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Aggressive lymphoma: improving treatment outcome with rituximab

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The standard therapy for patients with aggressive lymphoma is cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy, which achieves a complete response in more than 60% of patients but is curative in only about 40–50%. More aggressive and/or dose-intensified chemotherapy regimens have failed to provide significant survival advantages compared with CHOP, and may have higher toxicity. Rituximab, a chimeric monoclonal antibody to the CD20 antigen, is effective as monotherapy in aggressive lymphoma and in combination with chemotherapy has demonstrated high response rates in phase II trials. A scheduled interim analysis of a randomized, prospective trial comparing rituximab plus CHOP with CHOP alone in elderly patients with untreated diffuse large B-cell lymphoma has shown significantly better response rates and survival with rituximab plus CHOP compared with CHOP alone. These results represent the first significant improvement in overall survival over CHOP in aggressive lymphoma for over 20 years. The addition of rituximab was not associated with significant additional toxicity over that seen with CHOP alone. Ongoing studies are underway to establish whether the survival benefit of rituximab plus CHOP is seen in younger patient populations. Rituximab in combination with chemotherapy is also being evaluated as salvage treatment for patients who relapse after initial chemotherapy. In a preliminary analysis of a study in 50 patients with refractory or relapsed aggressive lymphoma, rituximab plus etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin (EPOCH) chemotherapy has demonstrated promising results when used as sole salvage therapy and as an induction therapy prior to autologous stem-cell transplantation, again without significant additional toxicity. [© 2002 Lippincott Williams & Wilkins.]

Key words: rituximab, aggressive lymphoma, immunochemotherapy, survival, salvage therapy.

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Introduction

The majority of patients with aggressive lymphoma are treated with anthracycline-containing regimens, of which cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) is the most widely used and is considered to be standard therapy. However, although CHOP achieves a complete response in more than 60% of patients, it is curative in only around 40–50%.[1] There is a clear need for improved treatment.

Over the past 20 years, many groups have attempted to improve the treatment outcomes obtained with CHOP by using more aggressive chemotherapy regimens, dose intensification through dose escalation and/or adding other drugs to the CHOP regimen. Third-generation chemotherapy regimens using six or eight drugs have been investigated, including low-dose methotrexate with leucovorin rescue, bleomycin, doxorubicin, cyclophosphamide, vincristine and dexamethasone (m-BACOD), prednisone, doxorubicin, cyclophosphamide and etoposide followed by cytarabine, bleomycin, vincristine and methotrexate with leucovorin rescue (ProMACE-CytaBOM), and methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin (MACOP-B). Initial pilot studies reported promising results, such as complete remission rates of 72% for m-BACOD[2] and 84% for MACOP-B.[3] However, a randomized trial comparing CHOP with m-BACOD, ProMACE-CytaBOM and MACOP-B found no statistically significant differences between the patient groups in overall survival at 3 years (Figure 1).[1] Moreover, there was a trend towards higher toxicity with the third-generation regimens; fatal toxic reactions occurred in 1% of CHOP patients compared with 3% in the ProMACE-CytaBOM group, 5% in the m-BACOD group, and 6% in the MACOP-B group ($p = 0.09$).[1]

