CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group

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Summary

Background The MInT study was the first to show improved 3-year outcomes with the addition of rituximab to a CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)-like regimen in young patients with good-prognosis diffuse large-B-cell lymphoma. Extended follow-up was needed to establish long-term effects.

Methods In the randomised open-label MInT study, patients from 18 countries (aged 18–60 years with none or one risk factor according to the age-adjusted International Prognostic Index [IPI], stage II–IV disease or stage I disease with bulk) were randomly assigned to receive six cycles of a CHOP-like chemotherapy with or without rituximab. Bulky and extranodal sites received additional radiotherapy. Randomisation was done centrally with a computer-based tool and was stratified by centre, bulky disease, age-adjusted IPI, and chemotherapy regimen by use of a modified minimisation algorithm that incorporated a stochastic component. Patients and investigators were not masked to treatment allocation. The primary endpoint was event-free survival. Analyses were by intention to treat. This observational study is a follow-up of the MInT trial, which was stopped in 2003, and is registered at ClinicalTrials.gov, number NCT00400907.

Findings The intention-to-treat population included 410 patients assigned to chemotherapy alone and 413 assigned to chemotherapy plus rituximab. After a median follow-up of 72 months (range 0·03–119), 6-year event-free survival was 55·8% (95% CI 50·4–60·9; 166 events) for patients assigned to chemotherapy alone and 74·3% (69·3–78·6; 98 events) for those assigned to chemotherapy plus rituximab (difference between groups 18·5%, 11·5–25·4, log-rank p<0·0001). Multivariable analyses showed that event-free survival was affected by treatment group, presence of bulky disease, and age-adjusted IPI and that overall survival was affected by treatment group and presence of bulky disease only. After chemotherapy and rituximab, a favourable subgroup (IPI=0, no bulk) could be defined from a less favourable subgroup (IPI=1 or bulk, or both; event-free survival 84·3% [95% CI 74·2–90·7] *vs* 71·0% [65·1–76·1], log-rank p=0·005). 18 (4·4%, 95% CI 2·6–6·9) second malignancies occurred in the chemotherapy-alone group and 16 (3·9%, 2·2–6·2) in the chemotherapy and rituximab group (Fisher's exact p=0·730).

Interpretation Rituximab added to six cycles of CHOP-like chemotherapy improved long-term outcomes for young patients with good-prognosis diffuse large-B-cell lymphoma. The definition of two prognostic subgroups allows a more refined therapeutic approach to these patients than does assessment by IPI alone.

Funding Hoffmann–La Roche.

Introduction

Young patients with low risk (no risk factors) and low-intermediate risk (one risk factor according to the age-adjusted International Prognostic Index [IPI]) diffuse large-B-cell lymphoma[1] are judged to have good prognosis and are distinguished from young patients with poor prognosis (intermediate-high and high risk), who present with two or three risk factors according to age-adjusted IPI. After a GELA and a US Intergroup study had shown that the addition of the monoclonal anti-CD20 antibody rituximab (Hoffmann-La Roche, Basel, Switzerland) to CHOP-21 (cyclophosphamide, doxorubicin, vincristine, and prednisone) improved outcomes[2,3] in elderly patients, the final analysis of the MInT study[4] showed that rituximab added to six cycles of CHOP-like chemotherapy improved 3-year event-free and overall survival in young patients with good-prognosis diffuse large-B-cell lymphoma, establishing a new standard treatment for this population.

By comparison with six cycles of CHOP-like chemotherapy alone, the addition of rituximab confers two major benefits: an increase of the rate of complete remissions and a decrease of the rate of progressions during treatment, which resulted in improved event-free, progression-free, and overall survival after a median follow-up of 3 years. Here, we report the 6-year follow-up analysis of patients treated within the MInT study, undertaken to establish whether the beneficial

Lancet Oncol 2011; 12: 1013–22

Published Online September 21, 2011 DOI:10.1016/S1470-2045(11)70235-2

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*Listed in webappendix

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See Online for webappendix

For the **MInT follow-up protocol** see http://www.uks.eu/mint-fu-protocol

effects of adding rituximab to chemotherapy in young patients with good prognosis are maintained over an extended period.

Methods

Patients

Eligible patients for this open-label randomised trial were aged 18–60 years with untreated CD20-positive diffuse large-B-cell lymphoma defined by the local pathologist according to WHO criteria,[5] and had no risk factors or one risk factor according to the age-adjusted IPI in stage II–IV disease or had stage I disease with bulk. Eligible patients had sufficient performance status as assessed by the treating physician (ie, 0–3 on Eastern Cooperative Oncology Group scale). Exclusion criteria have been described previously.[4]

The stage of lymphoma was defined before enrolment of the patient by the referring physician on the basis of the Cotswolds modification of the Ann Arbor classification.[6] Details of the staging procedures have been reported previously.[4] For all patients, the local radiologist or treating physician measured maximum tumour mass, and bulky disease was defined as the presence of a tumour mass with a diameter of more than 5 cm, more than 7·5 cm, or more than 10 cm according to the cutoff points predefined by every cooperative group.

Histological diagnosis was reviewed by an experienced national expert haematopathologist in every participating country, and was available for 99% of patients. The study was done in accordance with the Helsinki declaration, the protocol was approved by the ethics review committee of each participating centre, and all patients gave written informed consent.

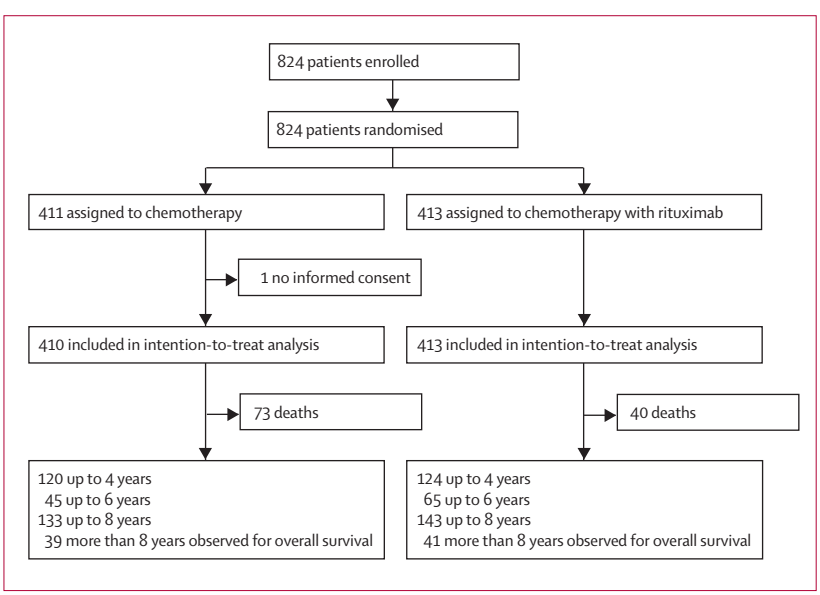

Figure 1: **Trial profile**

Randomisation and masking

Patients were randomly assigned to receive six cycles of CHOP-like chemotherapy and rituximab or six cycles of CHOP-like chemotherapy alone. The trial was unmasked. Patients were randomly assigned centrally by a data manager at the Intergroup Data Centre (Leipzig, Germany) using a computer-based randomisation tool; no blocks were used. Patients were stratified by centre, bulky disease, age-adjusted IPI, and chemotherapy regimen by use of a modified minimisation algorithm that incorporated a stochastic (ie, random) component.

