Original article

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Rituximab–EPOCH, an effective salvage therapy for relapsed, refractory or transformed B-cell lymphomas: results of a phase II study

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Background: Relapsed or refractory diffuse large B-cell and mantle-cell lymphoma have a poor prognosis. The EPOCH regimen and rituximab monotherapy have demonstrated activity as salvage therapies. Because of their non-overlapping toxicity, we evaluated their combination as salvage therapy in a phase II study.

Patients and methods: Patients with relapsed or refractory CD20-positive large B-cell and mantle-cell lymphoma were offered treatment with rituximab 375 mg/m^2 intravenously (i.v.) on day 1, doxorubicin 15 mg/m^2 as a continuous i.v. infusion on days 2–4, etoposide 65 mg/m^2 as a continuous i.v. infusion on days 2–4, vincristine 0.5 mg as a continuous i.v. infusion on days 2–4, cyclophosphamide 750 mg/m^2 i.v. on day 5 and prednisone 60 mg/m^2 orally on days 1–14.

Results: Fifty patients, with a median age of 56 years (range 23–72), entered the study. Twenty-five had primary diffuse large B-cell lymphoma, 18 transformed large B-cell lymphoma and seven mantle-cell lymphoma. The median number of prior chemotherapy regimens was 1.7 (range one to four). The median number of treatment cycles was four (range one to six). Possible treatment-related death occurred in two patients. Objective responses were obtained in 68% of patients (28% complete responses, 40% partial responses). Nineteen patients received consolidating high-dose chemotherapy with autologous stem-cell transplantation. The median follow-up was 33 months. Three patients developed a secondary myelodysplastic syndrome. The median overall survival was 17.9 months; the projected overall survival at 1, 2 and 3 years was 66, 42 and 35%, respectively. The median event-free survival was 11.8 months; the projected event-free survival at 1, 2 and 3 years was 50, 30 and 26%, respectively.

Conclusion: The rituximab–EPOCH regimen is effective and well tolerated, even in extensively pretreated patients with relapsed or refractory large B-cell lymphoma and mantle-cell lymphoma.

Key words: autologous stem-cell transplantation, EPOCH, high-dose chemotherapy, refractory aggressive B-cell non-Hodgkin's lymphoma, relapsed aggressive B-cell non-Hodgkin's lymphoma, rituximab, salvage chemotherapy

Introduction

Relapsed or refractory diffuse large B-cell lymphoma and mantle-cell lymphoma have a poor prognosis, with a long-term survival <15% at 5 years when treated with conventional chemotherapy [1]. High-dose chemotherapy improves the prognosis, but is not feasible in a considerable number of patients due to either advanced age, co-morbidities or lack of response to regimens used for remission induction [2, 3]. The EPOCH regimen and rituximab monotherapy have proven activity as salvage regimens, but they rarely provide long-lasting remissions when used as a single modality [4–6]. Since the majority of our patients had previously been treated with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy, we chose the EPOCH regimen, in which doxorubicin is administered as a continuous infusion over 72 h, thereby reducing the risk of cardiotoxicity [7–10]. Furthermore, the experimental finding that MDR-1-mediated resistance in tumor cells can be overcome by continuous exposure at low drug concentrations rather than by a short exposure at higher concentrations supports the continuous drug application [11].

Because of the non-overlapping toxicity of rituximab and chemotherapy, we evaluated the combination of rituximab and EPOCH chemotherapy as salvage therapy for CD20-positive large B-cell and mantle-cell lymphoma in a phase II study.

Patients and methods

Patient selection

Eligible patients had to have histologically confirmed relapsed or refractory diffuse large B-cell or mantle-cell lymphoma with positive CD20 immuno-

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histochemistry, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, age 16–75 years, adequate bone marrow, hepatic and renal function, a life expectancy of >3 months, and a normal cardiac ejection fraction. Exclusion criteria were: a cumulative dose of doxorubicin received >400 mg/m^2, a history of gastrointestinal bleeding, gastroduodenal ulcers, uncontrolled infections, HIV infection, viral hepatitis, immunosuppression, previous chemotherapy for other tumors, pregnancy or breast feeding. Written informed consent was required. The study was carried out with ethics committee approval.