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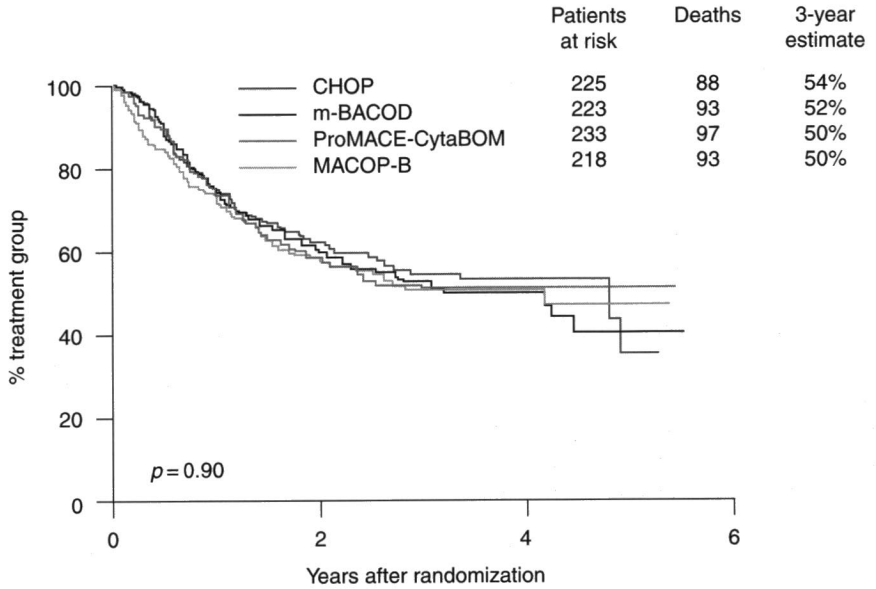

Figure 1. CHOP versus other regimens: overall survival. CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; m-BACOD, low-dose methotrexate with leucovorin rescue, bleomycin, doxorubicin, cyclophosphamide, vincristine and dexamethasone; ProMACE-CytaBOM, prednisone, doxorubicin, cyclophosphamide and etoposide followed by cytarabine, bleomycin, vincristine and methotrexate with leucovorin rescue; MACOP-B, methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin. Reproduced with permission from Fisher *et al.*[1]

Doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone (ACVBP) consists of a short intensified regimen followed by sequential consolidation therapy. A randomized study compared ACVBP with m-BACOD in patients with low-risk aggressive lymphoma, and found no statistically significant difference between the two regimens in failure-free survival or overall survival.[4] There was a significantly higher risk of pulmonary toxicity with m-BACOD, while ACVBP was associated with more severe and life-threatening infections, and the overall number of treatment-related deaths was similar between the two regimens.[4] Thus, more intensive treatment regimens have not generally succeeded in improving overall survival. Recent data suggest that increasing the dosing of CHOP to every 14 days rather than 21 days (CHOP-14), or adding etoposide (CHOEP), can be of benefit in some patients. The CHOEP regimen was found to be no more toxic than the CHOP regimen in younger, low-risk patients, and CHOP-14 no more toxic than CHOP-21 in the elderly.[5,6] However, the final analysis of these trials is pending, and CHOP has remained the gold standard of therapy in aggressive lymphoma for more than 20 years.

Prognostic factors play a major role in selecting the most appropriate treatment regimen for patients with aggressive lymphoma. Differentiating between patients who are likely to have a good or poor outcome to standard treatment allows those with the poorest prognosis to receive more aggressive treatment, while patients with a good prognosis are not subjected to unnecessary toxicity. The International Prognostic Index (IPI) was developed from a study of 2031 adults with aggressive lymphoma who were treated with doxorubicin-containing combination chemotherapy regimens.[7] Pretreatment clinical features that remained independently significant in step-down regression analyses of survival were incorporated into models that defined groups of patients with different risks of death. In the whole group of patients, five pretreatment features were found to be independently significant for prognosis. These were (1) age (60 years or younger versus older than 60 years); (2) tumor stage (localized disease versus advanced disease); (3) the number of extranodal disease sites (one or fewer versus more than one); (4) performance status (0–1 versus 2 or more); and (5) serum lactate dehydrogenase (LDH) level (up to and including normal level versus more than normal level). The number of risk factors present defines the IPI score. The IPI score identified four groups of patients with different risks of death: low risk (IPI = 0 or 1); low-intermediate risk (IPI = 2); high-intermediate risk (IPI = 3); and high risk (IPI = 4 or 5). In a subgroup of 1274 patients aged 60 years or younger, three of these risk factors remained predictive of survival: tumor stage, LDH level, and performance status. The number of these

risk factors present in a patient aged less than 60 years (0, 1, 2 or 3) defines the age-adjusted IPI score for that patient. Since its inception, the IPI has become an important consideration in the selection of patient groups for clinical trials.

