

Treatment of Diffuse Large B-cell Lymphoma in Elderly Patients; Replacing Doxorubicin with either Epirubicin or Etoposide (VP-16)

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Abstract

Diffuse large B-cell lymphoma (DLBCL) is the most common type of lymphoma. The standard therapy for DLBCL is R-CHOP. The current 5-year overall survival (OS) is 60-70% using standard frontline therapy. However, the use of doxorubicin and its cardiotoxicity is a major clinical problem and pre-existing cardiac disease may prevent the use of doxorubicin. Age greater than 65 years is a significant risk factor for anthracycline-induced cardiotoxicity and therefore the use of R-CHOP is often withheld from elderly patients. The feasibility of replacing doxorubicin with either epirubicin or etoposide in patients who have risk factors for heart complications is analysed here.

Clinical data of 223 DLBCL patients was retrospectively collected from hospital records. Fifty-five patients were treated with R-CHOP, 105 with R-CIOP (epirubicin instead of doxorubicin), 17 with R-CEOP (etoposide instead of doxorubicin) and 31 with R-CHOEP. Matched-pair analysis was carried out between 30 patients treated with R-CEOP and R-CHOP. For all patients, the 2-year PFS was 73.6 %. In patients treated with R-CHOP, the 2-year PFS was 84.2 %, with R-CIOP 64.4 %, with R-CEOP 87.7 % and with R-CHOEP 83.2

%. In matched-pair analysis, the 2-year PFS was 92.3 % with R-CHOP and 86.2 % with R-CEOP. The 2-year DSS was 100 % with R-CHOP and 86.2 % with R-CEOP.

In conclusion, R-CEOP offers reasonable PFS and DSS in the treatment of DLBCL and good disease control can be achieved in elderly patients. Elderly patients with impaired cardiac function could benefit from the use of R-CEOP instead of R-CHOP. The results with R-CIOP were unsatisfactory and we do not recommend using this protocol in elderly patients with cardiac disease.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma accounting for 30–40% of all new cases.^{1,2} The standard therapy for DLBCL is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) immunochemotherapy³. The use of rituximab has significantly improved the prognosis of DLBCL⁴ and the improved results with rituximab have also been shown in elderly patients.³ The current 5-year overall survival (OS) is 60-70% using standard frontline therapy.² However, the use of doxorubicin is an important clinical problem due to its cardiotoxicity.⁵

Approximately 50% of all DLBCL patients are aged between 60 and 85 years.⁶ Many patients in this age group have several comorbidities. Pre-existing cardiac disease may prevent the use of doxorubicin, which has an integral impact on the efficacy of R-CHOP therapy.⁷ Age over 65 years is also a significant risk factor for anthracycline-induced cardiotoxicity⁸ and therefore the use of R-CHOP is often withheld from elderly patients.⁷ There is no standard therapy protocol for this group of patients.^{9,10} A common way to solve this problem

has been to treat these patients with alternative regimens such as R-CVP, R-mini-CHOP or R-bendamustine, which have all shown unsatisfactory results in DLBCL.^{11,12}

Etoposide (VP-16) is an active agent in lymphomas and the efficiency of etoposide was investigated in the pre-rituximab era in particular.¹³ Epirubicin is an anthracycline that is less cardiotoxic compared to doxorubicin.¹⁴ In Oulu University Hospital between 2001–2015, doxorubicin was replaced with epirubicin (R-CIOP) in some elderly patients as a less cardiotoxic regimen. Since 2007, in Oulu University Hospital anthracyclines have been replaced with etoposide in lymphoma patients who have contraindications to anthracyclines. In this study we analysed the feasibility of these regimens.

