Hematology Meeting Reports 2007; 1(4):27–41

Aggressive non-Hodgkin's lymphoma – long-term survival for all patients?

Bertrand Coiffier[1]
Jacques Tabacof[2]
Zhi-Xiang Shen[3]
Ulrich Jäger[4]

[1]Hospices Civils de Lyon and the University Claude Bernard, Lyon, France, [2]Department of Oncology, Hospital Israelita Albert Einstein, São Paulo, Brazil, [3]Department of Haematology, Rui-jin Hospital, Shanghai, China, [4]Division of Hematology and Hemostaseology, Medical University of Vienna, Austria

Corresponding author:
Bertrand Coiffier

Email: bertrand.coiffier@chu-lyon.fr

A B S T R A C T

Aggressive non-Hodgkin's lymphoma (NHL) comprises a clinically and biologically heterogeneous group of neoplasms, of which diffuse large B-cell lymphoma (DLBCL) is the most common. The treatment goal for patients with DLBCL is cure with first-line treatment. However, the outlook for patients for many years was grim, with no real advance in treatment options since the 1970s, when cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) was held as the best available therapy.

The clinical introduction of rituximab has rejuvenated the first-line treatment of DLBCL. Since the landmark GELA-LNH 98.5 study established eight cycles of rituximab in combination with CHOP chemotherapy as the gold standard for all patients with DLBCL, significant improvements in event-free survival and overall survival have been observed. Five-year follow-up data recently demonstrated that the benefit of rituximab is sustained over time.

Such is the momentum of research in aggressive NHL that rituximab combined with salvage chemotherapy regimens in relapsed/refractory aggressive NHL has also shown significant improvements in response rates, progression-free survival and overall survival. Furthermore, rituximab-based immunochemotherapy has improved patient outcomes in non-DLBCL aggressive lymphomas, such as mantle cell lymphoma (MCL) and Burkitt's lymphoma. An important role for rituximab-based maintenance therapy is also emerging, both in DLBCL and MCL. Much further investigation is warranted to fully explore the potential of rituximab-based treatment for patients with all subtypes and stages of aggressive lymphoma. Ongoing large-scale studies such as the GELA's LNH 03 programme, the CORAL and NHL-13 trials will provide valuable insight into the optimisation of rituximab-based treatment in aggressive NHL.

Introduction – current status of clinical practice in aggressive non-Hodgkin's lymphoma

Aggressive non-Hodgkin's lymphoma (NHL) comprises a clinically and biologically heterogeneous group of neoplasms. Of these, diffuse large B-cell lymphoma (DLBCL) is the most common, accounting for approximately 30% of new cases.[1] Most patients present with advanced disease and before the rituximab era less than half were cured with available treatment; the remainder eventually succumbed to the disease.[1,2]

The International Prognostic Index (IPI) was devised to predict outcomes in DLBCL,[3] with the aim of tailoring each individual's treatment to their prognosis. Using the IPI, patients are assigned to one of four risk groups based on five characteristics – age, tumour stage, serum lactate dehydrogenase concentration, performance status and number of extranodal disease sites.[3] Unfortunately, considerable variation has been observed in the prognosis of patients within a single category of the IPI; the factors underlying these differences are not yet completely understood.[4] Several studies have investigated molecular methods of characterising DLBCL tumours and linking gene-expression

signatures with clinical outcomes.[5–7] However, there is a lack of overlap between resulting models, different techniques were used to obtain them and the clinical relevance of the observed genetic alterations remains poorly defined.[4] In an attempt to capture the prognostic significance of a small number of genes using methods more widely suited to clinical laboratories, Lossos *et al*. built a predictive model based on six genes which correlate with prolonged (*LMO2, BCL6, FN1*) or reduced (*BCL2, CCND2, SCYA3*) overall survival (OS) independently of the IPI.[8] Current prognostic models are limited by the fact that many studies drew on patient samples which were obtained before rituximab was used widely in DLBCL and prognostic factors can be modified by therapy. For example, the combination of rituximab with CHOP (R-CHOP) or dose-adjusted EPOCH (etoposide, doxorubicin, vincristine, prednisolone and cyclophosphamide; R-EPOCH) chemotherapy regimens overcomes the adverse prognostic effects of *BCL2* expression or of lack of *BCL6* expression.[9–11] Parameters used in this context therefore need some redefinition, and further work which reflects the central role of rituximab in current treatment paradigms would be welcomed. To this end, Farinha *et al*. have determined that *p53* overexpression remains an independent indicator of inferior survival when patients are treated with R-CHOP.[12] Furthermore, Sehn *et al*. have recently published a revised IPI for DLBCL which better reflects prognosis in the R-CHOP era.[13]

Since the 1970s, combination chemotherapy with CHOP has been the mainstay of treatment for patients with aggressive NHL.[1] Complete response (CR) rates observed with this regimen were 40–50%,[14,15] leaving considerable room for improvement. Intensified chemotherapy regimens, such as ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisolone) significantly improved event-free survival (EFS) and OS compared with CHOP (5-year EFS: 39% versus 29%, p = 0.005; OS: 46% versus 38%, p = 0.036).[16] Regrettably, ACVBP was also associated with a significant increase in the number of treatment-related deaths compared with CHOP (13% versus 7%, respectively; p = 0.014).[16] CHOP therefore remained widely held as the best available therapy for DLBCL.

Over the past 5 years, the introduction of rituximab has produced unprecedented advances in the treatment of DLBCL, improving clinical outcomes and introducing novel standards in clinical practice. We will examine data which established rituximab-based treatment as the new gold standard for patients with newly diagnosed DLBCL. Building on this, we will assess available data which suggest that rituximab-based treatment holds considerable promise for patients with relapsed DLBCL and for patients with non-DLBCL aggressive lymphomas. Finally, we will examine the role of rituximab-based maintenance therapy, which is currently under investigation in aggressive NHL.

Is the gold standard applicable to all DLBCL patient groups?

The primary objective for patients with DLBCL is cure with first-line treatment. Rituximab-based therapy has demonstrated significant benefits in DLBCL, with results from large-scale trials leading to the modification of treatment paradigms to include rituximab. Rituximab's activity as monotherapy in DLBCL was demonstrated in a Phase II study in 54 patients with various aggressive NHL histologies: a response rate of 37% was observed in patients with DLBCL.[17] Subsequently, large-scale trials explored the effects of rituximab combined with chemotherapy as first-line treatment in DLBCL.