Procedures

Webappendix p 1 shows the CHOP-like chemotherapy regimens used in the trial. Patients assigned to chemotherapy plus rituximab were scheduled to receive a chemotherapy regimen shown on webappendix p 1, plus 375 mg/m² rituximab given intravenously on days 1, 22, 43, 64, 85, and 106 of the chemotherapy regimen. Radiotherapy (30–40 Gy, according to national standards) was given to sites of primary bulky disease; radiotherapy (30–40 Gy) to primary extranodal disease was given at the physician's discretion. Filgrastim or lenograstim could also be given at the treating physician's discretion for alleviation or prophylaxis of neutropenia.

The primary endpoint was event-free survival; secondary endpoints were response, progression during treatment, progression-free survival, overall survival, and frequency of toxic effects. Event-free survival was defined as time to progressive disease during treatment, the events for which were: progressive disease; no achievement of complete remission; no achievement of unconfirmed remission; partial remission associated with treatment in excess of that stipulated in the protocol (eg, more than six cycles of chemotherapy; radiotherapy to non-bulky areas, or use of rituximab in chemotherapy-only group); no change; relapse after achievement of complete remission or unconfirmed complete remission; or death from any cause, whichever came first.

Response was assessed according to the International Workshop criteria[7] by the treating physician on day 155 after starting treatment and was defined as the proportion of patients with complete remission or unconfirmed complete remission after study treatment for all patients evaluable for response. Progression during treatment was defined as the proportion of patients with progressive disease during treatment and within 3 months after the end of treatment for all patients evaluable for response. Progression-free survival was defined as time to progression during treatment, relapse, or death from any cause; additional treatment was censored for this endpoint. Overall survival was defined as time to death from any cause. Data for patients without an event in event-free, progression-free, relapse-free, or overall survival, respectively, were censored at the last day of having valid information for that endpoint.

Methods of assessment were physical examination, relevant laboratory tests (as those done for staging), CT of the chest and abdomen, bone-marrow biopsy in case of previous involvement by lymphoma, and the control of all other previous pathological findings by adequate investigational procedures.

Follow-up evaluation was done by the referring physician every 3 months in the first 2 years after treatment, and every 6 months thereafter by use of physical examination, relevant laboratory tests (same as those done for staging), and CT of the chest and abdomen. CT scans were not mandatory after 5 years of follow-up and data for patients without CT scans were not censored. No functional imaging (gallium or PET) was used to define response. Complete remission and unconfirmed complete remission were defined according to the International Workshop criteria[7] and were defined as progression if they lasted less than 3 months. Furthermore, we planned a subgroup analysis to assess CHOP-21 chemotherapy compared with that of CHOEP-21 (CHOP plus etoposide).

Statistical analysis

We aimed to identify a difference of 10% in 3-year event-free survival with a two-sided significance level of 5% and a power of 80%, requiring 820 patients. Interim analysis was planned after 100 events had been recorded according to an α-spending approach, where α used at the point of interim analysis depends on the amount of information already accumulated.

Main analyses were by intention to treat. Response and progression during treatment were analysed by use of Fisher's exact test. Event-free, progression-free, and overall survival were measured from the date of randomisation and relapse-free survival from the date of complete remission or unconfirmed complete remission and were estimated according to Kaplan-Meier. Kaplan-Meier estimates at 6 years, with 95% CI, were calculated for the probability of a patient not having an event in the endpoints of event-free survival, progression-free survival, and overall survival. Multivariable analyses were done by use of Cox proportional-hazard models to estimate hazard ratios (HRs) for having an event. Sensitivity analyses (ie, per-protocol analyses) of the primary and secondary endpoints were done to assess the robustness of the results. Differences between groups were regarded as significant for p values less than 0·05. For subgroup analyses of event-free, progression-free, and overall survival, interaction terms were included and tested in the Cox proportional-hazard models. Interaction terms were treatment group and IPI, treatment group and bulky disease, IPI and bulk, IPI and chemotherapy regimen, and bulk and chemotherapy regimen. Statistical analyses of efficacy were done with SAS version 9.1.3; safety analyses were done with SAS version 8.2.

The MInT trial was registered at ClinicalTrials.gov, number NCT00064116. This observational follow-up study is also registered, number NCT00400907.

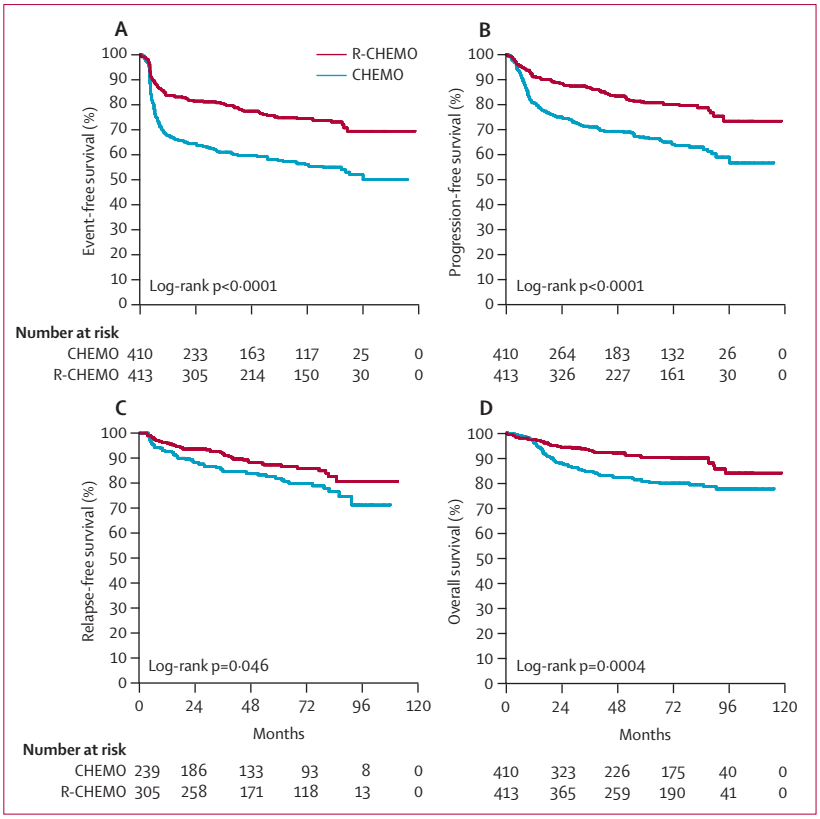

Figure 2: **Event-free (A), progression-free (B), relapse-free (C), and overall survival (D) of 823 patients assigned to six cycles of CHOP-like chemotherapy (CHEMO) or the same chemotherapy plus six applications of rituximab (R-CHEMO)**