Treatment plan

Patients received rituximab 375 mg/m^2 intravenously (i.v.) on day 1, doxorubicin 15 mg/m^2 as a continuous i.v. infusion on days 2–4, etoposide 65 mg/m^2 as a continuous i.v. infusion on days 2–4, vincristine 0.5 mg as a continuous i.v. infusion on days 2–4, cyclophosphamide 750 mg/m^2 i.v. on day 5 and prednisone 60 mg/m^2 orally on days 1–14. The infusional part of the EPOCH regimen was shortened by 1 day while maintaining the original cumulative dose of etoposide, vincristine and doxorubicin [4] in order to allow for a 5-day in-patient stay. The rituximab–EPOCH regimen was given for four to six cycles every 21 days. Patients with normal echocardiography after four cycles and <300 mg/m^2 of doxorubicin prior to study entry were allowed to receive up to six cycles of rituximab–EPOCH if they were not candidates for high-dose chemotherapy. Patients <60 years old who had not received high-dose chemotherapy prior to study entry were offered to undergo stem-cell collection and high-dose chemotherapy with autologous stem-cell transplantation if at least a partial response was achieved after three cycles of rituximab–EPOCH salvage therapy. In those patients the fourth cycle was used for stem-cell mobilization. Safety evaluation consisting of a physical examination and full blood cell counts were performed weekly; routine chemical values were measured prior to each cycle.

Criteria for response and toxicity evaluation

Computer tomography scans were required within 3 weeks of registration and assessment was repeated after cycle 2 and 4, at the end of treatment, and every 3 months until disease progression. Response was evaluated by bidimensional measurements of lesions according to WHO criteria. After progression, patients were followed to determine overall survival. ECOG criteria were used to define PS. Toxicity was evaluated according to the National Cancer Institute (NCI) criteria [12].

Statistical analysis

Event-free survival was calculated from the date of study entry to the last control, progression or relapse, or death due to any reason. Overall survival was measured from study entry to the date of the last control or death. Projected survival was calculated using the Kaplan–Meier method.

Table 1. Patient characteristics

Characteristic	*n*
Number of patients	50
Males/females	30/20
Age (years) [median (range)]	56 (32–72)
Histological findings	
Diffuse large B-cell lymphoma	25
Transformed B-cell lymphoma[a]	18
Mantle-cell lymphoma	7
Stage	
II	6
III	10
IV	34
International Prognostic Index[b]	
Low	8
Low/intermediate	13
High/intermediate	18
High	11
B-symptoms	20
Elevated lactate dehydrogenase	36
Median (range) time from diagnosis to study participation (months)	14 (2–173)
Response to the first-line chemotherapy	
Complete remission	17
Partial remission	19
Stable disease	5
Progressive disease	9
Previous treatment	
Radiotherapy	19
Average No. (range) prior chemotherapy lines	1.7 (1–4)
1 regimen	26
≥2 regimens	24
Rituximab	8
High-dose chemotherapy	5

[a]Initial histology was follicular lymphoma in 14 and composite lymphoma in four patients.
[b]At the time of study entry.

Results

Patient characteristics

In this phase II study, 50 patients were enrolled at five centers in Switzerland between July 1998 and February 2001. Table 1 shows the characteristics of the 50 patients. Forty-seven of 50 patients had previously been treated with anthracyclines: 43 with CHOP or a variation of CHOP, and four with VACOP-B chemotherapy. The median dose of prior doxorubicin in these patients was 300 mg/m^2 (range 50–400).

Response and survival data

A total of 181 chemotherapy cycles of rituximab–EPOCH were given to the 50 patients (median four, range one to six). Response evaluation was possible in 47 patients. Fourteen patients (28%) achieved a complete remission and 20 patients (40%) a partial remission, thus an objective response was obtained in 68% of patients. The median follow-up time was 33 months. The median event-free survival was 11.8 months and the median overall survival was 17.9 months (Figure 1). Event-free survival was more favorable among patients with a low or low-intermediate

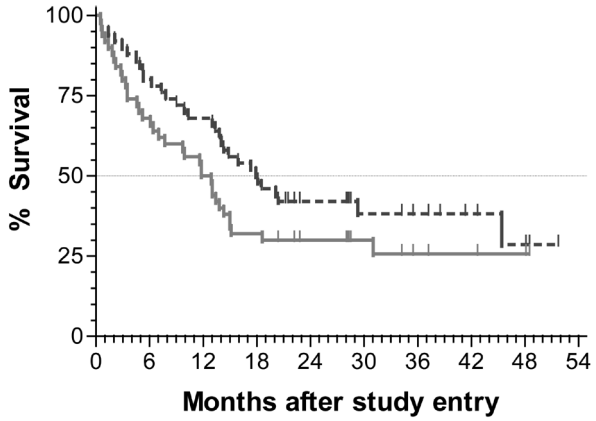

Figure 1. Event-free (solid line) and overall (dashed line) survival among 50 patients assigned to chemotherapy with rituximab–EPOCH.

