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ORIGINAL ARTICLE: CLINICAL

Cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab versus epirubicin, cyclophosphamide, vinblastine, prednisone and rituximab for the initial treatment of elderly "fit" patients with diffuse large B-cell lymphoma: results from the ANZINTER3 trial of the Intergruppo Italiano Linfomi

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Abstract

We conducted a prospective study to compare epirubicin, cyclophosphamide, vinblastine, prednisone and rituximab (R-miniCEOP) with cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab (R-CHOP) for the treatment of "fit" elderly patients with diffuse large B-cell lymphoma (DLBCL). Patients over the age of 65 with stage II–IV DLBCL were screened with a comprehensive geriatric assessment. Patients were randomized to receive six courses of R-miniCEOP ($n = 114$) or R-CHOP ($n = 110$). Overall, the rate of complete remission was 70% ($p = 0.466$). After a median follow-up of 42 months, 5-year event-free survival (EFS) rates were 46% and 48% for R-miniCEOP and R-CHOP, respectively ($p = 0.538$). Patients older than 72 years and with low-risk disease had a better outcome when treated with R-miniCEOP ($p = 0.011$). Overall R-CHOP and R-miniCEOP are similarly effective for elderly "fit" patients with DLBCL. The less intense R-miniCEOP may be an acceptable option for the treatment of relatively older patients with low-risk disease.

Keywords: R-CHOP, R-miniCEOP, diffuse large B-cell lymphoma, elderly, fit patients

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most frequent subtype of non-Hodgkin lymphoma (NHL) and frequently affects elderly people [1]. For more than 20 years, combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) has been the standard treatment for patients with aggressive NHL [2], with recent data supporting addition of the anti-CD20 monoclonal antibody rituximab (R-CHOP). The R-CHOP combination given every 3 weeks is the standard treatment for elderly patients with DLBCL and is associated with a 5-year overall survival (OS) rate of ~60% [3,4].

Management of elderly patients with lymphoma, however, is frequently a challenge for clinicians, mainly due to the presence of one or more co-morbid conditions and/or functional status impairments. Different strategies have been adopted to try to manage elderly patients better; these include the use of regimens with reduced doses of drugs, or less toxic drugs [5–8].

Fewer attempts have been made to try to prospectively identify patients who are eligible to receive full-dose treatment.

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There is an accompanying commentary that discusses this paper. Please refer to the issue Table of Contents.

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Although several tools are available to identify "fit" patients among the elderly population, published clinical trials usually leave the decision of whether or not to include a patient to the clinician's judgement.

In 2003 the Intergruppo Italiano Linfomi started a randomized trial to compare standard R-CHOP with a combination of rituximab and miniCEOP (epirubicin, cyclophosphamide, vinblastine and prednisone), a less intensive regimen specifically designed for elderly people and already tested by the same group [5]. In order to be registered and randomized, elderly patients with DLBCL had to be prospectively defined as "fit" according to comprehensive geriatric assessment (CGA) [9,10].

Materials and methods

The trial was conducted in compliance with the Declaration of Helsinki. It was also accepted by the appropriate Research Ethics Committees, and required each patient to give written informed consent prior to registration and randomization. The study was registered at the Clinicaltrial.gov website and assigned code NCT01148446.

Previously untreated patients older than 65 years of age, with a histologically confirmed diagnosis of DLBCL of follicular lymphoma grade IIIb, clinical Ann Arbor stage II, III or IV disease and Eastern Cooperative Oncology Group (ECOG) performance status of 0–3, were eligible. Moreover, all patients were required to undergo a CGA that included evaluation of the following parameters: (1) activities of daily living (ADL), (2) co-morbidity score according to the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) [11] and evaluated in all organs/systems as detailed by Balducci and Beghe [9]. Patients were classified in the category of "fit" if they had an ADL score of 6, less than three grade 3 CIRS-G co-morbidities and no grade 4 co-morbidities (hematological co-morbidities were not investigated), and none of the criteria defining the presence of geriatric syndrome. All other patients were classified as "unfit," and were excluded from randomization. Moreover, instrumental activities of daily living (IADL) were also tested for each patient (IADL score did not affect definition of patient status).

Eligible "fit" patients were randomly assigned to receive six courses of R-CHOP or R-miniCEOP. Patients with a less than partial response (PR) after the first three cycles of chemotherapy were removed from the study. R-CHOP was administered as originally reported [3]; the R-miniCEOP schedule is shown in Table I. Prophylactic granulocyte-colony stimulating factor (G-CSF) was recommended in cases of persisting grade 4 neutropenia or febrile neutropenia. All patients had to receive cotrimoxazole as anti-infectious prophylaxis. Erythropoietin use was allowed in cases of anemia (hemoglobin <11 g/dL) but was not mandatory.

At the end of chemotherapy, radiotherapy (RT) was scheduled for sites of previous bulky disease or partially responding sites.