Most notably, the landmark GELA-LNH 98.5

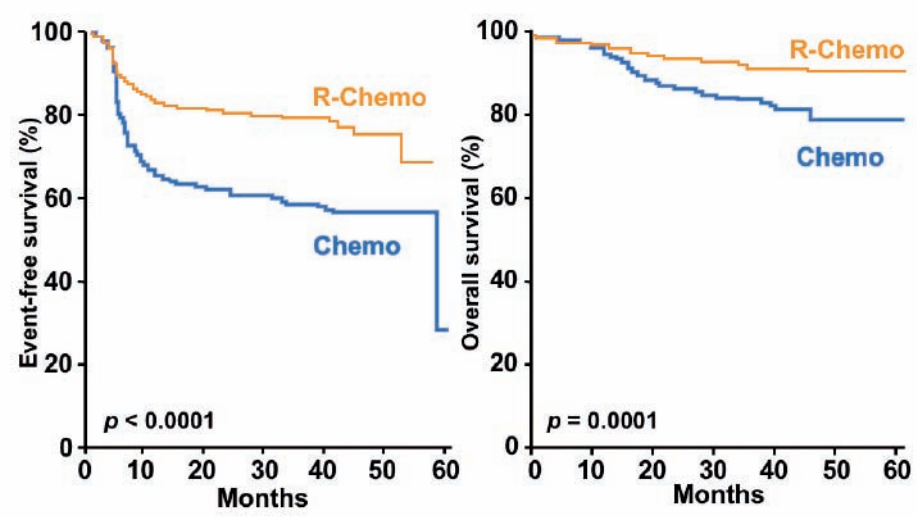

Figure 1: The MInT study showed that rituximab plus CHOP significantly improves EFS and OS in young patients. (*Reprinted with permission from Elsevier. Pfreundschuh M, et al. The Lancet Oncology 2006; 7:379–391*).

study established eight cycles of R-CHOP as the gold standard for the first-line treatment of DLBCL in elderly patients (> 60 years). In this study, 399 patients were randomised to receive either eight cycles of R-CHOP or CHOP alone.[18] Rituximab plus CHOP significantly improved the CR rate (R-CHOP: 76%, CHOP: 63%, p = 0.005), EFS (p < 0.001) and OS (p = 0.007) compared with CHOP alone. Rituximab-based treatment also significantly reduced the risk of death, disease progression or another event and of death from any cause (relative risk: 0.58 and 0.64, respectively).[18] This was the first study to show a survival benefit of R-CHOP compared with CHOP in aggressive lymphoma.

Improvements in EFS and OS initially observed in the GELA-LNH 98.5 study have been sustained over time: with a median follow-up of 5 years, EFS and OS were significantly increased with eight cycles of R-CHOP compared with CHOP alone (EFS: 3.8 years versus 1.1 years, p = 0.00002; OS: not reached versus 3.1 years, p = 0.0073).[19] At this point, 26% more patients were alive in the R-CHOP group than in the CHOP group.[19] Subgroup analyses showed that R-CHOP significantly prolonged EFS in patients with both high- and low-risk age-adjusted IPI scores.[19] R-CHOP was not associated with any long-term toxicity and was generally well tolerated.[19] The eagerly awaited 7-year follow-up data were recently presented at ASCO 2007, further substantiating that the beneficial effects of rituximab on survival are maintained: OS in the R-CHOP arm was more than double that in the CHOP arm (7.669 years versus 3.469 years, p = 0.0004).[20]

A growing evidence base now suggests that the gold standard should extend across all patients with DLBCL, as the benefit of rituximab-based therapy is durable and offers the best chance for cure in aggressive lymphoma. Valuable lessons for further improving the treatment of elderly patients with DLBCL can be gained from the RICOVER-60 trial. In this study, including 1,222 evaluable patients, the use of eight cycles of rituximab with six cycles of biweekly CHOP (CHOP-14) resulted in the best data ever reported in a randomised trial in elderly patients with DLBCL: 3-year EFS and OS were significantly increased with rituximab plus CHOP-14 compared with CHOP-14 alone (EFS: 66% versus 47%, p < 0.001; OS: 78%

versus 68%, p = 0.018).[21] These data suggest that using eight cycles of rituximab allows the number of dose-dense chemotherapy cycles to be reduced from eight to six with no loss of efficacy – longer follow-up is required to be certain that relapses do not occur. Of additional interest in this context is whether R-CHOP-14 or R-CHOP-21 should be the standard of care for first-line treatment of DLBCL. Two ongoing Phase III studies by the GELA[22] and the British National Lymphoma Investigation are investigating the potential advantages of R-CHOP-14 over R-CHOP-21, in particular in terms of EFS. Results from these trials should provide further insight on this matter.

The MInT study established that rituximab-based first-line treatment is highly effective in young patients (< 60 years) with low and low–intermediate risk DLBCL (age-adjusted IPI 0 or 1).[23] After a median follow-up of 34 months, results from 823 patients showed that rituximab combined with CHOP-like chemotherapy significantly increased 3-year EFS and OS compared with CHOP-like chemotherapy alone (EFS: 79% versus 59%, p < 0.0001; OS: 93% versus 84%, p = 0.0001; Figure 1).[23] There were nearly twice as many failures in the chemotherapy-only arm compared with the rituximab arm (41% and 21%, respectively), indicating that rituximab-based treatment could halve the proportion of young patients requiring salvage therapy, with no concomitant increase in adverse events.[23] From another perspective, strong evidence from a Phase II trial conducted by the DSHNHL group suggests a role for rituximab added to high-dose chemotherapy (MegaCHOEP) followed by autologous stem cell transplantation (ASCT) in the first-line treatment of younger high-risk patients, specifically when compared to historical data from the same patient group.[24]

An observational analysis of 376 young patients (< 60 years) with DLBCL complements the MInT and GELA findings, showing that rituximab plus chemotherapy significantly improved 2-year progression-free survival (PFS) and OS in both low- and high-risk groups.[25] Moreover, the dramatic improvements observed with rituximab-based regimens in patients of all ages (> 15 years) have been confirmed by a retrospective, population-based analysis of 292 patients with newly diagnosed advanced-stage DLBCL.[26] The estimated 2-year PFS with R-CHOP was 69%, compared with 51% for CHOP alone (p = 0.002); rituximab also significantly prolonged 2-year OS (78% versus 52%, respectively; p < 0.0001). The addition of rituximab to CHOP reduced the risk of dying within 2 years of diagnosis by approximately 50%.[26]

It has been shown that data from clinical trials supporting the use of rituximab are corroborated by population-based studies in the setting of routine patient care. Taken together, the studies examined in this section show that the gold standard – treatment with eight cycles of rituximab in combination with CHOP chemotherapy – is applicable to all patients with DLBCL (Figure 2).

Ongoing studies will explore whether the addition of new substances, such as the monoclonal antibody and vascular endothelial growth factor inhibitor bevacizumab, to the R-CHOP regimen will further increase rates of EFS and OS. A large multinational randomised double-blind trial has recently begun to address this important issue. In addition, studies are underway to investigate how positron emission tomography imaging can guide induction treatment. Further investigations are looking at how outcomes can be improved by assigning patients to treatment according to their DLBCL subtype: whether they show a gene expression profile characteristic of normal germinal centre B cells, or whether it is more similar to that of an activated B-cell-like expression profile. Variants of the R-CHOP regimen, such as R-EPOCH, may also lead to improved results.

