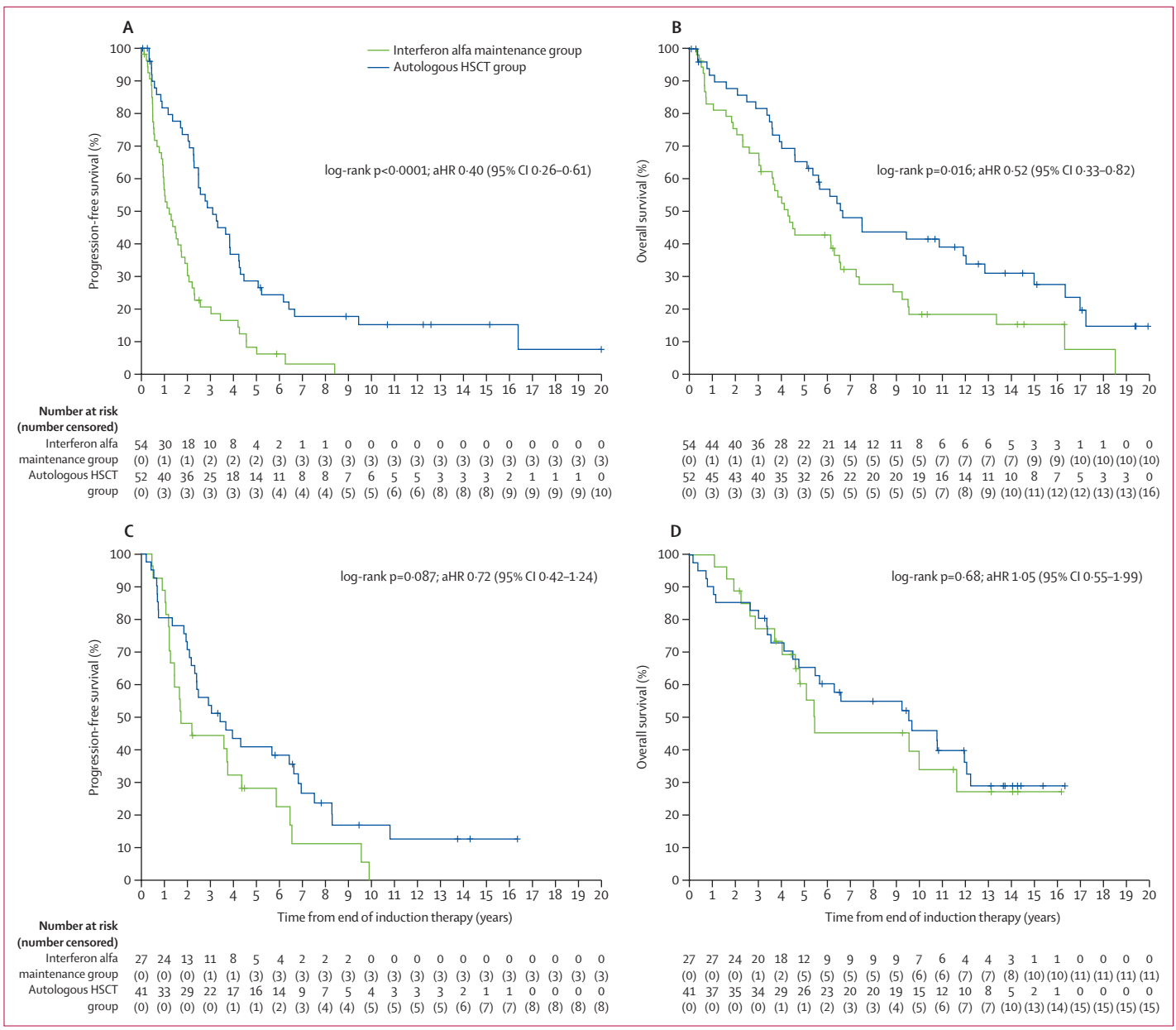

Figure 3: **Progression-free survival and overall survival of responding patients stratified by rituximab use in induction regimen**
(A) Progression-free survival with no rituximab in induction regimen. (B) Overall survival with no rituximab in induction regimen. (C) Progression-free survival with rituximab in induction regimen. (D) Overall survival with rituximab in induction regimen. The HR has been adjusted for MIPI score. aHR=adjusted hazard ratio. HR=hazard ratio. HSCT=haematopoietic stem-cell transplantation. MIPI=mantle cell lymphoma international prognostic index.