Role of the funding source

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

Results

Between May 16, 2000, and Oct 22, 2003, 824 patients were enrolled at 172 participating institutions from 18 countries, of whom 411 were randomly assigned to receive chemotherapy alone and 413 to receive chemotherapy plus rituximab. Informed consent was not available from one patient assigned to the chemotherapy-only group, leaving 823 patients for evaluation. Figure 1 shows the trial profile; baseline characteristics of patients are shown in the webappendix pp 2–3.

After a median follow-up of 72 months (range 0·03–119), 6-year event-free survival was 55·8% (95% CI 50·4–60·9; 166 events) for patients assigned to chemotherapy alone and 74·3% (69·3–78·6; 98 events) for those assigned to chemotherapy plus rituximab (difference between groups 18·5%, 11·5–25·4; log-rank p<0·0001; figure 2). 6-year progression-free survival was significantly lower for the chemotherapy-alone group (63·9%, 95% CI 58·4–68·9)

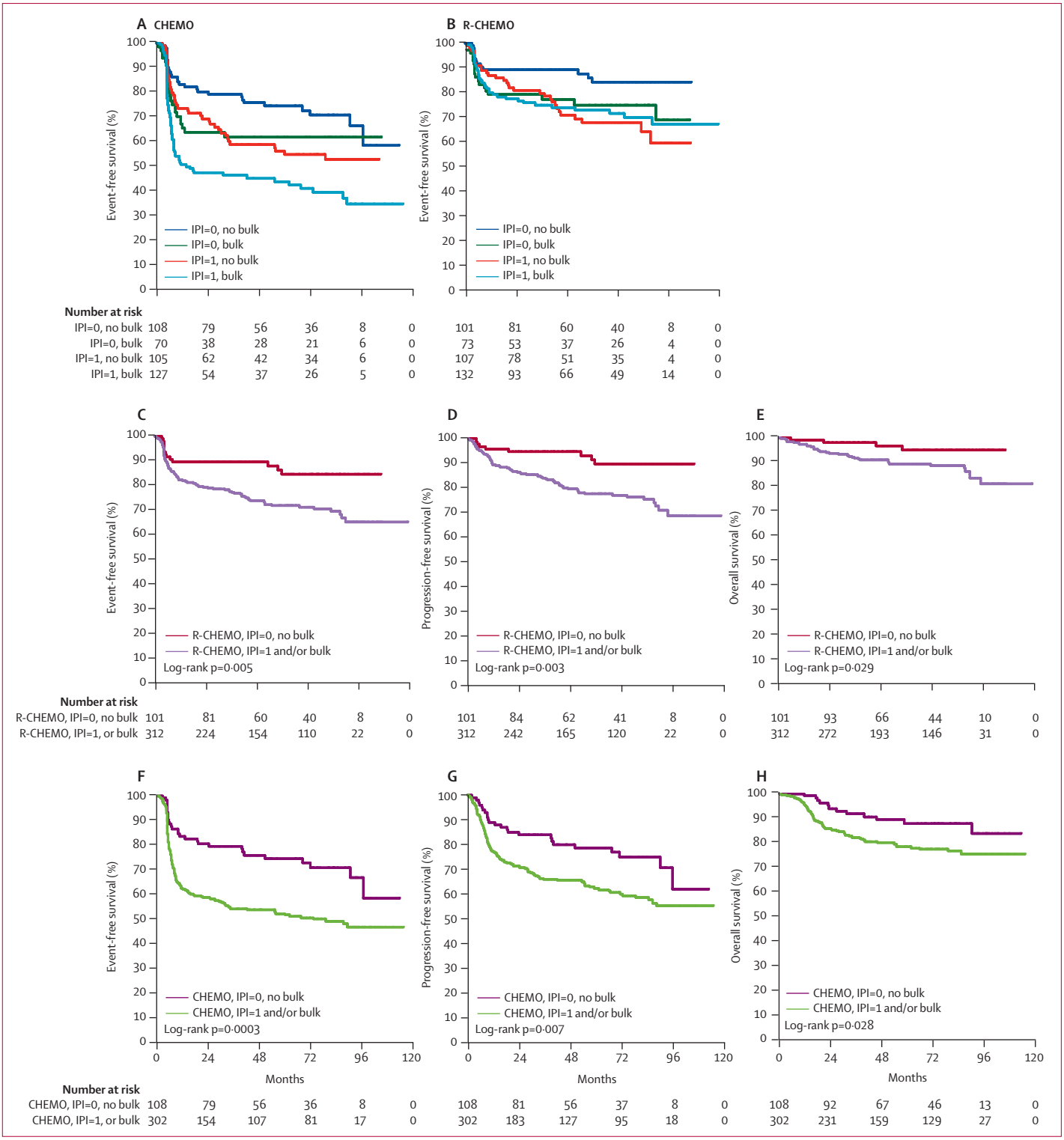

***Figure 3*: Outcomes in different prognostic subgroups of young patients with good-prognosis diffuse large-B-cell lymphoma**
Although three subgroups can be distinguished with respect to event-free survival after chemotherapy alone (A; best group, no bulk and no age-adjusted IPI risk factor; intermediate group, one age-adjusted IPI risk factor or bulk; worst group, both bulk and age-adjusted IPI risk factor), two subgroups emerge after chemotherapy plus rituximab (B): a very favourable subgroup (age-adjusted IPI=0, no bulk) with significantly better event-free (C), progression-free (D), and overall survival (E) than a less favourable subgroup (IPI=1 or bulk, or both). Similarly, after chemotherapy only, the best subgroup (IPI=0, no bulk) had a better event-free (F), progression-free (G), and overall survival (H) when contrasted with the pooled other subgroups. IPI=International Prognostic Index. CHEMO=chemotherapy alone. R-CHEMO=chemotherapy plus rituximab.

than for the group allocated chemotherapy plus rituximab (80·2%, 75·4–84·1; difference between groups 16·3%, 9·5–23·0; log-rank p<0·0001; figure 2).