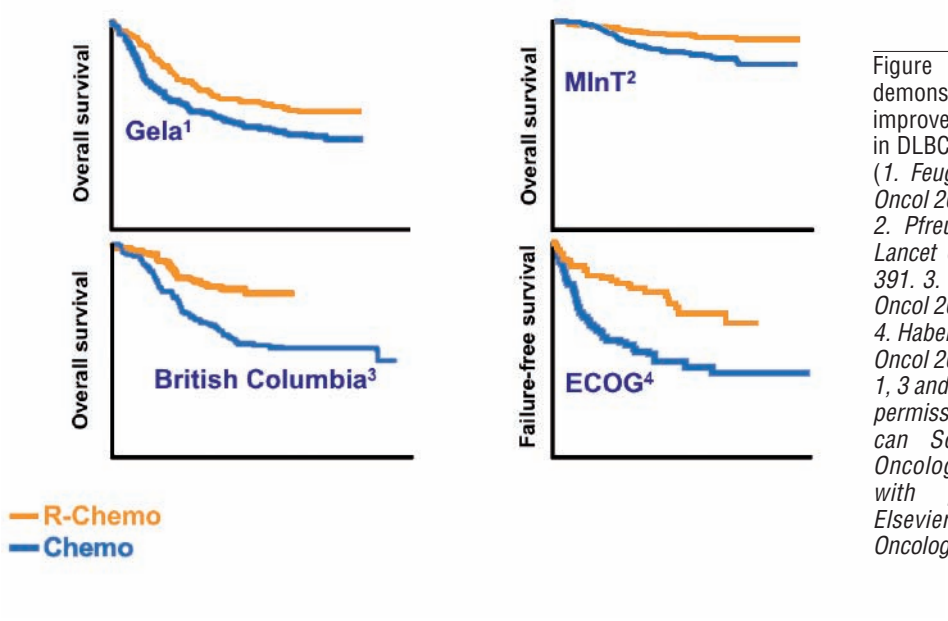

Figure 2: Several studies demonstrate that rituximab improves patient outcomes in DLBCL.
(*1. Feugier P, et al. J Clin Oncol 2005; 23:4117–4126. 2. Pfreundschuh M, et al. Lancet Oncol 2006; 7:379-391. 3. Sehn L, et al. J Clin Oncol 2005; 23:5027–5033. 4. Habermann T, et al. J Clin Oncol 2006; 24:3121–3127. 1, 3 and 4 are reprinted with permission from the American Society of Clinical Oncology. 2 is reprinted with permission from Elsevier. The Lancet Oncology 2006;7: 379–391*)

Using rituximab to enhance treatment in relapsed aggressive NHL

What treatment goals can be established for patients with relapsed aggressive NHL? Encouragingly, some patients who relapse or do not achieve remission with initial treatment can still be cured, although elderly patients, those with extensive disease, or individuals with poor performance status are more likely to receive palliative care and treatment to alleviate symptoms.

Mostly, however, the goal of treatment in relapsed DLBCL is to achieve a CR, thus offering patients a further chance for a cure. The PARMA study compared the efficacy of high-dose chemotherapy (HDT) and ASCT with that of continuous treatment with DHAP (dexamethasone, cytarabine and cisplatin) without transplantation in patients with relapsed DLBCL.[27] ASCT was associated with significantly higher 5-year OS compared with DHAP (53% versus 32%, respectively; p = 0.038).[27] Concerns have been raised regarding the statistical design and clinical conclusions of this trial.[28–31] Nonetheless, improvements in supportive care have lead to stem cell transplantation being offered to an extended patient population in relapsed DLBCL.[4]

Patients in relapse are usually offered salvage regimens with non-cross-resistant agents. The most popular regimens are DHAP, ESHAP (etoposide, methylprednisolone, cytarabine and cisplatin), ICE (ifosfamide, carboplatin and etoposide) and mini-BEAM (carmustine, etoposide, cytarabine and melphalan). These regimens have an overall response rate (ORR) of around 60% and a CR rate of about 30%.[27,32–35] Individuals who respond to salvage therapy may then be eligible for HDT and ASCT, with about a 50% chance of a cure.

Remission status at transplantation appears to have a significant effect on subsequent outcome, with patients achieving a CR having better PFS than those achieving only a partial response (PR). Second-line chemotherapy regimens are associated with CRs of 25–35% and it is imperative to find regimens which can improve this proportion. Increasing evidence suggests that rituximab added to salvage chemotherapy significantly improves outcomes in relapsed aggressive NHL.

Kewalramani *et al*. investigated rituximab in combination with ICE chemotherapy (R-ICE) in rituximab-naive patients with relapsed/refractory DLBCL.[36] In 34 evaluable patients, R-ICE significantly increased the CR rate compared with 147 similar historical controls who had received ICE alone (53% versus 27%, respectively; p = 0.01); the advantage of R-ICE was particularly significant in patients with relapsed disease (CR: 65% versus 34%, p = 0.01).[36] A further 25% of patients treated with R-ICE achieved a PR, yielding an ORR of 78% compared with 71% in the control group.[36] Interestingly, disease status (relapsed or primary refractory) was a predictor of response to R-ICE (96% versus 46%, p < 0.01), but second-line age-adjusted IPI was not.[36] Treatment with R-ICE allows for good stem cell mobilisation and harvest. Of 25 responding patients who underwent ASCT, those who had received R-ICE had a better 2-year PFS than controls (54% versus 43%).[36] These results are encouraging, although the difference between groups in 2-year OS did not reach significance (67% and 56%, respectively). Importantly, R-ICE was well tolerated and treatment-related side effects did not preclude transplantation.[36]

Reports of rituximab used in combination with intensified chemotherapy followed by ASCT also show markedly improved results. A recent study reveals that rituximab plus DHAP used as a salvage regimen in patients with relapsed/refractory aggressive NHL increases the ORR to 62%.[37] In another study, of 22 patients with relapsed/refractory aggressive NHL, rituximab was incorporated into two cycles of DHAP and high-dose sequential chemotherapy; myeloablative treatment with BEAM and ASCT followed.[38] After 2 years, 57% of patients in the rituximab group were free from failure compared with 18% of historical controls who had received the same treatment without rituximab (p = 0.0051); 2-year OS was 77% and 37%, respectively (p = 0.0051).[38] This highlights that the addition of rituximab to intensified salvage chemotherapy regimens can improve prognosis. Data from the HOVON-44 trial strongly support this conclusion. In this study, 239 patients with relapsed/progressive aggressive NHL were randomised to receive DHAP-VIM-DHAP (VIM: ifosfamide, methotrexate and etoposide) in conjunction with rituximab and ASCT or DHAP-VIM-DHAP followed by BEAM and ASCT. The addition of rituximab significantly improved 2-year estimates of disease-free survival (DFS) and OS (DFS: 82% versus 46%, p = 0.003; OS: 62% versus 48%, p = 0.03).[39]

Khouri *et al*. investigated high-dose rituximab (HD-R) before and after BEAM/ASCT in relapsed aggressive NHL.[40] HD-R was administered to 67 patients during stem cell mobilisation (1 day before chemotherapy at 375 mg/m^2 and 7 days after chemotherapy at 1,000 mg/m^2) and again on days 1 and 8 after BEAM/ASCT. Results were compared with 30 matched historical controls who had received similar treatment minus rituximab. After a median follow-up of 20 months, the actuarial 2-year OS was 80% for patients receiving HD-R compared with 53% in the control group (p = 0.002); DFS was 67% and 43%, respectively (p = 0.004).[40] These results were achieved with no significant increase in the risk of infection or toxicity; there were no treatment-related deaths in either group.[40]