Table I. Drug doses and time schedules for R-CHOP and R-miniCEOP.

Drug	Dose (mg/m^2)	Route	Days
R-CHOP (every 21 days)			
Cyclophosphamide	750	IV	1
Doxorubicin	50	IV	1
Vincristine	1.4 (max. 2 mg)	IV	1
Prednisone	100 mg (fixed dose)	IV/PO	1–5
Rituximab	375	IV	1
R-miniCEOP (every 21 days)			
Cyclophosphamide	750	IV	1
Epirubicin	50	IV	1
Vinblastine	5	IV	1
Prednisone	50	IV/PO	1–5
Rituximab	375	IV	1

R-CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab; R-miniCEOP, epirubicin, cyclophosphamide, vinblastine, prednisone and rituximab; IV, intravenously; PO, orally.

Statistics and assessment of efficacy

All analyses were conducted according to the intention-to-treat (ITT) principle, with the provision that patients for whom an exclusion criterion was discovered after randomization would be considered ineligible. Baseline disease assessment was described with the Ann Arbor staging system; performance status was described on the five-point ECOG scale. Nodal sites were defined as bulky when larger than 10 cm if occurring outside the mediastinum; mediastinal masses were defined as bulky if their transverse diameter measured at the D5 level was larger than a third of the transverse diameter of the thorax at the same level, or if larger than 6 cm at computed tomography (CT) scan. For outcome assessment, the age-adjusted International Prognostic Index (aaIPI) was used as originally described [12].

The principal study endpoint was event-free survival (EFS), defined as the interval between the date of randomization and the occurrence of one the following events: lack of complete response, relapse, death from any cause, treatment interruption or treatment change, or late toxic events correlated to study treatment. Secondary endpoints were response rate (RR), overall survival (OS), relapse-free survival (RFS) and toxicity. OS was calculated for all patients from date of randomization to date of death, from whatever cause, or to date of last visit; tumor size and treatment response were estimated on the basis of international criteria [13].

Toxicity was measured and graded according to the standard ECOG criteria [14]; the toxicity of the two study regimens was analyzed, comparing the rate of grade III–IV events, and dose intensity (DI) was calculated according to Hryniuk [15].

All statistical analyses were accomplished using Stata Statistical Software, Release 8.2 (Stata Corp, College Station, TX). Survival curves were plotted using Kaplan–Meier estimates [16], and statistical comparisons between curves were made using the log-rank test. Comparisons between curves that had been adjusted by potential confounding factors (aaIPI, age, extranodal sites and bulky disease) were obtained using the Cox proportional hazards regression method [17]. The χ^2 test and Fisher exact test were used to compare variables when appropriate [18]. Effect modifier analysis was performed to assess lack of homogeneity of an arm effect across the levels of putatively influential factors [19]. Each factor was analyzed separately in dichotomous form, with continuous factors dichotomized according to the usual clinical thresholds, when possible, or at the median. The effect modifier analysis assessed the arm by factor interaction in a statistical model that also included the arm and factor main effects. The evidence of effect modification was expressed using hazard ratio (HR) with 95% confidence interval (CI). Finally, a multivariate Cox proportional hazards (PH) regression was performed with a stepwise selection guide cut-off of 0.10. Proportionality of a hazard was graphically examined by means of the scaled Schoenfeld residuals [20]. Stability of the model was confirmed using 1000 bootstrap replications.

All statistical tests were two-sided. Sample size was calculated considering that the study was designed as a comparative two-arm randomized trial for testing the superiority of R-CHOP compared to R-miniCEOP, assuming EFS as the principal study endpoint, and assuming a 2-year EFS rate for R-miniCEOP of 40% and a 2-year EFS of 60% for R-CHOP. With a two-sided 5% significance test (α error = 0.05) and a power of 80% (β error = 0.2), 214 patients were enough to have 108 events, required to show a 44% risk reduction between arms. Taking into consideration a dropout rate of 5% after randomization, the sample size was defined at 226 patients (113 patients per arm). Enrollment was stopped in December 2006 when 228 patients from 37 centers had been enrolled and randomized.

Results

Between January 2003 and December 2006, 334 potentially eligible patients were referred to the study datacenter. Ninety-nine patients were considered as "unfit" at CGA and not randomized. Seven patients were subsequently excluded due to lack of data before randomization. Two hundred and twenty-eight patients were randomized, and four were excluded due to violation of inclusion criteria after randomization (diagnosis not allowed in two cases; concomitant prostate cancer in one; stage I disease in one). Among the remaining 224 patients, 110 and 114 were randomly allocated to R-CHOP and R-miniCEOP, respectively. Thus, 224 of the eligible subset of cases were analyzed according to intention-to-treat. A diagram of patient flow is reported in Fig. 1 and the baseline characteristics of our patients are shown in Table II.