1·2 years (1·0–1·9) in the interferon alfa maintenance group (p<0·0001; table 2). The Cox regression analysis adjusted for MIPI score yielded an adjusted HR of 0·40 (95% CI 0·26–0·61; figure 3A). The median overall survival was 6·7 years (95% CI 5·4–12·9) in the autologous HSCT group and 4·3 years (3·6–6·6) in the interferon alfa maintenance group (p=0·016; table 2). The Cox regression analysis adjusted for MIPI score yielded an adjusted HR of 0·52 (95% CI 0·33–0·82; figure 3B).

For patients treated with a rituximab-containing induction regimen, the median progression-free survival was 3·4 years (95% CI 2·4–6·8) in the autologous HSCT group versus 1·7 years (1·4–5·9) in the interferon alfa maintenance group (p=0·087; table 2). The Cox regression analysis adjusted for MIPI score yielded an adjusted HR of 0·72 (95% CI 0·42–1·24; figure 3C). The overall survival was comparable despite a median of 9·6 years (95% CI 5·5–12·2) in the autologous HSCT group versus 5·5 years (4·6–not reached) in the interferon alfa

maintenance group (p=0·68; table 2). The Cox regression analysis adjusted to MIPI score gave an adjusted HR of 1·05 (95% CI 0·55–1·99; figure 3D). The adjusted HRs for rituximab-treated patients were substantially closer to 1 compared with patients treated without rituximab. The formal interaction analyses suggested the adjusted HR differences were due to the addition of rituximab during induction therapy ($p_{interaction}$=0·087 for progression-free survival; $p_{interaction}$=0·086 for overall survival).

Discussion

This mature analysis, with a median follow-up of 14 years, confirms the initially reported long-term results of Dreyling and colleagues,[1] which compared autologous HSCT with interferon alfa maintenance after a CHOP-like induction therapy in previously untreated patients with mantle cell lymphoma. With this longer follow-up, we reported a significant improvement in the median progression-free survival after clinical remission and in median overall survival after autologous HSCT. These data underline the value of autologous HSCT-containing treatment strategies in the first-line setting, which is the current recommended standard of care in young patients in Europe.[5]

On the basis of these mature data, the significantly improved progression-free survival after autologous HSCT is independent of remission status (ie, complete remission or partial remission) after induction therapy, with overall survival showing the same trend. Therefore, these data from the first randomised phase 3 trial of the European Mantle Cell Lymphoma Network underline the relevance of a post-induction autologous HSCT in the context of a CHOP-like induction therapy.

The treatment of mantle cell lymphoma has changed since the start of this trial, with the addition of high-dose cytarabine during induction and rituximab maintenance improving outcomes for patients with mantle cell lymphoma;[2,6,7,15,16] however, to the best of our knowledge, no other phase 3 trial data for a head-to-head comparison of autologous HSCT are available. To address the introduction of new treatment options for mantle cell lymphoma and the absence of such data, we did an explorative, post-hoc subgroup analysis regarding the addition of rituximab to induction therapy. In this analysis, progression-free survival for patients with chemotherapy only induction was again significantly improved in the autologous HSCT group compared with the interferon alfa maintenance group. This benefit translates also into an improved median overall survival. For patients treated with a rituximab-containing induction regimen neither progression-free survival or overall survival were significantly different between the two groups. A tendency for an increased risk of secondary non-haematological tumours with interferon alfa was observed with no clear effect of autologous HSCT versus interferon alfa on the risk of secondary myelodysplastic syndrome or leukaemia. In fact, in a previous publication,[17] including some patients from this trial, the rate of secondary myelodysplastic syndrome or acute myeloid leukaemia after autologous HSCT was only slightly increased (3·8% at 5 years; p=0·0248).

In context of the study design and the nature of explorative analyses, several factors have to be considered in the interpretation of these findings from today's perspective. Since rituximab was approved and taken into clinical practice during the same period of recruitment to this trial, the proportion of patients treated with R-CHOP was only 39%. In total, 68 patients with rituximab-containing chemotherapy and 106 with chemotherapy-only induction were analysed in this post-hoc long-term study. On the one hand, the low number of patients in the rituximab-treated sub-cohort might have contributed to the absence of any significant differences between the autologous HSCT group and interferon alfa maintenance group in terms of progression-free survival and overall survival. On the other hand, based on these mature data, the value of an effective first-line treatment could be confirmed, with patients not receiving rituximab or autologous HSCT having the lowest progression-free survival and overall survival rates. These results support data from other phase 2 studies and retrospective series that show superiority of autologous HSCT over other treatments for mantle cell lymphoma.[16,18–21]