Methods

Data from patients diagnosed in 2001–2015 was retrospectively collected from records at Oulu University Hospital. We gathered 234 patients in total. After excluding patients who did not receive R-CHOP, R-CIOP (rituximab, cyclophosphamide, epirubicin, vincristine, prednisone), R-CEOP (rituximab, cyclophosphamide, etoposide, vincristine, prednisone) or R-CHOEP (rituximab, cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone) 208 patients were available for analysis. Clinical information such as age, stage, CG phenotype, IPI, details of treatment, possible relapse and the current status was recorded. Staging included clinical examination, clinical history, blood tests, whole body CT scanning, bone marrow biopsy and aspirate. Data from matched-pair analysis was collected from Kuopio and Oulu University Hospitals from patients treated in 2003–2009.¹⁵ This study was approved by the Ethical committee of North Ostrobothnia's hospital district.

The following treatment protocols were administered. R-CHOP: rituximab 375 mg/m² day 1, cyclophosphamide 750 mg/m² day 1, doxorubicin 50 mg/m² day 1, vincristine 1.4 mg/m² day 1, prednisone 100 mg days 1–5. R-CIOP: rituximab 375 mg/m² day 1, cyclophosphamide 750 mg/m² day 1, epirubicin 60 mg/m² day 1, vincristine 1.4 mg/m² day 1, prednisone 100 mg days 1–5. R-CEOP: rituximab 375 mg/m² day 1, cyclophosphamide 750 mg/m² day 1, etoposide 100 mg/m² days 1-3, vincristine 1,4 mg/m² day 1, prednisone 100 mg days 1–5. R-CHOEP: rituximab 375 mg/m² day 1, cyclophosphamide 750 mg/m² day 1, doxorubicin 50 mg/m² day 1, vincristine 1.4 mg/m² day 1, etoposide 100 mg/m² days 1–3, prednisone 100 mg days 1–5. A full body CT scan was carried out after the fourth and sixth cycles and if there was any response between those cycles, treatment was continued to an eighth cycle.

Elderly patients with normal cardiac function received R-CIOP instead of R-CHOP as a less cardiotoxic regimen at Oulu University Hospital. Patients received R-CEOP if the left ventricular ejection fraction (LVEF) was less than 50% or the patient had significant heart disease such as cardiomyopathy. Patients were treated with R-CHOEP if the IPI was 2 or higher and the patient was younger than 60 years. If substantial cardiotoxicity developed during the chemotherapy with R-CHOP or R-CIOP, the regimen was changed to R-CEOP. If the initial therapy was switched to R-CEOP after a maximum of 2 cycles, the patient was included in the CEOP group.

Statistical analysis

Differences between the treatment groups were assessed using the Pearson's two-sided chi-squared test. Kaplan-Meier analysis was used to assess survival rates. Log-rank tests were used to find out if there was a statistically significant difference between the treatment groups. Values of p under 0.05 were considered statistically significant. PFS was calculated

from the first day of treatment to the date of progression, date of relapse, date of last status for patients who died due to treatment or the last follow-up date. Disease specific survival (DSS) was calculated from the date of diagnosis to disease or treatment associated death or last follow-up date. OS was calculated from the date of diagnosis to the last follow-up date or death from any cause. All the data were analysed with SPSS version 23.

Matched-pair analysis

Matched-pair analysis was carried out between R-CHOP and R-CEOP. Patients were matched based on IPI and age (within 6 years). Two patients treated with R-CEOP were excluded from analysis because a pair was not found.

PFS was calculated in this analysis from the day of diagnosis to date of progression, date of relapse, date of last status for patients who died due to treatment or last follow-up date.

Results

Patients

Patient demographics are presented in Table 1. Out of 208 patients, 55 (26.4%) were treated with R-CHOP, 105 (50.5%) with R-CIOP, 17 (8.2%) with R-CEOP and 31 (14.9%) with R-CHOEP. Four patients changed to the R-CEOP group during treatment. In two patients the original regimen was R-CHOP, in one patient R-CHOEP and R-CIOP in one patient.