We recorded 77 relapses: 43 in the chemotherapy-alone group and 34 in the chemotherapy plus rituximab group. 72-month relapse-free survival after complete remission or unconfirmed complete remission for patients allocated chemotherapy alone was significantly lower compared with those allocated combined rituximab and chemotherapy (80·0% [95% CI 73·7–85·0] *vs* 86·1% [81·0–89·9]; difference between groups 6·1% [1·1–13·2]; log-rank p=0·046; figure 2).

We noted 113 deaths: 73 in the chemotherapy-alone group (61 lymphoma-associated, one treatment-related, three due to a second neoplasm, one suicide, one due to a concomitant disease, one due to infection, and five due to other reasons) and 40 in the chemotherapy plus rituximab group (20 lymphoma-associated, six treatment-related, three due to a second neoplasm, two due to a concomitant disease, two due to an infection, and seven due to other reasons). 6-year overall survival was higher for patients allocated chemotherapy plus rituximab than for those allocated chemotherapy alone (90·1% [95% CI 86·4–92·9] *vs* 80·0% [75·3–83·9]; difference between subgroups 10·1% [4·8–15·4], log-rank p=0·0004; figure 2).

In a multivariable analysis of event-free survival in the intention-to-treat population, the occurrence of events was affected by treatment with rituximab (HR 0·49, 95% CI 0·38–0·62; p<0·0001), one risk factor according to the age-adjusted IPI (1·70, 1·31–2·21; p<0·0001), and bulky disease (1·43, 1·12–1·83; p=0·005). We found no interactions between treatment group and bulky disease (0·72, 0·44–1·20; p=0·210) and between treatment group and age-adjusted IPI (0·85, 0·50–1·45; p=0·547). In a Cox model restricted to patients assigned to rituximab, interaction between bulky disease and age-adjusted IPI was not significant (0·45, 0·19–1·06; p=0·068).

For progression-free survival, hazard ratios were 0·48 (95% CI 0·36–0·64; p<0·0001) for treatment with rituximab, 1·75 (1·30–2·36; p=0·0003) for one risk factor according to age-adjusted IPI, and 1·26 (0·95–1·66; p=0·107) for bulky disease. For overall survival, hazard ratios were 0·49 (95% CI 0·33–0·72; p=0·0003) for treatment with rituximab, 1·43 (0·96–2·13; p=0·076) for one age-adjusted IPI risk factor, and 1·82 (1·24–2·68; p=0·002) for bulky disease.

Figure 3 shows Kaplan-Meier estimates for event-free, progression-free, and overall survival by stratified risk groups in both treatment groups. Patients with non-bulky disease and IPI of 0 had a favourable 6-year event-free survival after chemotherapy plus rituximab compared with the other subgroups (ie, IPI of 1 or bulk, or both): event-free survival was 84·3% (95% CI 74·2–90·7) for patients with non-bulky disease and IPI of 0 *vs* 71·0% (65·1–76·1) for the other subgroups (log-rank p=0·005). Progression-free survival (89·6% [95% CI 79·8–94·8] *vs* 77·1% [71·4–81·8], log-rank p=0·003) and overall survival (94·9% [95% CI 86·5–98·1] *vs* 88·6% [84·0–91·9], log-rank p=0·029) were also improved for patients with non-bulky disease and IPI of 0 compared with patients in the other subgroups. In the favourable subgroup, ten (77%) of 13 event-free survival

	CHOP-21 (n=396)	CHOEP-21 (n=361)	MACOP-B (n=34)	PMitCEBO (n=32)
Age (years)	49 (36–55)	47 (35–54)	41 (29–47)	49 (37–57)
Bulky disease	205 (52%)	168 (47%)	12 (35%)	17 (53%)
Stage III and IV	111 (28%)	100 (28%)	8 (24%)	7 (22%)
Raised LDH	116 (29%)	109 (30%)	6 (18%)	11 (34%)
ECOG ≥1	111 (28%)	110 (30%)	5 (15%)	5 (16%)
IPI >0	230 (58%)	209 (58%)	14 (41%)	18 (56%)
Less favourable (IPI 1 and/or bulk)	307 (78%)	263 (73%)	20 (59%)	24 (75%)

Data are median (IQR) or n (%). CHOP=cyclophosphamide, doxorubicin, vincristine, prednisone. CHOEP=CHOP plus etoposide. MACOP-B=cyclophosphamide, doxorubicin, methotrexate, vincristine, bleomycin, prednisone. PMitCEBO=mitoxantrone, cyclophosphamide, etoposide, vincristine, bleomycin, prednisone. LDH=lactate dehydrogenase. ECOG=Eastern Cooperative Oncology Group. IPI=International Prognostic Index.

Table 1: **Characteristics of patients treated with CHOP-21, CHOEP-21, MACOP-B, and PMitCEBO, with or without rituximab**

