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Cyclophosphamide, pegylated liposomal doxorubicin (Caelyx®), vincristine and prednisone (CCOP) in elderly patients with diffuse large B-cell lymphoma: results from a prospective phase II study

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Background and Objectives. Anthracycline-based combination chemotherapy regimens are the standard therapy for patients with diffuse large B-cell lymphoma (DLBCL), but such regimens may be poorly tolerated in elderly patients.

Design and Methods. In a prospective phase II study we analyzed the feasibility of a regimen (CCOP) that includes pegylated liposomal doxorubicin (Caelyx®) plus vincristine, cyclophosphamide and prednisone in patients with DLBCL above the age of 60 years.

Results. Thirty-three patients, with a median age of 74 years, were enrolled in the study. The overall response rate was 64% (49% complete remissions and 15% partial remissions). The estimated one-year overall and event-free survivals were 55% (95% CI, 38-72) and 45% (95%CI, 28-62), respectively. The only relevant toxicity was neutropenia, which reached grades 3-4 in 21 cases (64%).

Interpretation and Conclusions. These results suggest that CCOP appears to be an acceptable alternative for elderly patients with DLBCL, and randomized trials against a conventional doxorubicin-containing regimen are justified.

Key words: liposomal doxorubicin, Caelyx®, non-Hodgkin's lymphoma, elderly.

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Anthracycline-based combination chemotherapy regimens are the standard therapy for patients with diffuse large B-cell lymphoma (DLBCL), which is the most frequent of the so-called aggressive non-Hodgkin's lymphomas.[1] The optimal standard management of patients with advanced chronological age is, however, controversial, since these patients tolerate much more poorly the toxicity of standard chemotherapy. Age is in fact the most important prognostic factor in patients with DLBCL,[2] and the response rate to and tolerance of cyclophosphamide, conventional doxorubicin (or adriamycin), vincristine and prednisone (CHOP) were much worse in patients over 65 years of age in several studies.[3-6] More recent reports on CHOP and other anthracycline-based regimens suggest that the outcome in selected elderly patients is similar to that in younger patients, but the treatment-related mortality is still between 10 to 15%, most deaths being caused by infections.[7-14] Among the non-hematologic toxicities of adriamycin, grade 3-4 cardiotoxicity occurred in 3-8% of patients in these studies.

Pegylated liposomal doxorubicin (Caelyx®, Schering Plough S.A., Spain) has been shown to reduce the cardiac toxicity of conventional doxorubicin while having at least similar efficacy in patients with Kaposi´s sarcoma and several solid tumors, especially breast cancer.[15,16] However, to our knowledge there have been no published studies in patients with lymphoma. We report here the first study of a CHOP-like regimen with the adriamycin substituted by Caelyx® in patients with DLBCL above 60 years of age.

Design and Methods

This prospective phase II study was carried out in six centers in Spain between December 1998 and December 2000. The study was approved by the Spanish Drug Agency (Protocol CCOP-LNH98) and each hospital's ethical committee, and patients

gave written informed consent to inclusion in the study. The inclusion criteria were: age above 60 years, diagnosis of previously-untreated DLBCL (patients with a transformed untreated low-grade lymphoproliferative disease were accepted), ECOG performance status < 3 (and higher if due to lymphoma), no symptomatic cardiac arrythmias or heart failure, and acceptable renal, hepatic and pulmonary function. Standard laboratory and radiological staging procedures and left ventricular ejection fraction analysis by echocardiography or scintigraphy were required before therapy in all cases.

CCOP treatment regimen

The CCOP regimen consisted of cyclophosphamide, 750 g/m^2 as a 30-minute intravenous (iv) infusion on day 1, Caelyx®, 30 mg/m^2 iv over 1 hour on day 1, vincristine, 2 mg iv over 15 minutes on day 1 and prednisone, 60 mg/m^2 on days 1 to 5 of each cycle. Caelyx® was kindly provided by Schering-Plough, S.A., España. Granulocyte colony-stimulating factor (G-CSF) and antiemetics were not allowed during the first cycles, but could be used in later cycles in case of febrile neutropenia and significant nausea/vomiting, respectively, during a prior cycle. Treatment cycles were scheduled to be given every 21 days for a total of six (or eight in case of partial response after six). If grade 3-4 World Health Organization (WHO) hematologic toxicity developed, the next cycle was delayed until recovery, and G-CSF was allowed in subsequent cycles if febrile neutropenia developed. Cycles could also be delayed if non-severe non-hematologic toxicities occurred, especially grades 2-4 mucous or cutaneous toxicity (i.e., palmo-plantar erythrodysesthesia).