The mean age of patients was 66 years. At the time of diagnosis, 63 patients (30.3%) were 70–79 years old, 29 patients (13.9%) were 80–89 years old and 3 (1.4%) patients were 90 years old. In patients treated with R-CHOP the mean age was 62.5 years, with R-CIOP 70.5 years, with R-CEOP 78.2 years, and with R-CHOEP 51.8 years ($p=0.000$). LDH was elevated

in 67.8% of patients. WHO performance status was 0 in 20.3% of patients, 1–2 in 62.8% of patients and 3–4 in 16.9% of patients.

The mean follow-up time was 48 months. In patients treated with R-CHOP the mean follow-up time was 52.7 months, with R-CIOP 45.1 months, with R-CEOP 27.7 months and with R-CHOEP 61.6 months ($p=0.008$). In the R-CIOP and R-CHOEP groups patients presented with higher stages than in the R-CHOP and R-CEOP groups ($p=0.005$). In the R-CEOP the group the mean EF was approximately 10% lower than in other groups ($p=0.004$). Patients in the R-CHOP group received more consolidative radiation therapy than other groups but the difference was not statistically significant ($p=0.467$). In the R-CHOP group 15 out of 55 patients presented with a non-GC phenotype, in the R-CIOP group 30 out of 105 and in the R-CEOP group 10 out of 17 ($p=0.074$).

Treatment outcome

The PFS and OS are presented in Figure 1 by treatment group.

For all patients, the 2-year PFS was 73.6 %. In patients treated with R-CHOP it was 84.2%, with R-CIOP 64.4%, with R-CEOP 87.7% and with R-CHOEP 83.2% ($p=0.010$). For all patients, the 2-year DSS was 81.5%. In patients treated with R-CHOP it was 95.8 %, with R-CIOP 72.1 %, with R-CEOP 87.8% and with R-CHOEP 85.9% ($p=0.003$). The 2-year OS was 77.7 % in all patients. In patients treated with R-CHOP it was 91.9 %, with R-CIOP 69.5 %, with R-CEOP 69.0 % and with R-CHOEP 85.9 % ($p= 0.000$).

When studying all patients over 70 years of age (n=88), the 2-year DSS was 80.2%. In the group of patients over 70 who were treated with R-CHOP it was 91.7%, with R-CIOP 65.5% and with R-CEOP it was 92.9%. Among patients treated with R-CEOP, one received only one cycle of treatment, two patients received four cycles, two received five cycles, ten received six cycles and two received eight cycles of treatment.

Toxicity

3.4% (n=7) of the patients died due to treatment-related complications. There were five fatal neutropenic infections, one pulmonary reaction and one allergic reaction to contrast agent. All of these seven patients were treated with R-CIOP. The mean age was 73.0 years at the time of diagnosis in this patient group.

Matched-pair analysis

The demographics of the matched-pair analysis are presented in Table 2. The PFS and DSS are presented in Figure 2. The Kaplan-Meier analysis showed that the 2-year PFS was 92.3% with R-CHOP and 86.2% with R-CEOP (p=0.260). The 2-year DSS was 100% with R-CHOP and 86.2% with R-CEOP (p=0.240). The 2-year OS was 86.7% with R-CHOP and 71.8% with R-CEOP (p=0.330).

Discussion

In this study we showed that R-CEOP therapy provides good disease control for the majority of elderly patients with DLBCL and the results are comparable with R-CHOP therapy. The 2-year PFS of 87.7%, DSS of 87.8% and OS of 69.0% were achieved with R-CEOP. In patients

with impaired cardiac function R-CEOP could offer a better risk-benefit profile than R-CHOP. The results with R-CIOP seemed to be inferior when compared to R-CHOP.