More prospective trials are necessary to verify the findings listed above and further define the best treatment approach in patients with relapsed/refractory DLBCL. The CORAL randomised trial is comparing R-ICE with R-DHAP; patients are stratified by previous exposure to rituximab and there is also a subsequent randomisation for maintenance rituximab versus observation after HDT/ASCT (Figure 3).[41] In addition, the Phase III LY-12 study will further assess the efficacy of second-

line treatment with two cycles of R-GDP (rituximab plus gemcitabine, dexamethasone and cisplatin) compared with two cycles of R-DHAP before BEAM/ASCT, in patients with relapsed/refractory DLBCL. Again, a second randomisation to rituximab maintenance or observation is planned. It is hoped that conclusions of these studies will guide the choice of rituximab-based treatment in patients with relapsed DLBCL. The overall benefit of rituximab in this context is highlighted by a large retrospective study in 957 patients with high-risk B-cell lymphoma, which demonstrated that 5-year EFS was significantly improved with rituximab plus HDT with autograft; in 415 relapsed patients, 5-year EFS was 59% for patients treated with rituximab and 34% for patients who were not.[42] Future treatment paradigms are likely to include additional consolidation or maintenance therapy to further optimise patient outcomes.

What is the role of maintenance therapy in aggressive lymphoma?

The underlying concept of maintenance therapy in aggressive NHL is to maintain the period of remission, which may increase the number of patients achieving a cure. Maintenance therapy involves the continued, regular treatment of patients after induction therapy in order to prevent malignant cells becoming re-established and therefore maintain remission. This type of treatment is gaining momentum, with maintenance therapy being incorporated into an increasing number of trials.

Rituximab has minimal acute side effects, a low risk of long-term toxicity and convenient administration, making it a suitable candidate for maintenance therapy. Elderly patients may particularly benefit from rituximab maintenance treatment, as they may be unable to withstand the side effects associated with dose-intensive chemotherapy regimens and stem cell transplantation.

The ECOG 4494 trial investigated the efficacy of induction therapy with CHOP or R-CHOP and also assessed the effectiveness of rituximab maintenance therapy compared with observation only in those patients who responded to induction treatment.[43] The study included 632 patients (≥ 60 years) with previously untreated DLBCL; of these, 415 responded to induction therapy and were randomised to rituximab maintenance or

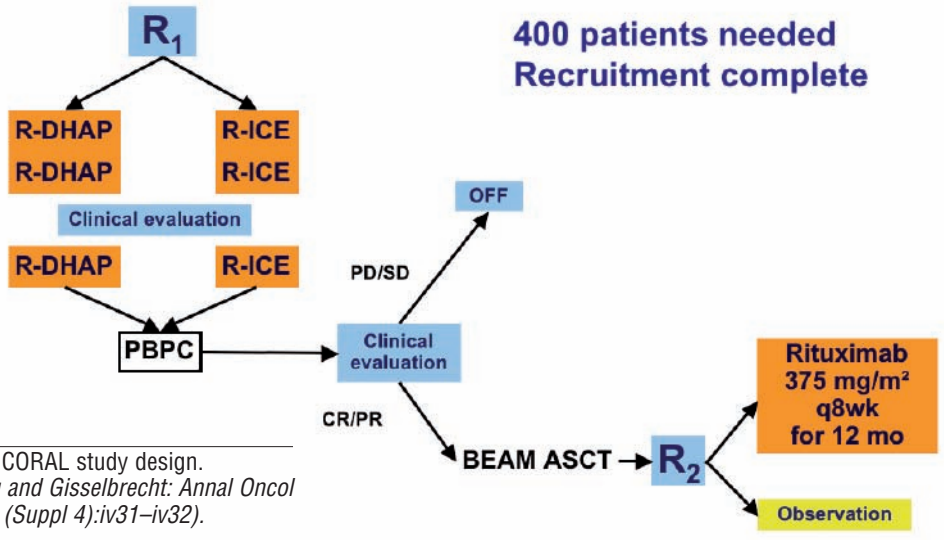

Figure 3: CORAL study design.
(Hagberg and Gisselbrecht: Annal Oncol 2006; 17 (Suppl 4):iv31–iv32).

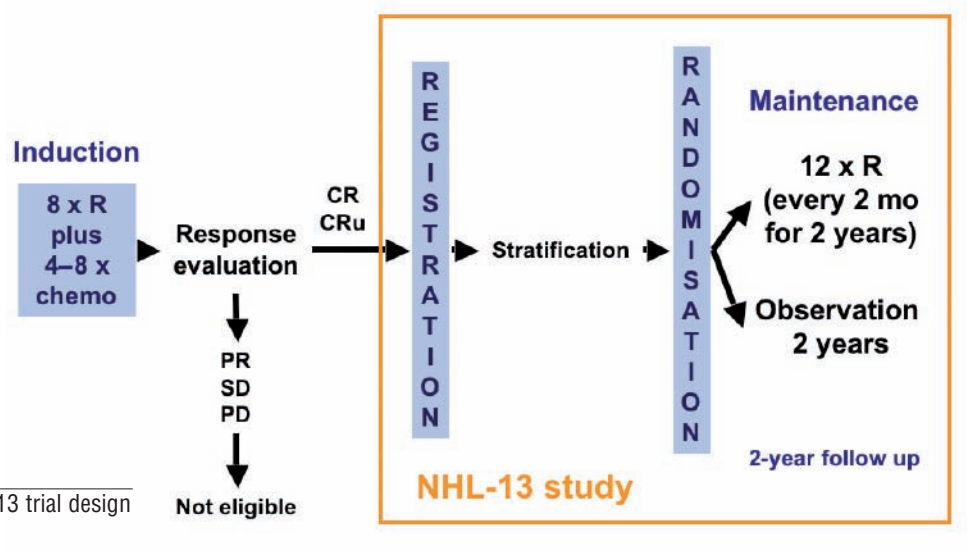

Figure 4: NHL-13 trial design

observation arms. R-CHOP induction therapy significantly improved 3-year failure-free survival (FFS), which was 53% compared with 46% for patients receiving CHOP alone ($p = 0.04$).[43] Rituximab maintenance therapy significantly prolonged 2-year FFS from the second randomisation (76% versus 61%, $p = 0.009$), but had no significant effect on OS.[43] Interestingly, rituximab maintenance therapy significantly prolonged FFS after CHOP, but not after R-CHOP, induction therapy ($p = 0.0004$ and $p = 0.81$, respectively).[43]