Rituximab is a chimeric monoclonal antibody to the CD20 antigen. The CD20 antigen is expressed by all cells of the B-lineage, including over 95% of B-cell non-Hodgkin's lymphomas (NHLs). Rituximab monotherapy has demonstrated efficacy in a phase II study in patients with relapsing or refractory aggressive lymphoma, producing a 31% overall response rate with low toxicity.[8] Combining rituximab with chemotherapeutic agents (immunochemotherapy) represents an innovative treatment for aggressive lymphoma. As this combination does not significantly increase the toxicity of chemotherapy, immunochemotherapy can be used in patients who are either high- or low-risk according to the IPI.

Rituximab plus CHOP (R-CHOP) was first tested in phase II trial patients with indolent lymphoma to determine whether it was tolerable and safe.[9] There was no increased toxicity over that expected with CHOP; the most frequent adverse effects attributed to rituximab were fever and chills, primarily during the first infusion.[9,10] A phase II study by Vose *et al.*[10] tested the combination in patients with aggressive lymphoma and demonstrated an objective response rate of 95% and a complete response rate of 61%.

The phase II trials have led to the initiation of randomized studies comparing R-CHOP with CHOP alone in patients with aggressive lymphoma.

Rituximab in combination with chemotherapy in aggressive NHL

The Groupe d'Etude des Lymphomes d'Adulte LNH-98.5 study

Trial LNH-98.5, conducted by the Groupe d'Etude des Lymphomes d'Adulte (GELA), is a randomized, prospective clinical trial comparing R-CHOP with CHOP alone. This study involved 399 elderly patients (aged 60–80 years) with previously untreated diffuse large B-cell lymphoma (DLCL) and was undertaken at 86 centers in France, Belgium and Switzerland. Interim analysis results from this study have been presented.[11,12]

Patients were randomized to receive either R-CHOP or CHOP alone every 3 weeks for eight cycles of treatment. Treatment schedules are shown in Table 1. Of the 399 patients, 328 had been randomized before 1 January 2000; these patients were included in the scheduled interim analysis. When randomized, patients were stratified by age-adjusted IPI score into high-risk (IPI score 2–3) and low-risk (IPI score 0–1) categories. Prognostic factors were similar for patients in both treatment arms. Patients receiving R-CHOP had a significantly better response to treatment than patients receiving CHOP alone at the interim analysis, with a median of 12 months' follow-up (Table 2). R-CHOP was also associated with significantly superior event-free survival (69% compared with 49%, $p < 0.0005$) and overall survival (83% compared with 68%, $p < 0.01$) at 12 months.[12]

Table 1. Treatment schedules for the GELA LNH-98.5 study: treatment was given every 3 weeks for eight cycles

Regimen/drug	Dose	Day
CHOP		
Cyclophosphamide	750 mg/m^2	1
Doxorubicin	50 mg/m^2	1
Vincristine	1.4 mg/m^2	1
Prednisone	40 mg/m^2	× 5 days
R-CHOP		
CHOP	As above	1
Rituximab	375 mg/m^2	1

GELA, Groupe d'Etude des Lymphomes d'Adulte; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHOP, rituximab plus CHOP.

Table 2. Response to treatment in the GELA LNH-98.5 study: interim analysis with a median of 12 months' follow-up

Response	CHOP ($n = 159$)	R-CHOP ($n = 169$)
Complete response/ unconfirmed complete response	62%	76%
Partial response	6%	6%
Progressive disease	21%	9%
Death during treatment	7%	5%
Non-evaluable/other	4%	4%
P value between treatments	0.01	

GELA, Groupe d'Etude des Lymphomes d'Adulte; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHOP, rituximab plus CHOP.