The R-CHOP regimen is the standard of care in DLBCL giving a 5-year OS rate of 60–70%.² However, DLBCL is common in elderly patients and there is no standard therapy for this patient group. Tolerance of standard therapy is often impaired and the presence of comorbidities, altered drug metabolism and diminished organ function may cause severe complications.¹⁶ Treatment-related mortality (TRM) is also higher, up to 8.7% in elderly patients.¹⁷

Cardiac diseases are common in elderly patients. Doxorubicin is an anthracycline chemotherapeutics, an essential agent in the R-CHOP regimen and its major problem is cardiotoxicity. In 3164 lymphoma patients treated with doxorubicin, 28% developed a subclinical cardiomyopathy during next five years following the initial treatment.¹⁸ High age, higher cumulative doses, pre-existing heart disease, hypertension, diabetes, comorbidities⁷ and chest radiation therapy¹⁹ increase the risk of doxorubicin-related congestive heart failure. There is a wide individual variability in cardiotoxic anthracycline doses and particularly in patients with risk factors, cardiotoxicity may also occur at a low cumulative dose.²⁰

Many other approaches have been used to treat these patients. When treating with dose-reduced R-CHOP²¹, or so called R-miniCHOP²² significantly worse treatment results have been achieved compared with full dose R-CHOP. Same holds true for R-bendamustine²³, R-CVP (R-CHOP without an anthracycline)^{12,24} and R-GCVP (rituximab, cyclophosphamide, vincristine, gemcitabine and prednisone).²⁵

Epirubicin has been regarded as a less cardiotoxic anthracycline than doxorubicin. One study of 88 patients treated with R-CIOP has been published previously. 63.6% of the patients were 60 or younger and 5-year OS of 70.5% was observed.²⁶ In Oulu University Hospital epirubicin has been used in elderly patients in R-CIOP regimen in order to reduce cardiotoxicity. In the patients treated with R-CIOP in the present series the 2-year PFS was 64.4% and the 2-year DSS was 72.1 %. The mean age of the patients was 70.5 years. Thus R-CIOP seems to be an inferior regimen compared to R-CEOP or R-CHOP.

Etoposide is a derivative of podophyllotoxin which blocks cells in the premeiotic stage of the cell cycle.²⁷ The results of etoposide only and etoposide combined with different chemotherapy regimens were investigated in the pre-rituximab era in particular.¹³ There are limited data available on the use of R-CEOP in DLBCL. In a series of 81 patients treated with R-CEOP with a median follow-up of 28 months, the 5-year time to progression -rate was 57% with R-CEOP and no statistically significant difference was found when compared to R-CHOP treated patients ($p=0.21$), suggesting that R-CEOP could be a curative, alternative treatment for patients not eligible for R-CHOP. The 5-year OS was 49% in the R-CEOP group and 64% in the R-CHOP group, reflecting the high number of comorbidities in R-CEOP group.²⁸ Another study of 26 patients introduced promising results with the R-CEOP regimen. With a median follow-up time of 19 months, the 2-year PFS and OS rates were 49% and 59%.²⁹ In our analysis of 17 elderly patients with impaired cardiac function, a 2-year PFS of 87.7% and OS of 69.0% were achieved with R-CEOP. The toxicity rate related to the R-CEOP regimen seems to be low according to our data. No treatment-related deaths occurred.

Because the patients treated with R-CEOP were older than those treated with R-CHOP, we performed a matched-pair analysis with a group of patients treated in another institution. The

matched-pair analysis between R-CEOP and R-CHOP showed that the treatment results with R-CEOP seem to be comparable to those with R-CHOP, as a 2-year PFS of 86.2% vs 92.3% and 2-year OS of 71.8% vs 86.7% were obtained. There was no statistically significant difference between these groups. The results with R-CEOP were better than those with R-CIOP with a 2-year PFS of 87.7% vs 64.4 % and a 2-year DSS of 87.8 % vs 72.1 %.

However, patients treated with R-CIOP had higher IPI than those in the R-CEOP group. When taking cardiac toxicity into account, R-CEOP might be a better choice for patients with impaired cardiac function than R-CHOP or R-CIOP.