Results of the ECOG study suggest that use of rituximab maintenance after R-CHOP was of limited benefit. However, it should be noted that the standard induction regimen of eight cycles of rituximab plus six to eight cycles of CHOP was not employed in this trial, which may have affected overall efficacy. In addition, patients with a CR or PR were included in the maintenance arm, and the study was not adequately powered to evaluate the efficacy of maintenance treatment.[43] The observations nonetheless give rise to as yet unanswered questions: does exposure to rituximab as part of first-line therapy affect the efficacy of subsequent therapy if it is required? And if so, what are the optimal schedules to maximise the efficacy of rituximab in both induction and maintenance therapy? In this context, results from the ongoing Phase III NHL-13 trial may provide more definitive information (Figure 4).[44] In NHL-13, an induction regimen of eight cycles of rituximab combined with four to eight cycles of CHOP-like chemotherapy will be administered to patients with DLBCL or grade 3b follicular lymphoma. Those patients who have shown a CR or an unconfirmed CR (CRu) following induction will subsequently receive rituximab maintenance therapy (1×375 mg/m^2 every 2 months for 2 years) or undergo observation only. The trial will evaluate the ability of rituximab maintenance to prolong EFS in these patients. Subgroup analyses according to lymphoma type, IPI and induction treatment will be performed. Recruitment of 440 patients in more than 20 countries is planned by the end of 2008 – currently, 89 patients have entered the trial. In addition to NHL-13, the CORAL and LY12 studies in relapsed/refractory DLBCL may be of particular interest, as they include standard rituximab-containing induction therapies, with a second randomisation to rituximab maintenance therapy or observation.[41]

The role of rituximab in consolidation treatment has also been explored in young

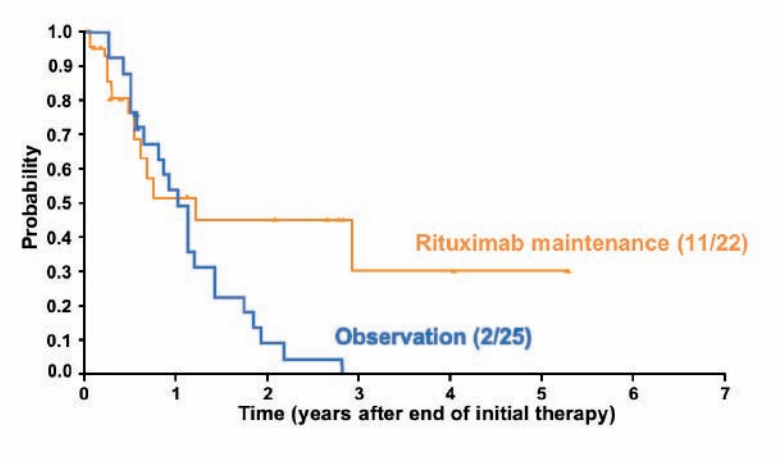

Figure 5: Rituximab mintenance therapy prolonged response duration compared with observation only in patients with MCL.
(This research was originally published in Blood. Forstpointner R, et al. Blood 2006;108:4003-4008. © the American Society of Hematology).

patients (< 60 years) with poor risk DLBCL, for example in the GELA LNH 98.3 trial, which compared rituximab consolidation treatment (375 mg/m^2 weekly for 4 weeks, 2 months after HDT) with observation only after ASCT.[45] After a median follow-up of 3 years, a trend towards improved 3-year EFS was observed in patients who had received rituximab compared with control (80% versus 72%, respectively; p = 0.10).[45]

Data regarding rituximab maintenance therapy in mantle cell lymphoma (MCL) are also encouraging. Ghielmini *et al*. examined the use of rituximab maintenance treatment (375 mg/m^2 every 2 months for four times) after induction with rituximab monotherapy in 61 patients with newly diagnosed, refractory or relapsed MCL.[46] Median EFS exhibited a non-significant improvement overall compared with observation only (12 months versus 6 months, respectively), and rituximab maintenance significantly improved median EFS in a subgroup of previously treated patients (11 months versus 5 months, p = 0.04).[46] Rituximab maintenance treatment also significantly prolonged response duration compared with observation only in patients with MCL who had received R-FCM (rituximab plus fludarabine, cyclophosphamide and mitoxantrone) induction treatment (p = 0.049, Figure 5); a substantially higher proportion of these patients who were treated with rituximab maintenance therapy had ongoing remissions beyond 2 years compared with those undergoing observation only (45% and 9%, respectively).[47] Authors of the Phase II study from the Wisconsin Oncology Network suggested that 2 years of maintenance rituximab after induction treatment with rituximab plus modified Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone, cytarabine and methotrexate) prolongs PFS.[48] This suggestion is strongly supported by a matched pair analysis of ASCT with rituximab purging followed by rituximab maintenance, compared with historical controls who had received standard chemotherapy.[49] A follow-up analysis showed superior 5-year PFS and OS with the rituximab-based regimen (PFS: 72% versus 19%, p = 0.0001; OS: 80% versus 38%, p = 0.0017).[50] Taken together, these results emphasise that rituximab shows sustained efficacy through all phases of treatment and provides considerable benefits when used as maintenance therapy in MCL.

Future studies aim to clarify the role of rituximab maintenance therapy in all subtypes of aggressive NHL and establish where and how intensive dose schedules need to be used to optimise patient outcomes.

Improving treatment options in non-DLBCL aggressive lymphomas

The term 'aggressive NHL' covers a highly varied group of malignancies. These histologies include MCL, HIV/AIDS-related NHL, Burkitt's lymphoma (BL), primary central nervous system lymphoma (PCNSL), primary mediastinal large B-cell lymphoma (PMLBCL) and primary testicular lymphoma. Although these are less common than DLBCL, progress in these areas is ongoing, often including the use of rituximab, and may involve extension of the treatment principles examined earlier.

Mantle cell lymphoma

Owing to its unique biology, MCL is now recognised as a distinct subtype of B-cell NHL, accounting for approximately 6–8% of all new lymphoma cases and occurring more frequently in men.[51] Its clinical course is characterised by a high response to induction treatment, but this is short-lived and median OS is generally around 3 years, with a low proportion of long-term survivors.[51–53] The main goal of treatment is to extend PFS, usually with HDT followed by transplant. The reclassification of MCL from an indolent to an aggressive lymphoma has important ramifications for its treatment and has instigated a flurry of clinical research, often involving targeted agents such as rituximab.

Induction chemotherapy regimens used in MCL can be broadly divided into three categories: doxorubicin-containing regimens such as CHOP, regimens based on purine analogues such as FCM, and intensive combination chemotherapy such as Hyper-CVAD.[51] A growing body of evidence underlines the potential of integrating rituximab into these regimens.

Lenz *et al*. performed a randomised trial comparing CHOP with R-CHOP in 122 patients with previously untreated MCL.[54] R-CHOP significantly increased the ORR, CR rate and time to treatment failure (TTF) compared with CHOP alone (ORR: 94% versus 75%, p = 0.0054; CR: 34% versus 7%, p = 0.00024; median TTF: 21 months versus 14 months, p = 0.0131).[54] These data merit further investigation, although no significant difference in PFS was noted between groups.[54] A more dramatic impact of rituximab-based induction therapy was observed by Forstpointner *et al.,* who assessed the efficacy of induction therapy with rituximab plus FCM or FCM alone in 147 patients with relapsed/refractory follicular lymphoma or MCL.[55] R-FCM improved ORR compared with FCM alone in 48 evaluable patients with MCL (58% versus 46%, respectively; not significant).[55] The benefit of R-FCM induction treatment in these patients extended to a significant increase in 2-year OS compared with FCM alone (median OS: not reached versus 11 months, respectively; p = 0.0042).[55] An improvement in response rates with R-MCP compared with MCP was also observed by Herold *et al.,* although these did not reach significance.[56] Despite this, taken together these data demonstrate that significant improvements in patient outcomes can be achieved with rituximab-based induction therapy in MCL.