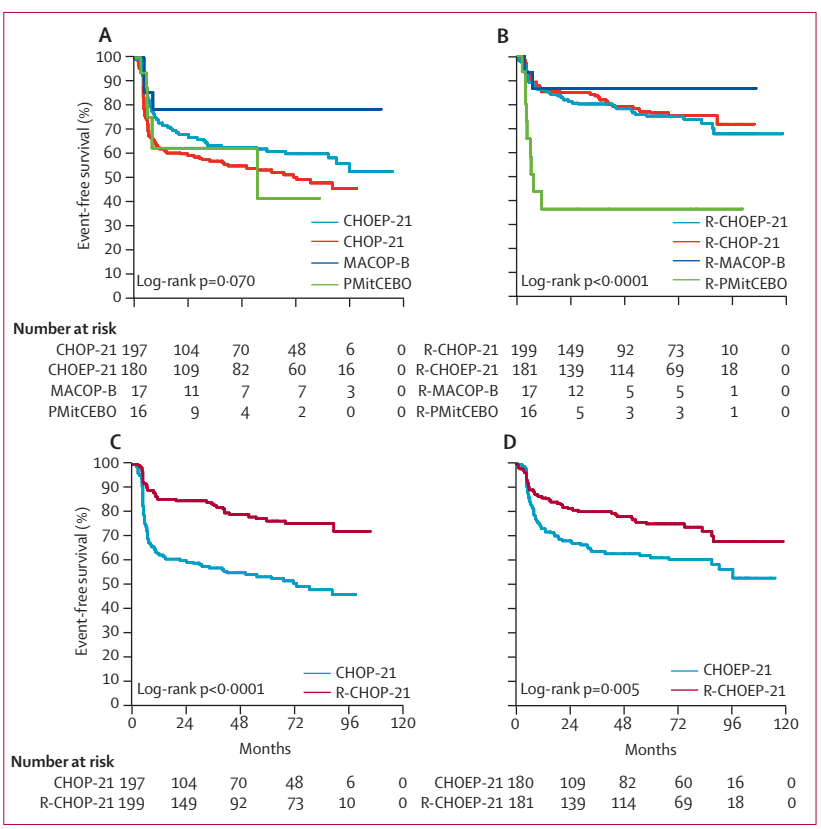

Figure 4: **Event-free survival of patients treated with different chemotherapy regimens**
(A) Event-free survival of patients treated with CHOP-21, CHOEP-21, MACOP-B, and PMitCEBO alone. (B) Patients treated with the same regimens in combination with rituximab. (C) Patients treated with CHOP-21 versus R-CHOP-21 and (D) CHOEP-21 versus R-CHOEP-21. Both patients treated with CHOP-21 and the patients treated with CHOEP-21 had a significantly improved event-free survival with addition of rituximab. CHOP=cyclophosphamide, doxorubicin, vincristine, prednisone. CHOEP=CHOP plus etoposide. MACOP-B=cyclophosphamide, doxorubicin, methotrexate, vincristine, bleomycin, prednisone. PMitCEBO=mitoxantrone, cyclophosphamide, etoposide, vincristine, bleomycin, prednisone. R=rituximab.

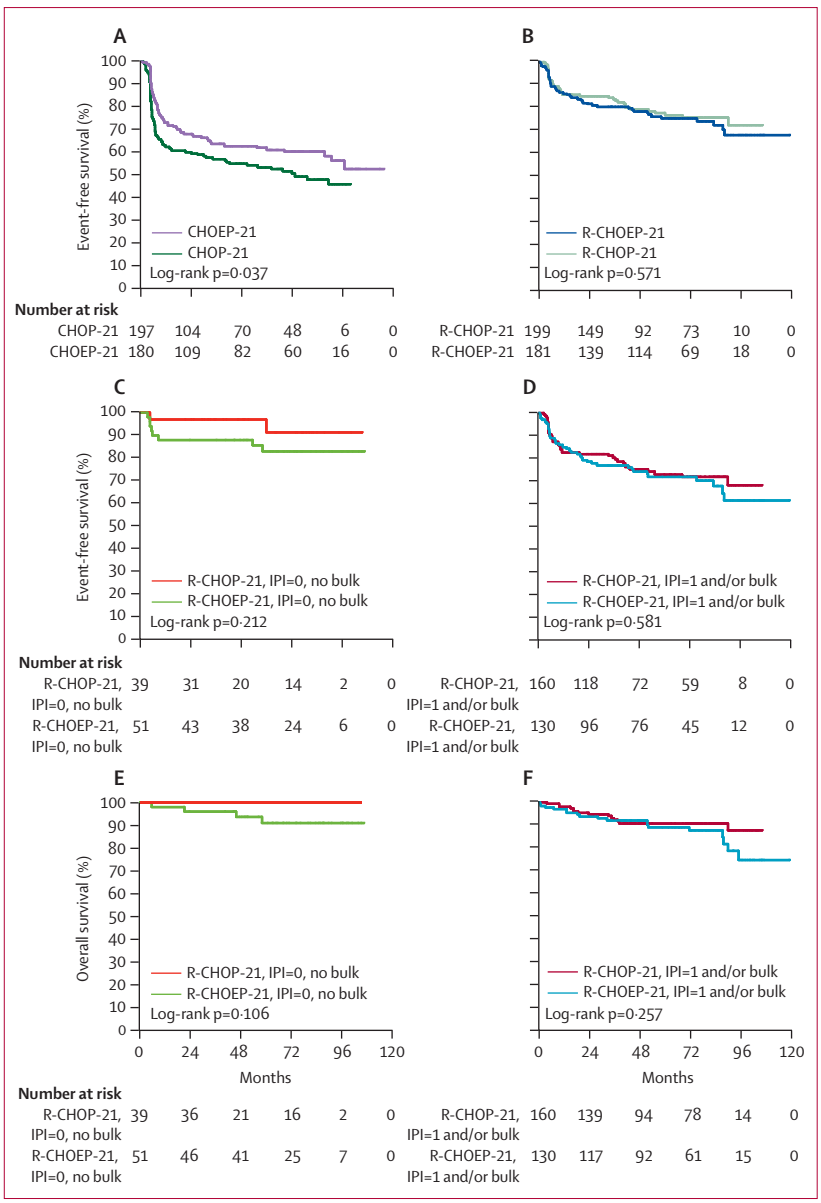

Figure 5: **Effect of addition of rituximab to CHOP-21 and CHOEP-21**
The significant event-free survival advantage of the more intensive regimen, CHOEP-21, over CHOP-21 disappears after addition of rituximab (A, B). This finding applies both to the event-free survival of the favourable (C) and unfavourable subgroups (D) and to the overall survival of the favourable (E) and unfavourable (F) subgroups. CHOP=cyclophosphamide, doxorubicin, vincristine, prednisone. CHOEP=CHOP plus etoposide.

events occurred within 1 year and all (100%) within 5 years of starting chemotherapy and rituximab. For progression-free survival, the respective figures were four (50%) of eight and four (50%) of eight events, within one and five years, and for overall survival were one (25%) of four and three (75%) of four, respectively, and a plateau in the less favourable subgroup did not appear until after 90 months. As can be seen from figure 3, late relapses after chemotherapy plus rituximab occurred in patients with age-adjusted IPI of 0 with bulky disease, and in patients with age-adjusted IPI of 1 with and without bulky disease at a similar rate, and in patients with IPI of 1 independent of whether the risk factor was defined by raised lactate dehydrogenase (LDH) concentration or advanced stage (data not shown). Therefore, without gene expression profiling data, no biological subgroup can be identified that is at high risk for late relapse after chemotherapy plus rituximab, and longer follow-up is necessary to establish the ultimate outcome of these patients.

Table 1 shows the characteristics of patients who received different chemotherapy regimens; most patients received CHOP-21 and CHOEP-21 and a few received MACOP-B (cyclophosphamide, doxorubicin, methotrexate, vincristine, bleomycin, and prednisone) or PMitCEBO (mitoxantrone, cyclophosphamide, etoposide, vincristine, bleomycin, and prednisone). Figure 4 shows event-free survival of patients who received the different chemotherapy regimens with and without rituximab. Although there were no significant differences between regimens without rituximab, the differences in event-free survival between the chemotherapy regimens were significant when combined with rituximab. This finding is attributable to the poor event-free survival of 16 patients who received PMitCEBO plus rituximab. PMitCEBO was the only chemotherapy regimen for which the addition of rituximab did not improve event-free survival. Patients treated with CHOP-21 and CHOEP-21 benefited from the addition of rituximab. 6-year event-free survival was 50·4% (95% CI 42·4–57·9) for those allocated CHOP-21 compared with 75·4% (67·7–81·5) for those allocated CHOP-21 plus rituximab (log-rank p<0·0001), and was 60·1% (52·0–67·3) for patients allocated CHOEP-21 and 75·1% (67·7–81·0) for patients allocated CHOEP-21 plus rituximab (log-rank p=0·005; figure 4).