The response and survival benefits observed with R-CHOP treatment were obtained without significantly increasing toxicity over that normally expected with CHOP alone. There were no major differences in safety profile between the two treatment arms.[11] An update of the interim analysis carried out after a median of 18 months' follow-up showed that this survival advantage with R-CHOP over CHOP alone was maintained (Figure 2).[13]

Sub-analyses of patients categorized as low- or high-risk according to the age-adjusted IPI were

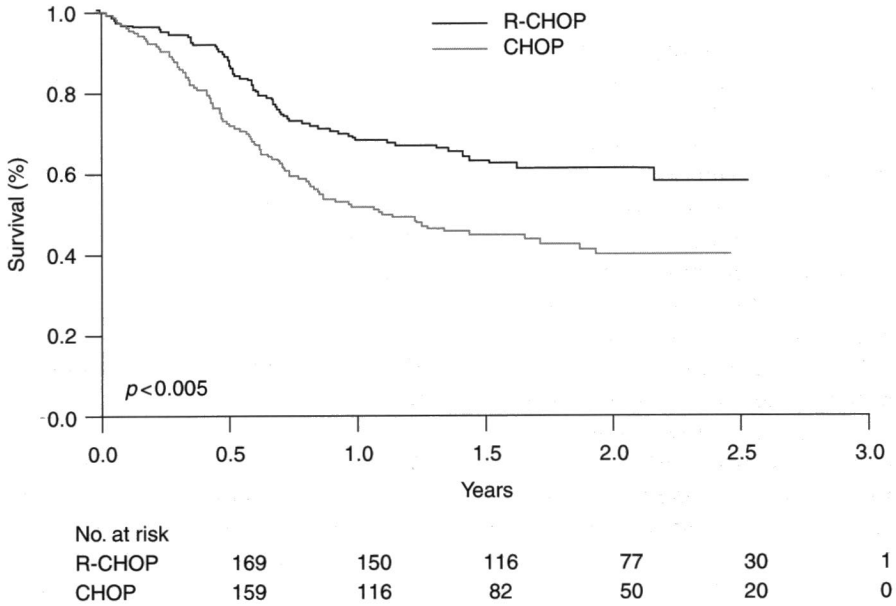

Figure 2. Overall survival in the GELA LNH-98.5 study: interim analysis with a median of 18 months' follow-up. GELA, Groupe d'Etude des Lymphomes d'Adulte; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHOP, rituximab plus CHOP.