Convincing data supports rituximab combined with Hyper-CVAD as induction therapy before ASCT in MCL. In particular, Romaguera *et al*. treated 97 previously untreated patients with MCL with rituximab plus Hyper-CVAD, alternating every 21 days with rituximab plus high-dose methotrexate and cytarabine (M-C), for six to eight cycles. This regimen provided a CR/CRu in 87% of patients, a 3-year FFS of 64% and OS of 82%.[57] The benefit was further increased in patients aged under 65 years (3-year FFS: 73%).[57] Initially, there appeared to be no plateau in survival curves, indicating that patients may still harbour minimal residual disease and may benefit from maintenance therapy.[57] Subsequent analyses at

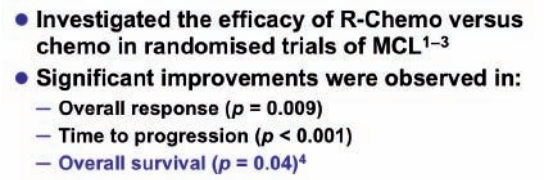

Figure 6: A Cochrane meta-analysis demonstrated that rituximab-based induction treatment significantly improves OS in MCL (*Lenz G. et al. J Clin Oncol 2005; 23:1984–1992. Forstpointer R, et al. Blood 2004; 104: 3064–3071 and unpublished data 2005. Herold M, et al. ICML 2005:abstract 060. Schulz H, et al. J Natl Cancer Inst 2007; 99:706–714*).

57 months revealed that FFS did in fact plateau in 14 patients who had presented with the blastoid cytological variant, and median OS had yet to be reached.[58] In this patient subgroup, treating with rituximab plus Hyper-CVAD may potentially provide longer-term disease control.[58] Another study supports this, showing that Hyper-CVAD/M-C with or without rituximab (± R) significantly prolongs 3-year PFS and OS compared with standard anthracycline induction therapy (PFS: 78% versus 55%, p = 0.05; OS: 97% versus 68%, p = 0.01).[59] The authors of this second study noted that in eligible patients HyperCVAD/M-C±R with ASCT was the most effective means of improving long-term DFS.[59]

The finding that immunochemotherapy is superior to chemotherapy alone as first-line treatment in MCL has been consolidated by a recent Cochrane meta-analysis (Figure 6). Analysis of seven trials with a total of 1,943 patients (260 with MCL) revealed that, in MCL, rituximab-based induction therapy significantly improved OR (p = 0.009), time to progression (p < 0.001) and OS (p = 0.04) compared with chemotherapy alone.[60] Recently published National Comprehensive Cancer Network guidelines now recommend rituximab-based chemotherapy for both first-line and salvage therapy of MCL.[61]

Following up-front treatment, improvements in PFS and OS have been demonstrated with ASCT when compared with interferon therapy.[52] The European MCL Network study in patients who had achieved PR or CR with CHOP-like induction therapy showed that a significantly longer PFS was obtained with consolidation by myeloablative radiochemotherapy followed by ASCT than with interferon-α maintenance treatment (39 months versus 17 months, respectively; p = 0.0108).[52]

Rituximab has been used in combination with high-dose chemotherapy as part of the preparatory regimen for ASCT in MCL with promising results. An OS and EFS of 89% and 79%, respectively, have been demonstrated at 54 months in patients aged 60 years and under.[62] This compared favourably with historical controls who had received standard-dose CHOP or CHOP-like chemotherapy and exhibited an OS of 42% and EFS of 18% at the same time point.[62] Rituximab-augmented myeloablation for first-line ASCT also significantly improved EFS compared with historical controls who did not receive rituximab, further supporting the benefit of including rituximab during the preparative stages of ASCT.[63] Ongoing separate studies run by the European MCL Network are addressing the question of which chemotherapy regimen rituximab is best incorporated into before ASCT in MCL, as well as the efficacy of rituximab maintenance treatment compared with that of interferon-α in patients with previously untreated MCL who are ineligible for ASCT. It is important to note that, as described earlier, several studies support the promising efficacy of rituximab maintenance in MCL.[46–50]

Primary mediastinal large B-cell lymphoma

PMLBCL is recognised as a separate disease entity from DLBCL in the WHO/REAL classification. It arises in the thymus, mainly in young adults, and accounts for approximately 5% of all patients with aggressive lymphomas.

Several groups have assessed the use of rituximab in combination with chemotherapy in patients with PMLBCL, with some promising results.[64–66] For example, in one study of 74 patients, R-CHOP significantly improved 3-year FFS compared with historical controls treated with CHOP alone (93% and 53%, respectively; p = 0.0006).[66]

Burkitt's and Burkitt-like lymphoma

In BL, rituximab plus dose-adjusted EPOCH has been effective induction therapy.[67] Results from the ongoing CALGB10002 Phase II trial in previously untreated patients with BL treated with rituximab and high-intensity chemotherapy with filgrastim (granulocyte-colony stimulating factor) may confirm these findings.

Primary central nervous system lymphoma

In PCNSL, high-dose methotrexate-based chemotherapy improves survival when compared with radiotherapy.[68] Currently, research is focused on improving survival and minimising neurotoxicity. As most PCNSLs are CD20-positive, and a limited amount of intravenous rituximab can cross the blood-brain barrier, intrathecal or intraventricular administration may allow the addition of rituximab to this regimen.

In summary, rituximab in combination with chemotherapy has demonstrated efficacy in diverse non-DLBCL aggressive lymphomas. An important question remains as to which of the various rituximab-based treatment options best translate into extended survival for these patients. Because these disease subtypes are rare, and only small numbers of patients are affected, larger-scale studies are not feasible and clinical decisions may need to be based on Phase II studies and comparisons with historical controls. However, experience gained with rituximab suggests that results from large-scale trials generally reflect those obtained during smaller studies. Additional research is required into minimising toxicity which, though expected with intensive chemotherapy, is considerable in many of the regimens used.

Conclusions

It is clear that the clinical introduction of rituximab has markedly changed treatment paradigms in aggressive NHL. In particular, the use of rituximab has rejuvenated the first-line treatment of DLBCL. Landmark studies have firmly established the gold standard of first-line therapy as eight cycles of rituximab in combination with CHOP-like chemotherapy. Application of this gold standard across the full spectrum of patient groups has seen a dramatic increase in survival and cure rate. In addition to building on this success to further improve patient outcomes after first-line treatment, efforts can now be directed towards optimising the treatment of relapsed patients. In this context, the combination of rituximab with salvage chemotherapy regimens has already shown significant improvements in response rates, PFS and OS. Ongoing large-scale prospective studies will help define which rituximab-based regimen is most effective in second-line treatment. In non-DLBCL subtypes of aggressive lymphoma, an increasing number of studies are using rituximab-based treatment; data from patients with MCL and PMLBCL, in particular, are encouraging. An important role for rituximab-based maintenance therapy is also emerging, both in DLBCL and MCL. Further investigation is warranted to fully explore the potential of rituximab-based treatment for patients with all subtypes and stages of aggressive lymphoma.