Use of CHOEP-21 alone resulted in a higher 6-year event-free survival than did CHOP-21 alone (log-rank p=0·037; figure 5). However, there was no difference in 6-year event-free survival between CHOP-21 plus rituximab and CHOEP-21 plus rituximab (log-rank p=0·571; figure 5). Cox regression analysis by intention to treat for event-free survival in patients assigned CHOP-21 or CHOEP-21 with or without rituximab showed a significant risk reduction with etoposide in the chemotherapy-alone group (HR for etoposide 0·73, 95% CI 0·53–1·00, p=0·048); an interaction compensating for this benefit in the rituximab group was not significant (HR for interaction between rituximab and etoposide 1·62, 0·96–2·75, p=0·071).

Intention-to-treat analysis showed that both for the favourable subgroup (ie, age-adjusted IPI of 0, no bulky disease) and unfavourable subgroup, event-free survival was much the same with CHOP-21 and rituximab as with CHOEP-21 and rituximab (figure 5). In the 39 patients in the favourable subgroup who received CHOP-21 and rituximab, two events occurred, one after 4 months and one after 59 months, resulting in 6-year event-free survival of 91·3% (95% CI 67·6–97·9); event-free survival for patients who received CHOEP-21 and rituximab was 82·9% (68·5–91·1; log-rank p=0·212). In the less favourable

subgroup, 6-year event-free survival was 71·8% (63·1–78·8) for patients who received CHOP-21 and rituximab and 71·9% (62·9–79·1; log-rank p=0·581) for those who received CHOEP-21 and rituximab. 6-year overall survival was 100% with CHOP-21 and rituximab and was 91·0% (95% CI 77·6–96·6) for CHOEP-21 and rituximab (log-rank p=0·106; figure 5) in the favourable subgroup. 6-year overall survival in the less favourable subgroup was 90·7% (84·5–94·5) with CHOP-21 and rituximab and was 87·4% (79·5–92·5) with CHOEP-21 and rituximab (log-rank p=0·257; figure 5).

After a median follow-up of 72 months, 34 second malignancies occurred (4·1%, 2·9–5·7), 18 (4·4%, 2·6–6·9) in the chemotherapy-alone group and 16 (3·9%, 2·2–6·2; Fisher's exact p=0·730) in the chemotherapy and rituximab group. Table 2 lists the type of second malignancies and the treatment after which they occurred.

	Chemotherapy alone (n=410)	Chemotherapy plus rituximab (n=413)
Patients with any second malignancy	18 (4%)	16 (4%)
Type of second malignancy*		
Acute myeloid leukaemia	2	4
Lung cancer	2	2
Head and neck	2	0
Melanoma	1	2
Skin, other than melanoma	1	0
Colorectal cancer	1	1
Thyroid cancer	1	1
Cutaneous T-cell lymphoma	1	1
Follicular lymphoma	2	0
Chronic lymphocytic leukaemia	1	0
Immunoblastic lymphoma	0	1
Breast cancer	1	0
Prostate cancer	0	2
Stomach cancer	1	0
Bladder cancer	1	0
Endometrial cancer	0	1
Kaposi's sarcoma	0	1
Lymphosarcoma	1	0

Data are number of patients (%) or number of malignancies. *Multiple second malignancies per patient possible.

Table 2: **Second malignancies**

Discussion

Follow-up of the MInT trial, the first randomised study comparing CHOP-like chemotherapy with and without rituximab in young patients with diffuse large-B-cell lymphoma with good prognosis, shows that the benefits of the addition of rituximab to a CHOP-like chemotherapy regimen reported after 3 years were maintained after 6 years (panel), with improvements in event-free, progression-free, and overall survival without increased toxicity[4] or at the cost of increased second neoplasms; this finding contrasts with a recent retrospective analysis of patients with this disease who received high-dose sequential chemotherapy, in which the addition of rituximab was associated with an increased incidence of second malignancies.[11] Bulky disease retains its strong prognostic power for event-free, progression-free, and overall survival after 6 years. In combination with age-adjusted IPI, this factor allows for a more refined therapeutic approach in young patients with good-prognosis diffuse large-B-cell lymphoma than does age-adjusted IPI alone. We have no indication that the open-label randomisation affected the results, because adherence to the protocol, both with respect to chemotherapy and radiotherapy, was the same in both treatment groups.[4]

The effect of rituximab in our study with young patients with good-prognosis disease was larger than expected from the GELA study in elderly patients.[8] Nearly twice as many patients failed after chemotherapy compared with chemotherapy plus rituximab in the MInT trial. Hence the proportion of young patients who need salvage therapy (usually high-dose chemotherapy with haemopoietic stem-cell transplantation) could be halved by the addition of rituximab.

During study design, the question of six or eight cycles had been a matter of debate, because in the absence of data from appropriately randomised trials some countries used six and others used eight cycles as standard. With the excellent results obtained with six cycles of chemotherapy plus rituximab in the MInT trial, six cycles of rituximab and CHOP-21 has become the standard of care for this population in many parts of the world. Moreover, in a recent trial of the DSHNHL (Deutsche Studiengruppe für Hochmaligne Non-Hodgkin-Lymphome) in elderly patients,[12] there was no difference between six and eight cycles of CHOP-14 with rituximab. Although not compared in a randomised fashion against the MInT standard of six cycles of CHOP-21 with rituximab, the results reported by SWOG (Southwest Oncology Group) from a small phase 2 trial with three cycles of CHOP-21 with four applications of rituximab followed by involved-field radiotherapy[13] seem to be inferior, in particular because the SWOG study excluded patients with stage II and bulky disease as well as those with stage III and IV, who were all included in the MInT trial. However, the trials are difficult to compare because 44 of the 60 patients in the SWOG trial were older than 60 years.

We allowed each country to choose their preferred modification of a CHOP-like regimen because we postulated that a clinically significant effect of rituximab should become evident over a spectrum of different chemotherapy regimens. This hypothesis was confirmed for all regimens except PMitCEBO, for which no improvement occurred with the addition of rituximab. The reasons for this finding are unknown, and a chance effect cannot be excluded since few patients received this regimen and the trial lacks power to identify a potential effect. Nevertheless, the poor results obtained with

PMitCEBO underline that no chemotherapy regimen other than CHOP should be combined with rituximab for the treatment of diffuse large-B-cell lymphoma outside of clinical trials.