This is a retrospective study with all the limitations associated with retrospective setting. Although the total number of patients, 208, is considerable, the number of patients in the R-CEOP group was limited. However, the matched-pair analysis with R-CHOP-treated patients improves the reliability of this study. We have reported the treatment related mortality, but the retrospective design hindered the detailed comparison of non-fatal toxicity between the groups. These results should be verified with a larger patient group and in prospective studies. However, because these elderly patients with cardiac comorbidities are usually excluded from clinical trials, we find that our study adds information to treatment selection in this patient group and implies that even these old fragile patients can be treated with curative intent.

Conclusions

In this retrospective analysis we found that R-CEOP offers favorable results and good disease control in the treatment of elderly patients with DLBCL. The result seems to be comparable with R-CHOP. In line with existing literature it seems that doxorubicin can safely be substituted with etoposide in patients with pre-existing cardiac disease. However, the results

with R-CIOP were unsatisfactory and we do not recommend using this protocol in elderly patients with cardiac disease.

Conflicts of interest

The authors report no conflicts of interest.

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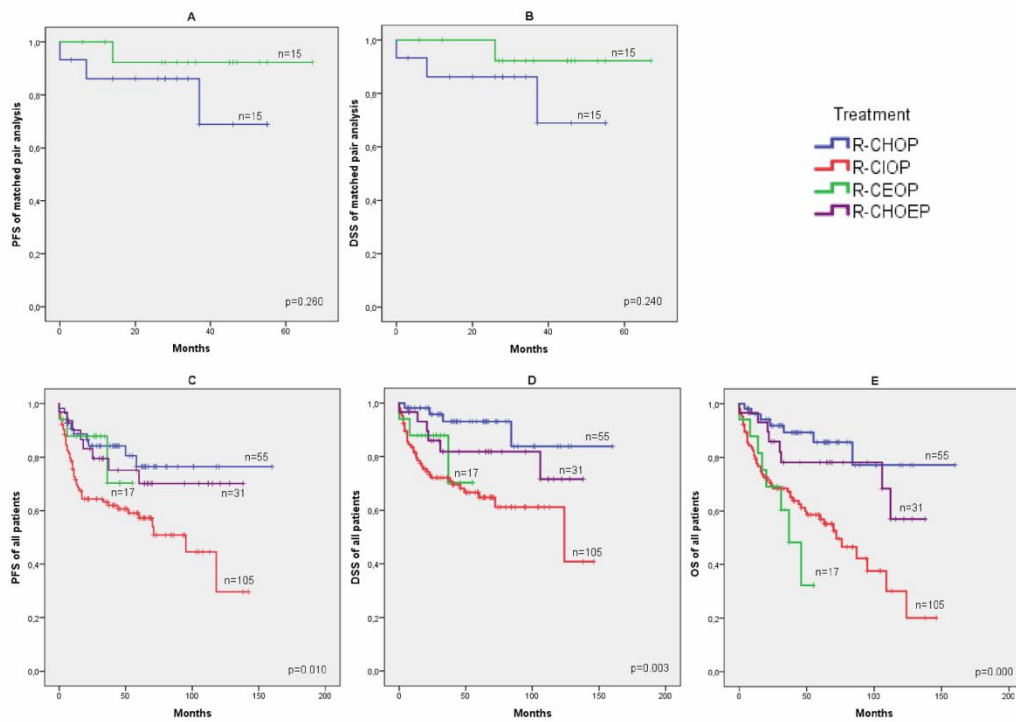


Figure 1: A) PFS of matched pair analysis, B) DSS of matched pair analysis, C) PFS of all patients regarding to treatment, D) DSS of all patients regarding to treatment, E) OS of all patients regarding to treatment