Response criteria

Disease response was assessed clinically and with standard radiological and histologic methods before and after treatment. Complete remission (CR) was defined as no measurable disease including no bone marrow (BM) involvement by conventional cytology and histology. Partial response (PR) consisted of at least a 50% reduction in the sum of the products of perpendicular diameters of all measurable lesions before treatment, BM involvement of less than 20%, and no new sites of disease. CR plus PR were assessed as overall response (OR). A response less than a PR was considered as no response (NR), and progressive disease (PD) reflected involvement of new sites during or after treatment, recurrence in originally involved sites (in case CR had been obtained), increase of any residual tumor masses (in case PR had been obtained) and/or reappearance of BM involvement.

Statistical considerations

The main parameters analyzed were treatment-related toxicity and disease response (CR, PR and OR). Secondary end-points analyzed were overall survival (OS), defined as the interval from the first day of treatment until death or last follow-up, progression-free survival (PFS), defined as the interval from the achievement of CR or PR until relapse or progression, death or last follow-up, and event-free survival (EFS), defined as the interval from the first day of treatment until disease progression, death or last follow-up. Survival calculations were made by the Kaplan-Meier method, and the closing date for analysis was December 31, 2001.

Results

Patients' characteristics

A total of 33 patients were enrolled and treated between December 1998 and December 2000. The patients' characteristics are shown in Table 1. Their median age was 74 years (range, 61-83). Twenty patients (60%) had stage III-IV disease, 16 (49%) had constitutional B-symptoms and 14 (42%) a poor performance status. The international prognostic index (IPI) was intermediate-to-high (≥ 3) in 16 cases (49%), and the β_2-microglobulin level was above normal in 18 patients (55%). Five patients had a history of prior untreated low-grade lymphoma.

Toxicity

Toxicity and treatment parameters are shown in Table 2. A total of 187 cycles of CCOP were given, with a median of six cycles per patient (range 2-8). Thirteen patients (39%) received fewer than six cycles of CCOP. Four patients died during therapy without confirmation of disease progression; three patients died at home from sudden death (n=2) or after a severe febrile illness, while one died of multiorgan failure. Two further patients did not complete therapy, one due to oral mucositis (which recurred after switching to CHOP chemotherapy) and the other's loss from follow-up, and seven patients progressed during CCOP and were withdrawn from the study.

Sixty-seven cycles (36%) were delayed in 22 patients (67%), mostly due to neutropenia. The only relevant toxicity was neutropenia, which reached grade 3 (neutrophils 0.5 to 1×10^9/L) in six and grade 4 (<0.5 to 1×10^9/L) in 15 cases. Only two patients developed febrile neutropenia, and G-CSF was used prophylactically in these two patients and in a third one who developed recurrent grade 4 neutropenia. There were no other relevant toxicities. The left ventricular ejection fraction was

Table 1. Patients' characteristics and response to CCOP chemotherapy (% in parentheses).

Feature	*N[a] of patients*	*Complete Remission*	*Partial Remission*
All patients	33	16 (49)	5 (15)
Median age [range]	74 [61-83]		
Age			
60-69	7	3 (43)	1 (14)
70-83	26	13 (50)	4 (15)
Sex			
Male	13	5 (39)	3 (23)
Female	20	11 (55)	2 (10)
Ann Arbor Stage			
II	13 (39)	9 (69)	0
III	6 (18)		
IV	14 (42)	7 (35)	5 (25)
B symptoms			
Present	16 (49)	9 (56)	2 (13)
Absent	17 (51)	7 (41)	3 (18)
Bulky disease			
Present	8 (24)	2 (25)	1 (13)
Absent	25 (76)	14 (56)	4 (16)
Any extranodal site	24 (73)		
≥ 2 extranodal sites			
Present	9 (27)	2 (22)	2 (22)
Absent	24 (73)	14 (58)	3 (13)
ECOG performance status			
0-1	19 (58)	10 (53)	3 (16)
≥ 2	14 (42)	6 (43)	2 (14)
LDH level			
High	15 (46)	5 (33)	3 (20)
Normal	18 (54)	11 (61)	2 (11)
β_2-microglobulin			
High	18 (55)	7 (39)	5 (28)
Normal	15 (45)	9 (60)	0
International Prognostic Index			
Low/low-intermediate (1-2)	17 (51)	10 (59)	2 (12)
Intermediate/high (≥ 3)	16 (49)	6 (38)	3 (19)
Transformed low-grade lymphoma			
Yes	5 (15)	0	2 (40)
No evidence	28 (85)	16 (57)*	3 (11)