References

1. Marcus R, Hagenbeek A. The therapeutic use of rituximab in non-Hodgkin's lymphoma. Eur J Haematol

Suppl 2007; 5–14.
2. Fisher RI, Miller TP, O'Connor OA. Diffuse aggressive lymphoma. Hematology (Am Soc Hematol Educ Program) 2004; 221–236.
3. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med 1993; 329: 987–994.
4. Sweetenham JW. Diffuse large B-cell lymphoma: risk stratification and management of relapsed disease. Hematology (Am Soc Hematol Educ Program) 2005; 252–259.
5. Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 2000; 403:503–511.
6. Rosenwald A, Wright G, Chan WC, et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. N Engl J Med 2002; 346:1937–1947.
7. Shipp MA, Ross KN, Tamayo P, et al. Diffuse large B-cell lymphoma outcome prediction by gene-expression profiling and supervised machine learning. Nat Med 2002; 8:68–74.
8. Lossos IS, Czerwinski DK, Alizadeh AA, et al. Prediction of survival in diffuse large-B-cell lymphoma based on the expression of six genes. N Engl J Med 2004; 350:1828–1837.
9. Winter JN, Weller EA, Horning SJ, et al. Prognostic significance of Bcl-6 protein expression in DLBCL treated with CHOP or R-CHOP: a prospective correlative study. Blood 2006; 107:4207–4213.
10. Mounier N, Briere J, Gisselbrecht C, et al. Rituximab plus CHOP (R-CHOP) overcomes bcl-2--associated resistance to chemotherapy in elderly patients with diffuse large B-cell lymphoma (DLBCL). Blood 2003; 101:4279–4284.
11. Wilson WH, Dunleavy K, Pittaluga S, et al. DA-EPOCH-R is highly effective in both BCL-6+ and BCL-6- untreated de novo diffuse large B-cell lymphoma (DLBCL): study update and analysis of survival outcomes for multiple biomarkers. Blood 2006; 108:Abstract 206.
12. Farinha P, Sehn L, Skinnider B, et al. Strong p53 expression is an independent predictor of outcome in de novo diffuse large B cell lymphoma (DLBCL) treated with either CHOP or CHOP-R. Blood 2006; 108:Abstract 812.
13. Sehn LH, Berry B, Chhanabhai M, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood 2007; 109:1857–1861.
14. Fisher RI, Gaynor ER, Dahlberg S, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 1993; 328:1002–1006.
15. Sonneveld P, de Ridder M, Van der LH, et al. Comparison of doxorubicin and mitoxantrone in the treatment of elderly patients with advanced diffuse non-Hodgkin's lymphoma using CHOP versus CNOP chemotherapy. J Clin Oncol 1995; 13:2530–2539.
16. Tilly H, Lepage E, Coiffier B, et al. Intensive conventional chemotherapy (ACVBP regimen) compared with standard CHOP for poor-prognosis aggressive non-Hodgkin lymphoma. Blood 2003; 102:4284–4289.
17. Coiffier B, Haioun C, Ketterer N, et al. Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: a multicenter phase II study. Blood 1998; 92:1927–1932.
18. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002; 346:235–242.
19. Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 2005; 23:4117–4126.
20. Coiffier B, et al. Long-term results of the GELA study comparing R-CHOP and CHOP chemotherapy in older patients with diffuse large B-cell lymphoma show good survival in poor-risk patients. ASCO. Chicago, IL; 2007; Abstract 8009 (30903).
21. Pfreundschuh M, Kloess M, Zeynalova S, et al. Six vs eight cycles of bi-weekly CHOP-14 with or without rituximab for elderly patients with diffuse large B-cell lymphomae (DLBCL): results of the completed RICOVER-60 trial of the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL). Blood 2006; 108:Abstract 205.
22. Delarue R, Mounier N, Haioun C, et al. Safety of prophylactic use of darbepoetin alfa in patients with diffuse large B-Cell lymphoma (DLBCL) treated with R-CHOP 14 or R-CHOP 21: preliminary results of the LNH03-6B randomized GELA study. Blood 2006; 108:Abstract 2436.
23. Pfreundschuh M, Trumper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol 2006; 7:379–391.
24. Glass B, Kloess M, Engert A, et al. Dose escalated CHOP + etoposide and repetitive autologous stem cell transplantation (MegaCHOEP) with and without rituximab for primary treatment of aggressive NHL. J Clin Oncol 2005; 23:Abstract 6654 and updates.
25. Trneny M, Belada D, Vasova I, et al. Rituximab Combination with Anthracyclin Based Chemothrapy Significantly Improved the Outcome of Young Patients with Diffuse Large B-Cell Lymphoma in Low as Well in High Risk Subgroups. Blood 2005; 106:Abstract 2444.
26. Sehn LH, Donaldson J, Chhanabhai M, et al. Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia. J Clin Oncol 2005; 23:5027–5033.
27. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med 1995; 333:1540–1545.
28. Koehne CH, Daniel P. Autologous bone marrow trans-