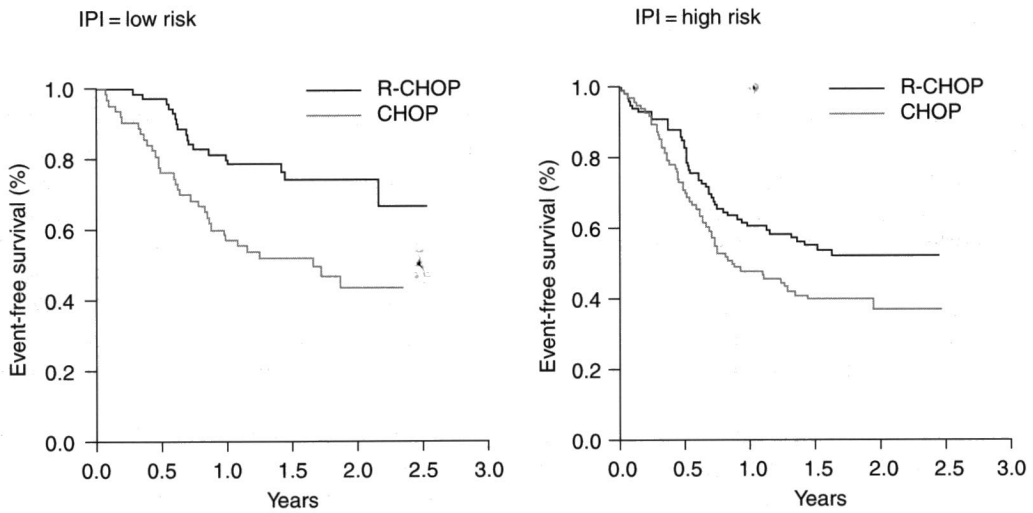

Figure 3. Event-free survival in the GELA LNH-98.5 study stratified by International Prognostic Index (IPI): interim analysis with a median of 18 months' follow-up. Patients were stratified by IPI before randomization. GELA, Groupe d'Etude des Lymphomes d'Adulte; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHOP, rituximab plus CHOP.

conducted after a median of 18 months' follow-up. These showed that R-CHOP prolonged event-free survival compared with CHOP in both groups of patients (Figure 3).

The median follow-up in the GELA LNH-98.5 study is now approaching 2 years, and the survival data continue to support the excellent results described above. This study reports the first improvement in overall survival for any regimen compared with CHOP in aggressive lymphoma in more than 20 years, suggesting that R-CHOP might become the new gold-standard treatment for aggressive lymphoma.

The optimal timing of rituximab administration in relation to CHOP chemotherapy has yet to be determined. There are three options for administering rituximab (1) interspersed throughout

chemotherapy treatment; (2) 2 days before each cycle; or (3) on the same day as the chemotherapy. *In vitro* evidence suggests that administration of rituximab before or together with chemotherapy may maximize its effectiveness. Pretreatment with rituximab can render previously resistant cell lines sensitive to cytotoxic drugs,[14] an effect which appears to be mediated by downregulation of the *Bcl-2* gene.[15] Concurrent administration of rituximab has been shown to increase the sensitivity of B-lymphoma cell lines to the cytotoxic effects of doxorubicin.[16]

In the LNH-98.5 GELA study, rituximab was administered on the same day as CHOP chemotherapy.[11] Other studies have used different regimens,[9,10] although the GELA study has a more convenient administration regimen and proven safety profile compared with the two phase II studies.

The MabThera International Trial

The GELA LNH-98.5. study has shown a survival benefit for R-CHOP in elderly patients with DLCL. The MabThera International Trial (MInT) is an ongoing study with the objective of determining whether the clinical benefits of R-CHOP observed in elderly patients in the GELA LNH-98.5 study can be replicated in a population of younger patients with good prognosis. MInT is an open-label, multicenter, randomized trial, comparing rituximab plus CHOP-like chemotherapy with CHOP-like chemotherapy alone in patients with DLCL.

The MInT trial was initiated in March 2000, and it is planned that 820 patients will be randomized within 3 years. Patients are eligible for inclusion if they have $CD20^+$ DLCL, are aged between 18 and 60 years, have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–3, have stages II–IV or stage I bulky disease, with an IPI score of 0–1. Low- and intermediate low-risk (age-adjusted IPI scores of 0–1) patients are being recruited to investigate whether immunochemotherapy can offer a clinical benefit over standard chemotherapy even in patients with low-risk IPI and a correspondingly good prognosis.

All centers in the MInT trial use CHOP-like chemotherapy, but the exact regimens vary in the different countries. CHOP and CHOEP are the most commonly used. Other regimens include MACOP-B and prednisolone, mitoxantrone, cyclophosphamide, etoposide, bleomycin and vincristine (PMitCEBO). All patients will receive six cycles of chemotherapy. Patients randomized to the rituximab plus CHOP-like chemotherapy arm will also receive six cycles of rituximab (375 mg/m^2), administered every 3 weeks.

The primary endpoint of the MInT study is the time to treatment failure. Secondary endpoints include complete response rate, survival, tumor control, disease-free survival and progression rate.

Early data from this study should be available by the end of 2003 and are eagerly awaited to show whether the clinical benefits of rituximab plus CHOP-like chemotherapy are also applicable to a younger patient population.