**p=0.04; LDH= lactate dehydrogenase.*

Table 2. Cycles received and toxicity to CCOP chemotherapy (% in parentheses).

		Toxicity Grade (WHO criteria)		
		2	*3*	*4*
Total number of cycles	187			
Median cycles per patient	6			
Range	2-8			
Number of cycles delayed	67 (36)			
Patients with delayed cycles	22 (67)			
Patients who received G-CSF	3 (9)			
Number who received < 6 cycles	13 (39)			
Early death (w/o progression)	4 (13)			
Disease progression	7 (21)			
Toxicity	2 (6)			
Number of deaths	16 (48)			
Lymphoma	12 (36)			
Other causes	4 (13)			
Patients who received antiemetics	18 (55)			
Toxicity				
Neutropenia		2 (15)	6 (18)	15 (46)
Thrombocytopenia		2 (6)	1 (3)	
Anemia		12 (36)	2 (6)	
Infections		2 (6)		
Nausea/vomiting		6 (18)	1 (3)	
Oral mucositis		1 (3)		
Cutaneous		1 (3)		
Cardiac		0	0	0
Hair loss		7 (21)	7 (21)	1 (3)

assessed in 16 patients both before and after treatment, without any relevant changes in any case.

Response and outcome

Sixteen patients (49%) achieved a CR and five (39%) a PR following CCOP, for an OR rate of 64%. Response rates according to the various patients' features are shown in Table 1. The only variable that was significantly associated with a lower CR rate was having a DLBCL that had transformed from a prior low grade lymphoma (0/5 vs 16/28 in *de novo* cases, $p = 0.04$).

The median follow-up for all 33 cases was 13 months (range, 1-32) and for the 17 survivors 20 months (range, 10-32). Twelve patients were alive without lymphoma, four were alive with lymphoma and one was lost from follow-up while in remission; sixteen patients had died, 12 from lymphoma progression and four during therapy without obvious disease progression. A total of 16 patients progressed during therapy (n=7) or after having achieved an OR (n=9). The estimated one-year OS and EFS are 55% (95% CI, 38-72) and 45% (95%CI, 28-62), respectively, for all patients (Figures 1a and 1b); the EFS was 54% (95%CI, 36-72) in the 28 *de novo* cases and 0% in the five transformed lymphomas. Among the 21 patients who reached an OR, the one-year PFS was 64% (95% CI, 43-85).

Discussion

Conventional anthracycline-containing combination chemotherapy can obtain objective responses in 50-80% of patients with aggressive NHL, with 1-year OS rates of 50-90% (Table 3). More or less stringent selection criteria undoubtedly influence these results; for instance, with similar protocols treatment-related deaths occur in 0 to 24% of cases, reflecting the inclusion of more or less debilitated elderly patients. Among the toxicities that have an influence on the high toxicity and poor tolerance of these patients, cardiotoxicity and neutropenia-related infections are probably the most relevant.[17] Among the risk factors for doxorubicin-induced cardiac toxicity, elderly age, hypertension, prior cardiac disease and combination therapy