plantation in relapsed non-Hodgkin's lymphoma. N Engl J Med 1996; 334:990–991.
29. Atkins CD. Autologous bone marrow transplantation in relapsed non-Hodgkin's lymphoma. N Engl J Med 1996; 334:990–992.
30. De Ruysscher D, Spaas P. Autologous bone marrow transplantation in relapsed non-Hodgkin's lymphoma. N Engl J Med 1996; 334:990–992.
31. McBride JA, Pugh WC. Autologous bone marrow transplantation in relapsed non-Hodgkin's lymphoma. N Engl J Med 1996; 334:991–992.
32. Girouard C, Dufresne J, Imrie K, et al. Salvage chemotherapy with mini-BEAM for relapsed or refractory non-Hodgkin's lymphoma prior to autologous bone marrow transplantation. Ann Oncol 1997; 8:675–680.
33. Moskowitz CH, Bertino JR, Glassman JR, et al. Ifosfamide, carboplatin, and etoposide: a highly effective cytoreduction and peripheral-blood progenitor-cell mobilization regimen for transplant-eligible patients with non-Hodgkin's lymphoma. J Clin Oncol 1999; 17:3776–3785.
34. Velasquez WS, McLaughlin P, Tucker S, et al. ESHAP--an effective chemotherapy regimen in refractory and relapsing lymphoma: a 4-year follow-up study. J Clin Oncol 1994; 12:1169–1176.
35. Velasquez WS, Cabanillas F, Salvador P, et al. Effective salvage therapy for lymphoma with cisplatin in combination with high-dose Ara-C and dexamethasone (DHAP). Blood 1988; 71:117–122.
36. Kewalramani T, Zelenetz AD, Nimer SD, et al. Rituximab and ICE as second-line therapy before autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. Blood 2004; 103:3684–3688.
37. Mey UJ, Orlopp KS, Flieger D, et al. Dexamethasone, high-dose cytarabine, and cisplatin in combination with rituximab as salvage treatment for patients with relapsed or refractory aggressive non-Hodgkin's lymphoma. Cancer Invest 2006; 24:593–600.
38. Sieniawski M, Staak O, Glossmann JP, et al. Rituximab added to an intensified salvage chemotherapy program followed by autologous stem cell transplantation improved the outcome in relapsed and refractory aggressive non-Hodgkin lymphoma. Ann Hematol 2007; 86: 107–115.
39. Vellenga E, Notenboom A, van't Veer M, et al. Rituximab (Mabthera) improves the treatment results of DHAP-VIM-DHAP and ASCT in relapsed/progressive aggressive CD20+ NHL. A prospective randomized HOVON Trial. Blood 2006; 108:Abstract 328.
40. Khouri IF, Saliba RM, Hosing C, et al. Concurrent administration of high-dose rituximab before and after autologous stem-cell transplantation for relapsed aggressive B-cell non-Hodgkin's lymphomas. J Clin Oncol 2005; 23:2240–2247.
41. Hagberg H, Gisselbrecht C. Randomised phase III study of R-ICE versus R-DHAP in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL) followed by high-dose therapy and a second randomisation to maintenance treatment with rituximab or not: an update of the CORAL study. Ann Oncol 2006; 17: iv31–iv32.
42. Tarella C, Zanni M, Magni M, et al. Benefit of rituximab addition to high-dose programs with autograft for B-cell lymphoma: a multicenter GITIL survey on 957 patients. ASH Annual Meeting Abstracts 2006; 108:207.
43. Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J Clin Oncol 2006; 24:3121–3127.
44. Jaeger U. A multicentre, randomized Phase III study of rituximab as maintenance treatment versus observation in patients with aggressive B-Cell lymphoma: NHL-13. Available at: http://www.clinicaltrials.gov/ct/show/NCT00400478?order. Date accessed: 12 April 2007.
45. Haioun C, Mounier N, Emile JF, et al. Rituximab vs observation after high-dose consolidative first-line chemotherapy (HDC) with autologous stem cell transplantation in poor risk diffuse large B-cell lymphoma. Final analysis of the LNH98-B3 GELA study. ASH Annual Meeting Abstracts 2005; 106:677.
46. Ghielmini M, Schmitz SF, Cogliatti S, et al. Effect of single-agent rituximab given at the standard schedule or as prolonged treatment in patients with mantle cell lymphoma: a study of the Swiss Group for Clinical Cancer Research (SAKK). J Clin Oncol 2005; 23:705–711.
47. Forstpointner R, Unterhalt M, Dreyling M, et al. Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients with recurring and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG). Blood 2006; 108:4003–4008.
48. Kahl BS, Longo WL, Eickhoff JC, et al. Maintenance rituximab following induction chemoimmunotherapy may prolong progression-free survival in mantle cell lymphoma: a pilot study from the Wisconsin Oncology Network. Ann Oncol 2006; 17:1418–1423.
49. Mangel J, Leitch HA, Connors JM, et al. Intensive chemotherapy and autologous stem-cell transplantation plus rituximab is superior to conventional chemotherapy for newly diagnosed advanced stage mantle-cell lymphoma: a matched pair analysis. Ann Oncol 2004; 15:283–290.
50. Hicks L, Connors JM, Mangel J, et al. Autologous stem-cell transplant with a rituximab purge and maintenance vs. standard chemotherapy for mantle cell lymphoma: extended follow-up of a matched pair analysis. ASH Annual Meeting Abstracts 2006; 108:3051.
51. Witzig TE. Current treatment approaches for mantle-cell lymphoma. J Clin Oncol 2005; 23:6409–6414.
52. Dreyling M, Lenz G, Hoster E, et al. Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle-cell lymphoma: results of a prospective randomized trial of the European MCL Network. Blood 2005; 105: 2677–2684.
53. Zelenetz AD. Mantle cell lymphoma: an update on management. Ann Oncol 2006; 17(suppl 4): iv12–iv14.

54. Lenz G, Dreyling M, Hoster E, et al. Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). J Clin Oncol 2005; 23:1984–1992.
55. Forstpointner R, Dreyling M, Repp R, et al. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2004; 104: 3064–3071.
56. Herold M, Haas A, Srock S, et al. Addition of rituximab to first-line MCP (mitoxantrone, chlorambucil, prednisolone) chemotherapy prolongs survival in advanced follicular lymphoma - 4 year follow-up results of a phase III trial of the East German Study Group Hematology and Oncology (OSHO#39). Blood 2006; 108:Abstract 484 (*and updates*).
57. Romaguera JE, Fayad L, Rodriguez MA, et al. High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine. J Clin Oncol 2005; 23:7013–7023.
58. Romaguera JE, Fayad L, Rodriguez MA, et al. Blastoid Mantle Cell Lymphoma (MCL): 5-yr failure-free survival (FFS) rate of 50%, without failures after 2.5 years following treatment with rituximab (R)-hyperCVAD alternating with R-methotrexate/cytarabine (M/A). Blood 2006; 108:Abstract 2749.
59. Vose J, Loberiza FR, Bierman P, et al. Mantle cell lymphoma (MCL): induction therapy with hyper-CVAD/high-dose methotrexate and cytarabine (M-C) (±rituximab) improves results of autologous stem cell transplant in first remission. ASCO; 2006; Abstract 7511.
60. Schulz H, Bohlius J, Skoetz N, et al. Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: a systematic review and meta-analysis. J Natl Cancer Inst 2007; 99:706–714
61. Zelenetz AD, Advani RH, Buadi F, et al. NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's Lymphoma. NCCN Practice Guidelines in Oncology v2. 2006.
62. Gianni AM, Magni M, Martelli M, et al. Long-term remission in mantle cell lymphoma following high-dose sequential chemotherapy and in vivo rituximab-purged stem cell autografting (R-HDS regimen). Blood 2003; 102:749–755.
63. Dreger P, Rieger M, Seyfarth B, et al. Rituximab-augmented myeloablation for first-line autologous stem cell transplantation for mantle cell lymphoma: effects on molecular response and clinical outcome. Haematologica 2007; 92:42–49.
64. Dunleavy K, Pittaluga S, Janik J, et al. Primary mediastinal large B-cell lymphoma (PMBL) outcome may be significantly improved by the addition of rituximab to dose-adjusted (DA)-EPOCH and obviates the need for radiation: results from a prospective study of 44 patients. Blood 2006; 108:Abstract 209.
65. Martelli M, Stefoni V, Cabras G, et al. Rituximab combined with M/VACOP-B and radiotherapy in primary mediastinal large B-cell lymphoma (PMLBCL): a prospective Italian phase II IIL study. Blood 2006; 108:Abstract 4697.
66. Vassilakopoulos TP, Angelopoulou MK, Galani Z, et al. Rituximab-CHOP (R-CHOP) and radiotherapy (RT) for primary mediastinal large B-cell lymphoma (PMLBCL). Blood 2006; 108:Abstract 2745.
67. Dunleavy K, Pittaluga S, Janik J, et al. Novel treatment of Burkitt lymphoma with dose-adjusted EPOCH-Rituximab: preliminary results showing excellent outcome. Blood 2006; 108:Abstract 2736.
68. DeAngelis LM, Seiferheld W, Schold SC, et al. Combination chemotherapy and radiotherapy for primary central nervous system lymphoma: Radiation Therapy Oncology Group Study 93-10. J Clin Oncol 2002; 20:4643–4648.