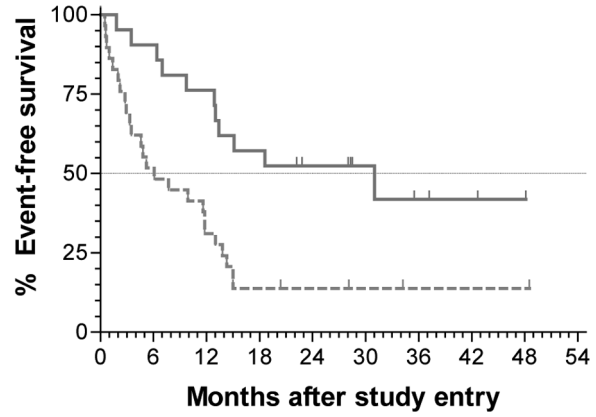

Figure 2. Event-free survival among 50 patients after therapy with rituximab–EPOCH according to the International Prognostic Index. Twenty-one patients with low (eight patients) or low-intermediate (13 patients) risk (solid line) versus 29 patients with high-intermediate (11 patients) or high (18 patients) risk (dashed line) (log-rank test $P = 0.0017$).

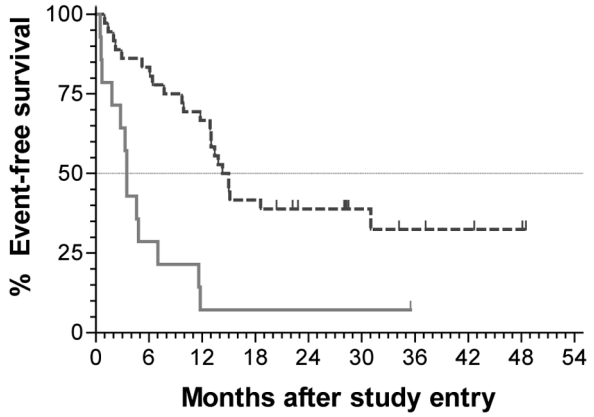

Figure 3. Event-free survival among 50 patients after therapy with rituximab–EPOCH according to the response to the first-line chemotherapy: 36 responders (dashed line) and 14 non-responders (solid line) (log-rank test $P = 0.0017$).

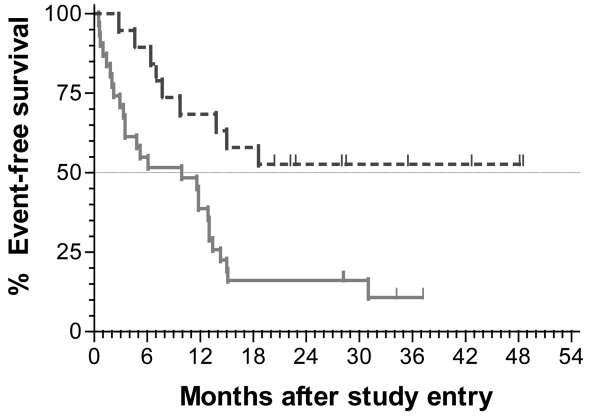

Figure 4. Event-free survival among 19 patients with (dashed line) and 31 patients without (solid line) autologous stem-cell transplantation after therapy with rituximab–EPOCH (log-rank test $P = 0.0025$).

International Prognostic Index (IPI) compared with the intermediate-high or high group ($P = 0.0017$) (Figure 2). Event-free survival according to histology showed only minor differences. The median event-free survival was 15 months in mantle-cell lymphoma patients ($n = 7$), 12.4 months in transformed B-cell lymphoma patients ($n = 18$) and 9.7 months in diffuse large B-cell lymphoma patients ($n = 25$). The 14 patients who did not respond to first-line chemotherapy (five stable disease, nine progressive disease) also had a worse prognosis after the rituximab–EPOCH chemotherapy. The median event-free survival for those patients was 4 versus 15 months for the responders and the median overall survival was 8 and 29 months, respectively ($P < 0.001$) (Figure 3).