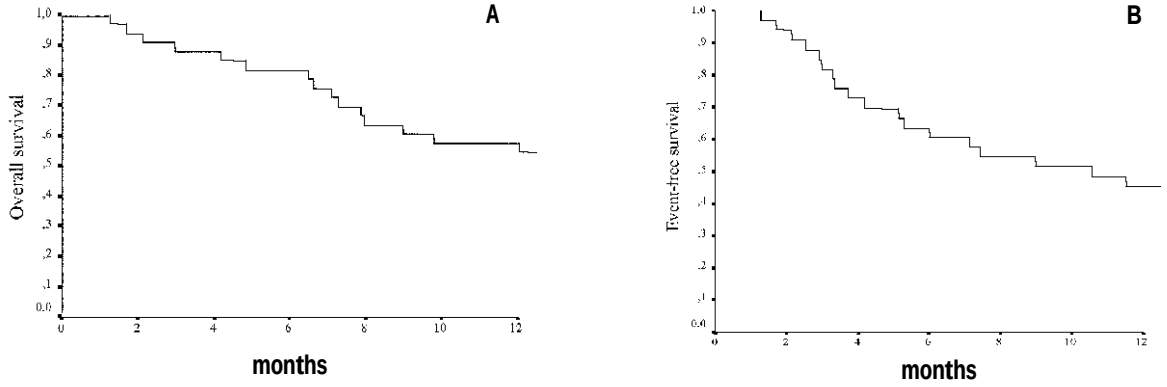

Figure 1. Overall survival (A) and event-free survival (B) among 33 patients with diffuse large B-cell NHL treated with CCOP.

undoubtedly explain the higher risk in our group of patients.[18,19] The inability of many such patients to tolerate these treatment regimens represents the loss of an important therapeutic option.

Because of the importance of doxorubicin in the treatment of NHL, considerable research has been undertaken to reduce its associated cardiac toxicity. Three options are currently available for this purpose; (i) dexrazoxane, an iron-chelating agent, has shown the ability to reduce the cardiac toxicity associated with doxorubicin; however, protection is not complete, and its use is associated with increased myelotoxicity that can be severe.[20] Additionally, because of the concern of possible tumor protection, dexrazoxane is not indicated for use until a cumulative dose of 300 mg/m^2 of doxorubicin has been administered, even though it is recognized that injury to the myocardium begins with the first dose;[21] (ii) administration of conventional doxorubicin as a continuous infusion over 72-96 hours has been reported to be less cardiotoxic, although its safety and efficacy have not been established in the

Table 3. Recent studies of various anthracycline-containing regimens in elderly patients with aggressive non-Hodgkin's lymphomas.

Author (year)	*Treatment*	*No. Pats.*	*Median age*	*% with DLBCL*	*% completed therapy*	*% treatment related deaths*	*% grades 2-4/3-4 hematologic toxicity*	*% grades 3-4 cardiac toxicity*	*% OR (CR-PR)*	*1-year OS/EFS*
Sonneveld (1995)	CHOP	72	70	38	NS	15	NS	6	79 (49/30)	70/NS
	CNOP	74	71	44		15		3	58 (31/27)	50/NS
Bastion (1997)	CVP	220	75	70	NS	12	NS	5	45 (33/12)	50/3
	CTVP	233	75	70		15		3	59 (48/11)	50/40
Tirelli (1998)	CHOP	60	74	NS	65	5	72/67	5	77 (45/32)	70/55
	VMP	60	76		45	7	88/78	2	50 (27/23)	50/35
Zinzani (1999)	VNCOP-B	350	69	80	NS	1	NS	NS	83 (58/25)	70/65
Mainwaring (2001)	PACEBO	243	71	100	NS	24	–/51	6*	69 (52/17)	60/–
	PMCEBO	230	71	100		20	–/66	8*	78 (60/18)	65/–
Chisesi (2001)	CEMP	139	64	NS	75	None	70/52	5	69 (52/17)	65/55
Cartron (2001)	VAD/ CHEP	77	70	83	66	8	–/52	7	66 (52/14)	70/60
Niitsu (2001)	CHOP	40	74	70	93	3	100 / 78	3	98 (88/10)	95/75
Coiffier (2002)	CHOP	202	69	81	72	6	NS	8	69 (63/6)	70/50
	CHOP+R	197	69	87	80	11	NS	8	82 (75/7)	85/70