Whether an autologous HSCT should be generally recommended despite the available additional therapeutic options cannot be appropriately addressed with this trial alone. However, the absence of any significant benefit of autologous HSCT for patients after rituximab-containing induction underlines the need to further explore the value of autologous HSCT in comparison with the most effective regimens available. This finding is in line with the retrospective analysis by Gerson and colleagues[22] who reported a progression-free survival benefit but only "a trend towards improved overall survival on multivariable regression analysis" in patients consolidated with an autologous HSCT in the rituximab era. However, since the completion of these trials, targeted small molecules such as Bruton's tyrosine kinase inhibitors, have become the preferred therapeutic approaches in relapsed mantle cell lymphoma and are nowadays tested in first-line trials.[5,23] Thus, results from the current generation of studies such as the European Mantle Cell Lymphoma Network's TRIANGLE trial (NCT02858258) might further challenge the role of autologous HSCT in young patients with mantle cell lymphoma.

Contributors

MU, HCK-N, WH, and MD designed and centrally coordinated the trial. MU, SS, KH, CT, BM, MT, LT, CS, KB, JK, GL, JD, HCK-N, KS-E, VV, MA, AvH, and WK locally coordinated the trial and did the data collection. MU and EH verified the underlying data. EH did the statistical analysis. A-KZ drafted the manuscript. EH and MD finalised the manuscript. All authors interpreted the data and revised the

manuscript. A-KZ, EH, and MD were responsible for the decision to submit the manuscript.

Declaration of interests

A-KZ declares that this work was done before her employment at Janssen-Cilag. Opinions expressed are solely her own and do not express the views or opinions of her employer. A-KZ has received stock or stock options from Johnson & Johnson. KH has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Roche, Celgene, Servier, Sanofi, EUSA Pharma, and Hexal; has received support for attending meetings or travel, or both, from Roche, Celgene, and Sanofi; and has participated on a data safety monitoring board or advisory board from Roche, Celgene, Servier, EUSA Pharma, and Gilead. MT has received consultancy fees and research funding from Amgen, Roche, Regeneron, Kite, and Macrogenics. CS has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Bristol Myers Squibb, Janssen, and Norvatis; and support for attending meetings or travel, or both, from Bristol Myers Squibb, Roche, Novartis, and Kite Gilead. GL has received grants or contracts from AQUINOX, AGIOS, AstraZeneca, Bayer, Gilead, Janssen, Morphosys, Roche, and Verastem (grant to institution); consulting fees from Roche, Gilead, Janssen, Bayer, Bristol Myers Squibb/Celgene, Novartis, AstraZeneca, Takeda, NanoString, AbbVie, Incyte, Morphosys, Genmab, and Karyopharm; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Roche, Gilead, Janssen, Bayer, Bristol Myers Squibb/Celgene, Novartis, AstraZeneca, AbbVie and Incyte; payment for expert testimony from Morphosys; support for attending meetings or travel, or both, from Roche, Janssen, and Bristol Myers Squibb/Celgene; and participated on a data safety monitoring board or advisory board from Roche, Gilead, Janssen, Bayer, Bristol Myers Squibb/Celgene, Novartis, AstraZeneca, Takeda, Nanostring, Oncopeptides, AbbVie, Incyte, Morphosys, Genmab, and Karyopharm. JD has received personal fees from Janssen, Roche, AbbVie, Celgene, Takeda, and AstraZeneca. VV has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Janssen; support for attending meetings or travel, or both, from Amgen and AbbVie; and participated on a data safety monitoring board or advisory board from Beigene, Gilead, and Bristol Myers Squibb. WK has received report grants from Roche, Amgen, Takeda, and Regeneron. WH has received support for the present manuscript in research funding from Roche. MD has received institutional research grants by AbbVie, Bayer, Celgene, Janssen, and Roche; honoraria for scientific advisory boards from AstraZeneca, Bayer, Beigene, Celgene, Genmab, Gilead, Incyte, Janssen, Novartis, and Roche; and speaker's honoraria from Amgen, AstraZeneca, Bayer, Celgene, Gilead, Janssen, and Roche. EH has received travel support for attending meetings or travel, or both, from Roche. All other authors declare no competing interests.

Data sharing

Anonymised clinical data underlying the analyses for this manuscript might be shared upon request to the corresponding author on the basis of a scientific collaboration.

Acknowledgments

This work was funded in part by a grant from the Deutsche Krebshilfe (70-2208-Hi2), the European Community (LSHC-CT-2004-503351), and the Bundesministerium für Bildung und Forschung, Kompetenznetz Maligne Lymphome (01 GI 9994).

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