The previously reported superiority of CHOEP-21 over CHOP-21 was confirmed and maintained after 6 years in the MInT study; however, it disappeared with the addition of rituximab. Because of the lower toxicity and easier handling of CHOP-21 plus rituximab (R-CHOP-21: 1-day regimen), this treatment is to be preferred over CHOEP-21 plus rituximab (R-CHOEP-21: 3-day regimen) for young patients with good-prognosis disease.

That R-CHOP-21 is equivalent to R-CHOEP-21 does not necessarily apply also for young patients with poor-prognosis disease, for whom R-CHOEP-14 was reported to be superior to R-CHOP-14 on the basis of results of a register study.[14] Similarly, the best results reported from a prospective trial in young patients with poor-prognosis disease have been achieved with eight cycles of CHOEP-14.[9] The results obtained with eight cycles of R-CHOEP-14 in that trial also compare favourably with those reported for eight cycles of R-CHOP-14 in a prospective French trial.[15]

Six cycles of R-CHOEP-21 in the MInT trial were also not superior to six cycles of R-CHOP-21 when the analysis was restricted to patients with one risk factor according to age-adjusted IPI. By contrast, in the randomised French study LNH03-2B with young patients and age-adjusted IPI of 1, four cycles of R-ACBVP (rituximab plus doxorubicin, cyclophosphamide, bleomycin, vindesine, and prednisone) followed by an intensive consolidation regimen that included high-dose methotrexate, ifosfamide, etoposide, and cytarabine were superior to eight cycles of R-CHOP-21 with respect to 3-year event-free, progression-free, and overall survival.[10] When comparing the MInT population with one risk factor according to the age-adjusted IPI with the respective population in the GELA LNH03-2B trial, they are very similar (table 3). Surprisingly, 3-year event-free, progression-free, and overall survival obtained with six cycles of any CHOP-like chemotherapy plus rituximab (or with six cycles of R-CHOP-21 alone) in the MInT trial are substantially better than are those obtained with eight cycles of R-CHOP-21 in the GELA trial. Indeed, the results obtained with six cycles of R-CHOP-21 or six cycles of any CHOP-like chemotherapy plus rituximab used in the MInT trial seem to be as good as the results in the French trial obtained with the intensive R-ACVBP programme, which is substantially more toxic than the R-CHOP-21 regimen.

With all the caveats of such a comparison, when looking for possible explanations for these findings, the most obvious difference between the GELA and the MInT trial

***Panel:* Research in context**

Systematic review

The MInT trial was designed in 1999 on the basis of a systematic review of reports listed in PubMed, including abstracts presented at the annual meetings of the American Society of Hematology and the American Society of Clinical Oncology. In this review, various chemotherapy regimens did not differ much with respect to efficacy in young patients with good-prognosis diffuse large-B-cell lymphoma. Since the monoclonal anti-CD20 antibody rituximab had shown activity in relapsed diffuse large-B-cell lymphoma and a trial comparing CHOP-21 with and without rituximab in elderly patients with the disease was ongoing,[2] the chairmen of 18 national cooperative groups decided to undertake the MInT trial. The aim was to show a 10% increase in event-free survival after 3 years by the addition of rituximab. The trial was stopped early by the data and safety monitoring board after a second planned interim analysis showed a highly significant superiority of the combination of chemotherapy plus rituximab over chemotherapy alone with respect to all endpoints. After the GELA trial in elderly patients,[2] MInT was the second trial to show a substantial improvement of outcome for patients with diffuse large-B-cell lymphoma with the addition of rituximab and the first to show this result for young patients.

Interpretation

The follow-up of the MInT study shows that the benefits of addition of rituximab to a CHOP-like chemotherapy regimen reported after 3 years were maintained after 6 years, with improvements in event-free, progression-free, and overall survival without increased acute or long-term toxic effects, including the incidence of second neoplasms, similar to the findings of the long-term follow-up of the GELA study in elderly patients.[8] In the meantime, another trial[9] has shown that rituximab also improves outcomes for young patients with poor-prognosis disease, establishing the combination of CHOP-like chemotherapy and rituximab as the standard of care for all subsets of patients with diffuse large-B-cell lymphoma. CHOP-21 chemotherapy plus rituximab is the standard of care for young patients with good-prognosis diffuse large-B-cell lymphoma to which new regimens should be compared. The outcomes for young patients in the favourable subgroup were so excellent that for the first time in the history of treatment of this disease, testing of reduction of treatment within controlled trials is justified. For the less favourable subgroup, further improvement is warranted. Although R-ACVBP (rituximab plus doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone) has been shown by GELA[10] to be superior to R-CHOP-21 for this subset of patients, no difference between R-CHOP-21 plus radiotherapy for bulky disease in the MInT study and R-ACVBP without radiotherapy in the GELA trial is apparent. Since dose escalation in the form of R-CHOEP alone was not superior to R-CHOP in the MInT study, the burning questions are now the role of radiotherapy in the less favourable subgroup and whether badly needed further improvement in this subset can be achieved by dose densification alone or only by a combination of dose escalation and dose densification.

is the use of additive radiotherapy (which was well adhered to in the MInT study). None was given in the French trial, whereas in the MInT trial patients with bulky disease received radiotherapy to this area at a dose that was predefined by each participating cooperative group, ranging from 30 Gy to 40 Gy. The IQR of the received doses ranged from 36 Gy to 40 Gy, with a median of 36·0 Gy in both treatment groups. Moreover, radiotherapy to extranodal sites was given at the discretion of the treating physician, but was rarely used (45 patients in the chemotherapy-only group and 30 in the chemotherapy plus rituximab group). The putative beneficial effect of radiotherapy comes as a surprise, since an analysis of the role of bulky disease in the MInT study,[16] which showed that the addition of rituximab decreased, but did not eliminate, the negative prognostic value of bulky disease, suggested only a minor effect—if any at all—of radiotherapy to bulky disease. The contradictory conclusions from the analysis of bulky disease in the MInT study and the comparison of the MInT patients with the patients in the LNH03-2B trial underscore the need for a randomised trial addressing the role of additive radiotherapy to bulky disease. Such a trial, the DSHNHL UNFOLDER study, is ongoing and should clarify the role of radiotherapy for this population in the rituximab era. The MInT trial was undertaken before ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET became part of the diagnostic armamentarium for diffuse large-B-cell lymphoma. Ongoing trials will show whether a negative PET after immunochemotherapy can guide the use of additive radiotherapy to bulky disease in the future.