Rituximab in salvage regimens for aggressive lymphoma

Although CHOP chemotherapy can be curative in aggressive lymphoma, a high proportion of patients either do not achieve a complete response or later develop recurrent disease, and the outlook for these patients is generally poor.[17] Durable responses to further chemotherapy are rare, and so younger patients with relapsed aggressive lymphoma are normally considered for high-dose chemotherapy with autologous stem-cell transplantation (ASCT). A high proportion of patients are not eligible for this aggressive therapy for reasons such as age, the presence of other concomitant diseases, or the failure of induction therapy. Thus, there is an urgent need for effective salvage therapy for patients with relapsed or refractory aggressive lymphoma who are not suitable for ASCT.

The chemotherapy regimen EPOCH has been studied as salvage therapy in relapsed and refractory aggressive NHL, and complete response rates of 24–27% and partial response rates of 50–60% have been reported.[17,18] However, EPOCH does not appear to be curative in the majority of patients; in the study by Gutierrez *et al.*,[18] Kaplan–Meier survival curves showed that at 36 months 41% of the patients were alive and 15% were event-free.

Rituximab monotherapy has demonstrated efficacy in a phase II trial in 54 patients with untreated, relapsed or refractory aggressive lymphoma, in which the overall response rate was 31%.[8] Building on these promising results, a recent phase II study has evaluated rituximab in combination with EPOCH chemotherapy in patients with relapsed or refractory aggressive lymphoma. Preliminary results have been presented,[19] and are summarized below. A total of 50 patients were recruited: 25 had DLCL, 18 had transformed B-cell lymphoma, and seven had mantle cell lymphoma (MCL). The median patient age was 56 years (range 32–72 years) and the average number of previous chemotherapy treatments was 1.7 (range 1–7). Five patients (10%) had previously failed high-dose chemotherapy with stem-cell transplantation.

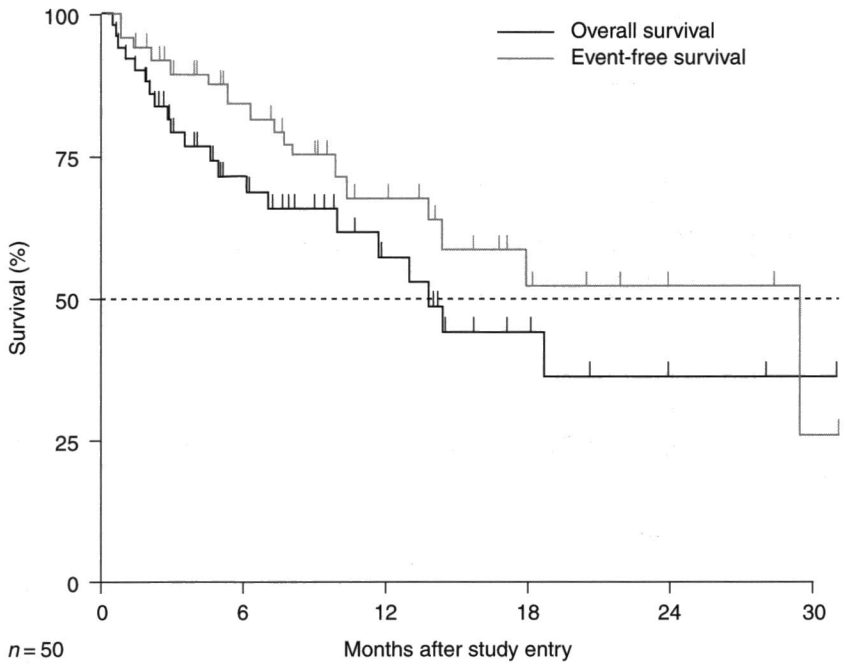

Figure 4. Rituximab plus EPOCH: overall and event-free survival.