**Refers to cardiac-related deaths during therapy. CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone; CHOP+R = CHOP plus rituximab; CNOP = cyclophosphamide, mitoxantrone, vincristine and prednisone; CVP = cyclophosphamide, teniposide and prednisone; CTVP = cyclophosphamide, pirarubicin, eniposide and prednisone; VMP = etoposide, mitoxantrone and prednimustine; VNCOP-B = vincristine, mitoxantrone, cyclophosphamide, etoposide, bleomycin and prednisone; PACEBO = doxorubicin, vincristine, cyclophosphamide, etoposide, bleomycin and prednisone; PMCEBO = mitoxantrone, vincristine, cyclophosphamide, etoposide, bleomycin and prednisone; CEMP = cyclophosphamide, etoposide, mitoxantrone and prednisone; VAD = vincristine, doxorubicin plus dexamethasone; CHEP = cyclophosphamide, doxorubicin, etoposide and prednisone.*

treatment of NHL.[22] Additionally, this schedule is cumbersome and requires a central venous catheter, which poses the additional catheter-related risks; and (iii) the use of liposomal doxorubicins. Both non-pegylated liposomal doxorubicin (Myocet®) and polyethylene glycol (PEG)-modified liposomal doxorubicin (Caelyx® or Doxil®) markedly modify the pharmacokinetics of doxorubicin.[23-25] The main feature that distinguishes Myocet® from Doxil® is that the latter persists in the circulation significantly longer. Both drugs have been shown to be less cardiotoxic than conventional doxorubicin in randomized and phase II high-dose trials.[16,26,27] In our phase II study we saw no cases of documented cardiotoxicity, as opposed to the 3-8% reported in other trials (Table 3), but the sample was small to detect such relatively rare, although serious, events.

A specific toxicity of Caelyx® is the occurrence of a form of cutaneous toxicity referred to as palmar-plantar erythodysesthesia and stomatitis/mucositis.[28,29] To reduce the risk of this complication, the manufacturers recommend not exceeding a weekly dose-intensity of 11-12.5 mg/m^2.[29] Thus, we chose a dose of 10 mg/m^2/week in our combination CCOP scheme. Since we saw no relevant cutaneous toxicity, the dose of Caelyx® could probably be increased to 35-40 mg/m^2 every 3 weeks in future studies. Liposomal doxorubicins produce hematologic toxicity similar to that caused by conventional doxorubicin. Grade 3-4 neutropenia occurs in 50-80% of elderly patients treated for aggressive NHL with CHOP-like protocols (Table 3), similar to our 64% rate. Thirty-one percent of elderly patients are admitted to hospital because of febrile neutropenia during CHOP therapy,[30] and in this population the prophylactic use of G-CSF reduces the risk of febrile neutropenia.[31,32] Thus, we suggest that future studies with the CCOP regimen be conducted with a slightly higher dose of Caelyx® plus prophylactic G-CSF. Our study sample is insufficient to show a reduction in several toxicities that appear to be lower with liposomal doxorubicins but that may be important in the morbidity and quality of life of these elderly patients, such as hair loss, generalized malaise and nausea and vomiting.[16,26] The trends we saw, however, do seem to indicate that these may be less frequent than with CHOP. In conclusion, from the results of our phase II trial we suggest that CCOP plus G-CSF should be compared to CHOP plus G-CSF in elderly patients with aggressive NHL. Other possible novel approaches that could be incorporated into such a randomized comparison are the use of anti-CD20 monoclonal antibody[33] and/or increasing the dose intensity of CHOP.[34]

Contributions and Acknowledgments

RM designed the study, participated in the patients' care, analyzed the data and wrote the various versions of the manuscript. GP acted as general data manager and collaborated in formatting the manuscript. MDC, MVV, JMR, JPO, RA and MJT participated in the patients' care and data management. JS and JFSM co-ordinated the various stages of the study and collaborated in the manuscript preparation. We are indebted to Schering-Plough, S.A., España for kindly providing Caelyx® free of charge and for their help in the logistics of this study.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

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Peer Review Outcomes

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Mario Cazzola, Editor-in-Chief. The final decision to accept this paper for publication was taken jointly by Professor Cazzola and the Editors. Manuscript received April 26, 2002; accepted june 19, 2002.

What is already known on this topic

Although anthracycline-based combination chemotherapy regimens are the standard therapy for patients with diffuse large B-cell lymphoma, such regimens may be poorly tolerated in elderly patients.

What this study adds

A regimen that includes pegylated liposomal doxorubicin plus vincristine, cyclophosphamide and prednisone appears to be an acceptable alternative for elderly patients with diffuse large B-cell lymphoma.

Potential implications for clinical practice

Prospective randomized clinical trials are required before any conclusion concerning clinical practice can be drawn. In addition, it should be noted that elderly patients could also benefit from novel therapeutic tools such as anti-CD20 monoclonal antibody.

Mario Cazzola, Editor-in-Chief