The 6-year results of the MInT study confirm the value of new prognostic subgroups after chemotherapy plus rituximab that are only partly reflected in age-adjusted IPI. That the very best prognostic group for patients with diffuse large-B-cell lymphoma (stage I without bulky disease) was excluded from the MInT trial does not weaken the prognostic model emerging after CHOP-like chemotherapy and rituximab, because the 6-year event-free survival of 84% (with the last event occurring within 5 years) after six cycles of a CHOP-like regimen plus rituximab and the 6-year overall survival of 95% (with the respective figures for six cycles of CHOP-21 plus rituximab being 91% and 100%, event-free survival events within 1 year and 5 years, respectively) in stage II patients with no age-adjusted IPI risk factor and no bulky disease can hardly be improved upon. The subgrouping of young patients with good-prognosis disease according to age-adjusted IPI and the presence and absence of bulky disease instead of age-adjusted IPI alone is further supported by the non-significant interaction between bulky disease and age-adjusted IPI (HR 0·45, 95% CI 0·19–1·06; p=0·068).

Likewise, separation of patients in stage I with no age-adjusted IPI risk factor and without bulky disease from the respective patients in stage II no longer seems to be justified because patients with stage II and no risk factor according to age-adjusted IPI did so well in the MInT trial that patients with stage I without risk factor (who were not included in the MInT trial) can hardly do better; with no difference in outcome between stage I and stage II after CHOP-like chemotherapy and rituximab, these patients should be grouped together with respect to any prognosis and therapeutic strategy in the rituximab era.

The excellent results achieved with CHOP-21 with rituximab in the very favourable subgroup justify, for the first time in the treatment of diffuse large-B-cell lymphoma, the reduction of the number of chemotherapy cycles for these patients. In the ongoing randomised DSHNHL FLYER trial, four cycles of CHOP-21 in combination with six applications of rituximab are compared with the MInT standard of six cycles of R-CHOP-21. A planned interim analysis with 200 patients, of whom 100 had received four cycles of CHOP-21 chemotherapy only, has confirmed that this study is safe, but 600 patients have to be recruited to show non-inferiority of only four compared with six cycles of CHOP-21 in combination with six applications of rituximab.

The less favourable subgroup had a 6-year event-free survival estimate of only 71% after chemotherapy plus rituximab. This finding definitely warrants further improvement. Although the 6-year overall survival of these patients was 89%, this result was achieved only because most of the young patients who did not respond to primary CHOP-like chemotherapy plus rituximab received high-dose chemotherapy and autologous stem cell transplantation as salvage therapy with all its well known acute and long-term toxic effects. The hallmark of this subgroup is bulky disease, which is expected to be prevalent in three-quarters of these patients. Although a cutoff point of 10 cm for bulky disease is commonly used,[2,3,10,13] the margins preset in the MInT trial by the

	LNH03-2B		MInT	
	R-ACVBP (n=196)	8×R-CHOP-21 (n=183)	6×R-CHOP-21, IPI 1 (n=118)	6×R-CHEMO, IPI 1 (n=239)
Age (years)	47 (18–59)	48 (19–59)	50 (19–60)	47 (19–60)
Men	116 (59%)	109 (60%)	73 (62%)	137 (57%)
ECOG 0–1	195 (99%)	182 (99%)	116 (98%)	237 (99%)
Stage III and IV	115 (59%)	93 (51%)	58 (49%)	113 (47%)
LDH >ULN	77 (39%)	89 (49%)	58 (49%)	124 (52%)
Bulk ≥10 cm	38 (19%)	45 (25%)	47 (40%)	94 (39%)
3-year EFS (%)	81% (75–86)	67% (59–73)	80% (71–87)	77% (71–82)
3-year PFS (%)	87% (81–91)	73% (66–79)	86% (78–91)	83% (78–88)
3-year overall survival (%)	92% (87–95)	84% (77–89)	92% (85–96)	91% (86–94)
Radiotherapy	0	0	58 (49%)	117 (49%)

Data are median (range) or n (%); data for survival are estimate (95% CI). IPI=International Prognostic Index. R=rituximab. ACVBP=doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone. CHOP=cyclophosphamide, doxorubicin, vincristine, prednisone. ECOG=Eastern Cooperative Oncology Group. LDH=lactate dehydrogenase. ULN=upper limit of normal. EFS=event-free survival. PFS=progression-free survival.

Table 3: **Characteristics and outcome of patients with one risk factor according to age-adjusted IPI in the MInT trial compared with the GELA LNH03-2B trial[10]**

different cooperative groups ranged from 5 cm to 10 cm. A detailed analysis of the role of maximum tumour diameter in the MInT trial has been published previously.[16] In summary, it showed that a cutoff point of only 6·0 cm separated two populations with a significant difference in overall survival (log-rank p values 0·0009–0·037). This finding should be considered together with the fact that 169 (52%) of 323 patients in the MInT trial who received radiotherapy had a maximum diameter less than 10 cm, suggesting that the optimum cutoff point for a bulky disease to receive radiotherapy might be less than 10 cm. If additive radiotherapy can be shown to improve results in patients with bulky disease with a diameter greater than 7·5 cm in the ongoing DSHNHL UNFOLDER study, a reappraisal of the optimum cutoff point for bulky disease would be indicated.

A subgroup analysis of the DSHNHL NHL-B1[17] and NHL-B2[18] trials showed that, with the exception of patients with raised LDH, patients with bulky disease had the greatest benefit from interval reduction from three-weekly CHO(E)P-21 to biweekly CHO(E)P-14. Because half the patients in the less favourable subgroup in the MInT study presented with raised LDH and two-thirds with bulky disease, increasing dose density is an attractive option for these patients, and R-CHOP-14 is being compared with R-CHOP-21 in the ongoing DSHNHL UNFOLDER trial for this population. This trial will show whether dose intensification (interval reduction) alone is sufficient, or whether increasing dose density should be combined with dose escalation of the chemotherapy (as pursued in the ACVBP regimen) to improve results in these patients over those achieved with CHOP-21.

Contributors

MP, LT, AO, RP, MT, LS, DSG, JW, P-LZ, RS, OS, UJ, NM, AL-G, SK, PdNB, and ML were involved in the study design and writing of the protocol. EK and ML did the statistical analysis and together with MP were involved in writing the manuscript, as were NMu, VP, and SG, who also coordinated and organised the follow-up study.

Conflicts of interest

MP and MT are on the Mabthera advisory board of Roche, the manufacturer of rituximab. JW has received travel grants from Roche. UJ has received honoraria and research grants to university from Roche. AL-G has provided consultancy for Roche. All other authors declare that they have no conflicts of interest.

Acknowledgments

Roche was the sponsor of the MInT trial, which covered the treatment period and the first 3 years of follow-up. The sponsor of this observational follow-up study was the University of Saarland and the study was funded by Roche.

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