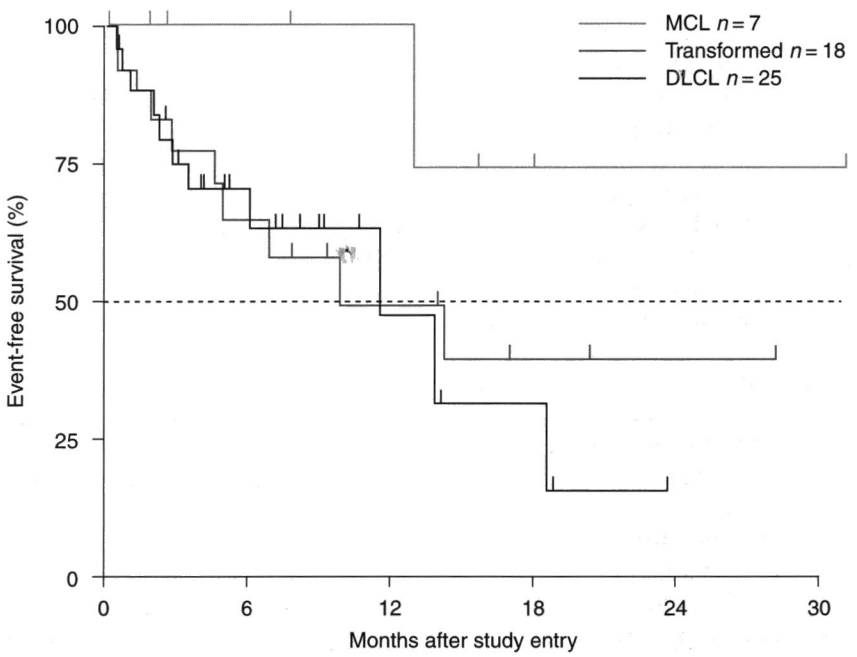

Figure 5. Rituximab plus EPOCH: event-free survival by tumor type. MCL, mantle cell lymphoma; DLCL, diffuse large B-cell lymphoma.

Rituximab (375 mg/m^2) was given on the first day of each EPOCH chemotherapy cycle. The planned number of treatment cycles was four to six; patients with normal echocardiography after four cycles and who had previously received doxorubicin doses of less than 300 mg/m^2 could receive up to six cycles of treatment.

Patients aged less than 60 years were offered high-dose chemotherapy and ASCT if a complete or partial response was achieved after three cycles of rituximab-EPOCH. The study thus evaluated rituximab-EPOCH as salvage therapy prior to stem-cell harvest in these patients, and as a sole salvage therapy in the remaining patients.