Nineteen out of 31 patients <60 years old without prior high-dose chemotherapy achieved a sufficient response to rituximab–EPOCH chemotherapy and underwent high-dose chemotherapy with autologous stem-cell support (61.3%). As might be expected, patients able to undergo high-dose chemotherapy had a better event-free survival as compared with the others (median event-free survival not reached versus 9.9 months; 2-year event-free survival 53% versus 16%, $P = 0.0025$) (Figure 4).

Toxicity

Infusion-related reactions (fever, chills, bronchospasm) occurred in 14 of 50 patients (28%), mainly during the first infusion of rituximab. Despite this, a dose reduction of rituximab was not necessary. Febrile neutropenia leading to hospitalization occurred in 13 of 181 cycles (7%). In eight patients a bacterial infection could be identified. One patient had a herpes zoster infection. Grade 3 or 4 anemia was observed in 15 of 181 cycles, and grade 3 or 4 thrombocytopenia in two of 151 cycles.

Two patients died a sudden death. A 66-year-old woman with stage IVA disease died of an unknown cause at home after the first chemotherapy cycle. A 70-year-old woman with stage IVB disease died 8 days after the fourth chemotherapy cycle after the onset of diarrhea. An autopsy was performed in the latter patient,

Table 2. Adverse events

Adverse event	*n*
Infusion-related reactions [*n* (%)]	14/50 (28)
Unplanned hospitalizations [*n* (%)]	13/18 (17)
Bacterial infections/herpes zoster	8/1
Neutrophil toxicity WHO grade (out of 181 cycles)	
II	4
III	6
IV	28
Platelet toxicity WHO grade (out of 181 cycles)	
II	5
III	1
IV	1
Hemoglobin toxicity WHO grade (out of 181 cycles)	
II	19
III	14
IV	1
Neurotoxicity WHO grade II	7
Secondary myelodysplastic syndrome	3
Possible treatment-related death	2
Probable treatment-independent death	1

but no obvious reason for death was discovered. A probably independent cerebral hemorrhage occurred in a 44-year-old man with stage IVB disease after the first chemotherapy cycle. The platelet count was normal at the time of hemorrhage. The main toxicities are listed in Table 2.

Two patients had signs of a secondary myelodysplastic syndrome at study entry, as judged by dysmorphorphic changes in all three lineages, and one patient after three cycles of treatment. Two patients had received two lines and one had received four lines of previous chemotherapy. All patients responded to the treatment, but two died of consequences of bone marrow failure and secondary leukemia, 10 and 14 months after study entry, and one of progressive disease.

Discussion

The EPOCH regimen for relapsed non-Hodgkin's lymphoma was based on the rationale that the continuous i.v. application of etoposide, vincristine and doxorubicin might be of advantage to overcome multidrug resistance associated with the overexpression of MDR-1 and its product *p*-glycoprotein [11]. The first report of results of an EPOCH study was based on 74 patients treated at the NCI for relapsed or refractory lymphoma after conventional i.v. therapy [6]. The overall response rate was 87%, with complete responses mostly restricted to the subgroup of patients with prior complete responses. The 1-year event-free survival was 28%. The regimen was well tolerated, with the major toxicity being hematological, with a 17% incidence of febrile neutropenia. An 8-year follow-up of 131 patients by Gutierrez et al. [5] demonstrated a response rate of 74%, a 3-year event-free survival of 15% and a 3-year overall survival of 41%. Again, hospitalization for neutropenia occurred in 18% of cycles. A multicenter study from the Baylor–Charles A. Sammons Cancer Center involving 93 patients reported a response rate of 57%, with a 3-year event-free survival of 7% and a 3-year overall survival of 19% [13]. The activity of the EPOCH regimen has since been confirmed by several other smaller studies [14, 15]. The cisplatin-based ESHAP regimen is another widely used regimen for refractory or relapsed lymphoma. The results reported are similar; however, its toxicity profile with regard to renal and hematological side effects is much less favorable than that of the EPOCH regimen [16], which might have the potential to preclude some patients from subsequent high-dose chemotherapy and is associated with a poorer quality of life.

Rituximab has single-agent activity in refractory and relapsed B-cell lymphoma. The first report from Coiffier et al. [4] on 55 patients demonstrated an overall response rate of 31%, including 37 and 33%, respectively, for large B-cell and mantle-cell lymphoma. Duration of response exceeded 3 months. These results have recently been confirmed in patients with large B-cell and mantle-cell lymphoma relapsing after high-dose chemotherapy and autologous stem-cell transplantation [17]. The median time to relapse was 10 months in that study.