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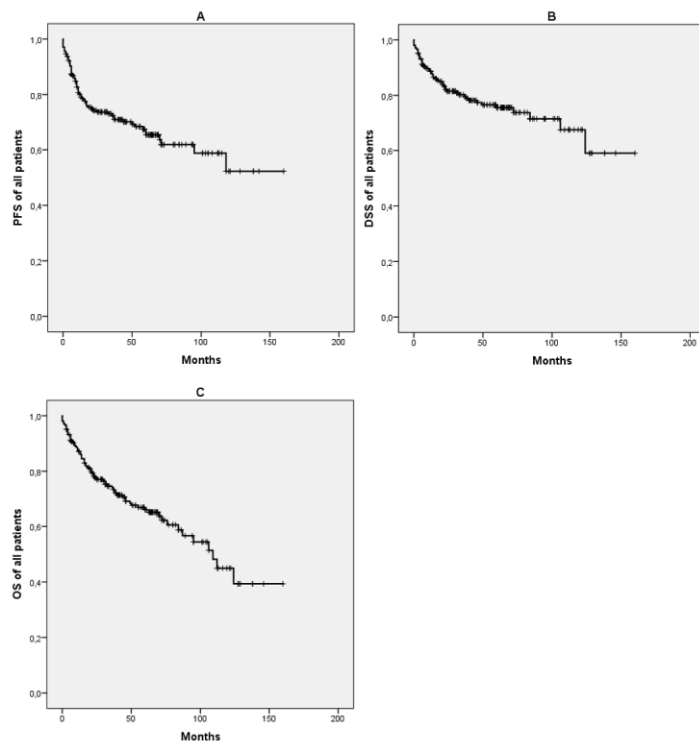


Figure 2: A) PFS of all patients in months B) DSS of all patients in months C) OS of all patients in months

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n (%)	R-CHOP n=55	R-CIOP n=105	R-CEOP n=17	R-CHOEP n=31
Age (mean) *	62.5 years	70.5 years	78.2 years	51.8 years
Male/ Female	30 (55%)/ 25 (45%)	60 (57%)/ 45 (43%)	9 (53%)/ 8 (47%)	16 (52%)/ 15 (48%)
Stage	n=55	n=104	n=17	n=31
I	19 (35%)	16 (15%)	4 (24%)	2 (6%)
II	9 (16%)	16 (15%)	6 (35%)	5 (16%)
III	11 (20%)	22 (21%)	1 (6%)	8 (26%)
IV	16 (29%)	50 (48%)	6 (35%)	16 (52%)
B-symptoms	n=52	n=97	n=15	n=28
A	29 (56%)	53 (55%)	9 (60%)	15 (54%)
B	23 (44%)	44 (45%)	6 (40%)	13 (46%)
GC fenotype	n=39	n=66	n=14	n=20
CG	24 (62%)	36 (55%)	4 (29%)	7 (35%)
non-GC	15 (38%)	30 (45%)	10 (71%)	13 (65%)
IPI*	n=55	n=103	n=17	n=31
0-1	16 (29%)	22 (21%)	6 (35%)	4 (13%)
2-3	34 (62%)	42 (41%)	7 (41%)	17 (55%)
4-5	5 (9%)	39 (38%)	4 (24%)	10 (32%)
LVEF (mean)*	n=28	n=82	n=14	n=16
	68 %	66.1 %	58.1 %	68.3 %
Radiation therapy				
Yes	25 (45%)	37 (35%)	5 (29%)	10 (32%)

Table 1. Patient demographics. Asterix (*) indicates if the difference was statistically significant ($P < 0.05$) between the treatment groups.

	R-CHOP	R-CEOP
Age (mean)	76.3	77.3
B-symptoms	40 % (n=6)	43 % (n=6)
Male/Female	9 (60%) / 6 (40%)	8 (53%) / 7 (47%)
Stage	n=15	n=15
1	5 (33%)	4 (27%)
2	1 (7%)	5 (33%)
3	3 (20%)	0 (0%)
4	6 (40%)	6 (40%)
IPI	n=15	n=15
0-1	5 (33%)	5 (33%)
2-3	7 (47%)	7 (47%)
4-5	3 (20%)	3 (20%)
Radiation therapy (yes)	6 (40%)	5 (33%)

Table 2. Patient demographics of matched-pair analysis.

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