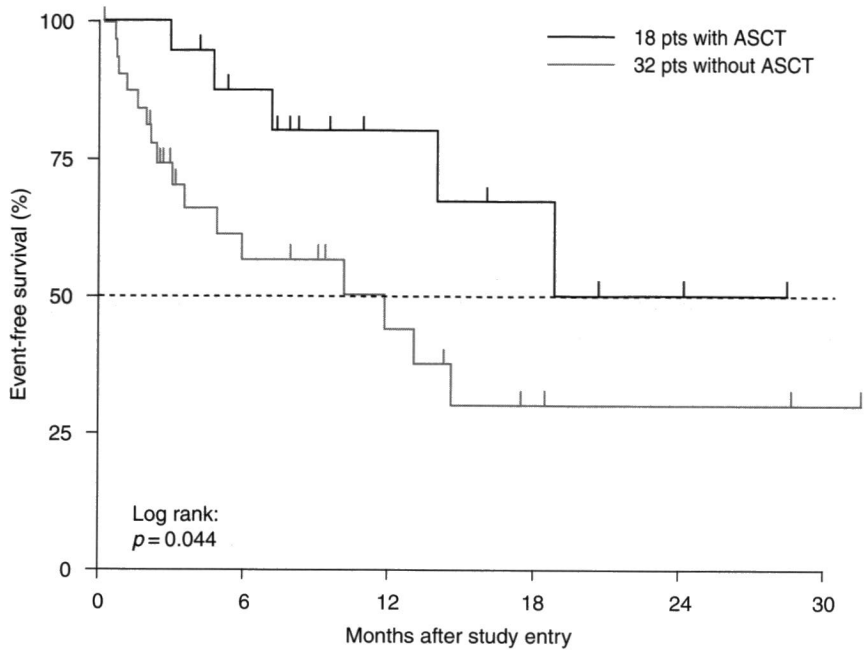

Figure 6. Rituximab plus EPOCH: event-free survival in patients treated with or without autologous stem-cell transplantation (ASCT).

A preliminary analysis of the data from this study has been presented.[19] An objective response was achieved in 32 patients (64%), with a complete response in 26% and a partial response in 38%. Overall and event-free survival are shown in Figure 4; the median overall survival was 29.3 months, and the median event-free survival was 13.8 months. Overall survival was 68% at 1 year and 52% at 2 years, with event-free survival of 57% at 1 year and 36% at 2 years.

Sub-analysis of the different histologic groups indicated that patients with MCL had a longer event-free survival than patients with either DLCL or transformed B-cell lymphoma (Figure 5).

Stem-cell harvests were successfully performed in 18 of the 27 eligible patients (67%). Patients who received rituximab-EPOCH and then went on to ASCT ($n = 18$) had significantly longer event-free survival than those patients who did not receive ASCT ($n = 32$) and who therefore received rituximab-EPOCH as the sole salvage therapy (Figure 6).

The tolerability profile of rituximab-EPOCH was similar to that experienced with EPOCH alone. Unplanned hospitalizations were required in 7% of cycles, grade 4 neutropenia occurred in 56% of patients, there were two treatment-related deaths, and three patients developed secondary myelodysplasia. There was no severe organ toxicity.

The results of this preliminary analysis indicate that rituximab-EPOCH is effective and well tolerated in patients with relapsed and refractory aggressive lymphoma, even in heavily pretreated patients and those with relapsed MCL. The regimen is also an effective induction therapy for relapsed patients prior to undergoing stem-cell transplantation.

Discussion

Immunochemotherapy, using rituximab in combination with chemotherapy regimens, represents a new era of therapy for aggressive lymphoma. Increasing evidence indicates that the addition of rituximab to chemotherapy can significantly enhance both response rates and survival. In particular, a prospective randomized trial has shown that R-CHOP confers a significant survival benefit over CHOP alone in elderly patients with aggressive DLCL, irrespective of their IPI score. This is the first improvement in overall survival over CHOP in aggressive lymphoma in over 20 years.

The improvement in response rate and survival observed with R-CHOP over CHOP alone was achieved with no significant additional toxicity over that expected with the CHOP regimen, an important consideration in successful treatment. Further studies, such as the MInT trial, are now ongoing to establish whether the improvements are reproduced in other patient populations, including young patients with a good prognosis.

The survival benefit of combining rituximab with other chemotherapy regimens and/or ASCT as salvage therapy for patients with relapsed or refractory aggressive lymphoma is also being evaluated. So far, the preliminary results are promising, and again the addition of rituximab has not resulted in significant additional toxicity.

The use of rituximab combined with chemotherapy thus looks likely to provide the clinician with a means of enhancing the treatment outcome with chemotherapy regimens without increasing toxicity. The issue of the most effective schedule for combining rituximab with chemotherapy remains to be resolved, and requires further study.

Patient expectations increasingly demand a better treatment outcome with fewer adverse events. As the treatment of aggressive lymphoma enters a new and promising phase, evidence so far suggests that immunochemotherapy with rituximab may help to meet these expectations, and offers clinicians a regimen that can achieve a significantly superior treatment outcome in aggressive lymphoma.

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