Our phase II trial evaluated the safety and efficacy of rituximab in combination with EPOCH chemotherapy in patients with relapsed or refractory diffuse large-cell or mantle-cell lymphoma. The rituximab–EPOCH regimen was found to be effective and well tolerated, even in extensively pretreated patients. A response rate of 68% was achieved. With a median follow-up of 33 months, median overall survival was 17.9 months and median event-free survival was 11.8 months. The projected 3-year event-free survival was 26%, and the projected 3-year overall survival was 35%. The regimen was well tolerated, the major toxicity being hematological, leading to hospitalization for fever and neutropenia in 7% of the treatment cycles. Two patients died a sudden death and three patients developed a secondary myelodysplastic syndrome.

The feasibility of combining rituximab with EPOCH has also been reported by another group [18]. In their study, 24 patients with untreated and 15 patients with relapsed or refractory lymphomas of different histologies were treated. In contrast to our study, hospitalization for febrile neutropenia occurred in 20% of treatment cycles.

How do our results compare with EPOCH alone? In the absence of randomized studies we had to compare our results with those from the two large published studies mentioned above [5, 13]. There does not appear to be a difference in the overall response rates or complete response rates. The overall response rate in our study is within the range of 57 to 74%, as published in studies with EPOCH alone. The median event-free survival in our study was 12 months, compared with 7 and 4 months in the studies with EPOCH alone [5, 13]. The median 3-year event-free survival in our study was 26%, compared with 15 and 7% in the studies with EPOCH alone [5, 13]. Thus rituximab–EPOCH chemotherapy appears to offer a benefit over EPOCH alone in relapsed or refractory large B-cell and mantle-cell lymphoma. It is unlikely that the benefit could be entirely explained by the fact that 38% of patients

in our study underwent subsequent high-dose chemotherapy and autologous stem-cell transplantation. High-dose chemotherapy with autologous hematopoietic stem-cell transplantation does improve the outcome in patients with relapsed or refractory aggressive non-Hodgkin's lymphoma [2], but only to a small degree, and a considerable number of patients in the two studies using EPOCH chemotherapy alone also received treatment intensification. One fact that has to be considered, however, is the eligibility bias in our study for patients with CD20 expression.

A major difficulty in comparing overall survival data regards the inclusion of ~25% of patients with low-grade lymphoma in the two reports of EPOCH chemotherapy alone [5, 6]. However, neither of these could identify histology as a prognostic factor for survival. Poor prognostic factors identified in our study were lack of response to first-line chemotherapy and high-intermediate/high IPI. Achieving a response to first-line chemotherapy appears to be a good prognostic factor [1, 19].

While it is obvious that patients <60 years of age eligible for subsequent high-dose chemotherapy with autologous stem-cell transplantation have a better outcome than the remainder of the patients, it remains of note that a long-term benefit with rituximab–EPOCH was also seen in the absence of high-dose consolidation. The 2-year event-free survival in this subgroup of patients was 16%.

Our study was restricted to patients who had received a cumulative dose of doxorubicin of ≤ 300 mg/m^2. This might have been an overly cautious selection of patients, since infusional doxorubicin is associated with a low cardiac toxicity [5]. Given the potential benefit of the treatment strategy used in our study, patients who have received larger cumulative doses of doxorubicin might also be considered for rituximab and EPOCH under appropriate cardiac monitoring

Based on Coiffier et al.'s [20] initial report of the combination of rituximab and CHOP and the prospectively randomized study of CHOP with or without rituximab as first-line therapy for large B-cell lymphoma in patients aged 60–80 years, there is currently an increasing trend towards using rituximab in first-line chemotherapy for aggressive non-Hodgkin's lymphoma [21, 22]. However, this is unlikely to influence the use of rituximab in combination for patients with relapsed or refractory disease. In follicular lymphoma, retreatment with rituximab has proven to be save and effective [23].

Our study demonstrated the combination of rituximab–EPOCH chemotherapy to be well tolerated and effective for patients with relapsed and refractory large B-cell and mantle-cell lymphoma. It suggests this regimen to be superior in event-free survival compared with EPOCH chemotherapy alone, with the potential bias that the regimen is only applicable to CD20-positive tumors. The high activity of this regimen suggests that drug resistance in aggressive lymphoma might not be drug specific *per se*, but could be due to an increase of the apoptotic threshold of tumor cells, which could, at least in part, be overcome by pretreatment with rituximab.

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