Outcomes

At the end of treatment, the complete remission (CR) rate was similar in both arms: 73% (95% CI, 63–81%) and 68% (95% CI, 58–76%) for cases treated with R-CHOP and R-miniCEOP, respectively ($p = 0.466$). A summary of study results by treatment arm is shown in Table III. The median delivered DI was R-CHOP 0.92 (range 0.68–1.00) and R-miniCEOP 0.96 (range 0.77–1.10). A total of 35 patients received RT after chemotherapy (13 treated with R-CHOP and 22 with R-miniCEOP).

Overall, chemotherapy had to be discontinued in nine and 12 patients in the R-CHOP and R-miniCEOP arms, respectively. The main reason for treatment discontinuation was lack of response or disease progression in both arms (R-CHOP six cases, R-miniCEOP eight cases); other reasons for treatment discontinuation were one case each of infection, trauma and physician decision for R-CHOP, and two cases of cardiac dysfunction, and one case each of hematological toxicity and physician decision for R-mini-CEOP. Thirteen patients out of 21 who discontinued the treatment died after the event. Another four patients died within 3 months from the end of treatment due to causes possibly related to treatment, resulting in a treatment related mortality (TRM) of 7.5%: 9.1% (10 patients) in the R-CHOP arm and 6.1% (seven patients) in the R-miniCEOP arm ($p = 0.457$).

After a median follow-up of 42 months for patients who were alive at the time of the last follow-up date ($n = 148$; range 5–81 months), 114 events had been recorded, including 69 responses less than CR, 34 relapses and 11 deaths in CR. Events occurred in 54 patients in the R-CHOP arm and in 60 patients in the R-miniCEOP arm. Overall, 76 patients died: 38 in the R-CHOP arm and 38 in the R-miniCEOP arm. Of these, 43 patients died as a result of lymphoma

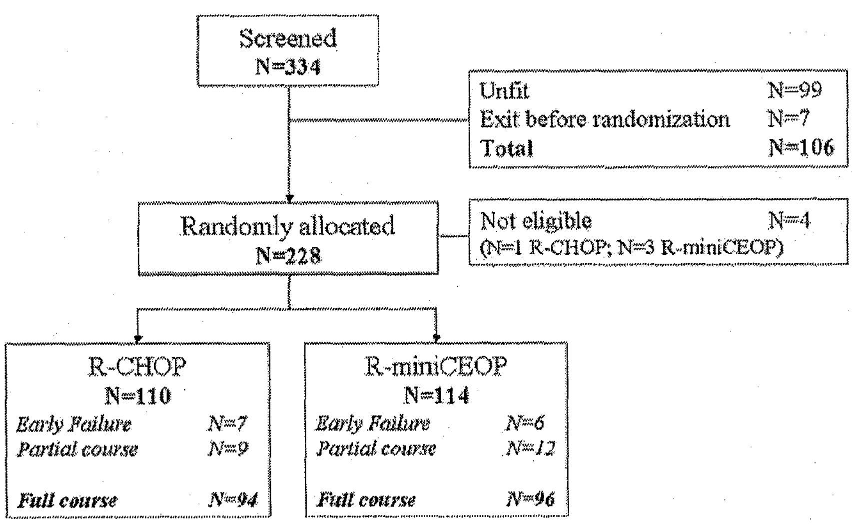

Figure 1. Treatment allocation and number of patients included in the analysis, according to the CONSORT statement. Note: After 334 patients had been screened, 99 patients were considered "unfit" for randomized trial and seven patients were excluded before the randomization. After randomization four patients were considered ineligible and were excluded. Patients were included in the analysis according to the intention-to-treat principle. Thirty-four patients did not receive all six scheduled cycles of chemotherapy (16 patients in R-CHOP and 18 patients in R-miniCEOP).

Table II. Patients' characteristics in the two treatment arms.

		R-CHOP (n = 110)		R-miniCEOP (n = 114)		Total (n = 224)		
		n	%	n	%	n	%	p-Value†
Gender	F	55	50	65	57	120	54	0.348
	M	55	50	49	43	104	46	
Age median (range)		71 (65–86)		73 (64–84)		72 (65–86)		0.341
Age	>72	43	39	58	51	101	45	0.082
AA stage	II	37	34	33	29	70	31	0.474
	III–IV	73	66	81	71	154	69	
PS	0–1	100	91	96	84	196	88	0.158
	2+	10	9	18	16	28	12	
LDH*	NV	44	41	47	44	91	42	0.678
	>1 UNL	64	59	59	56	123	58	
B2M*	NV	27	34	22	26	49	30	0.393
	>1 UNL	53	66	61	74	114	70	
Bulky*	–	79	72	90	79	169	76	0.277
	+	30	28	24	21	54	24	
ENS*	0–1	81	75	79	69	160	72	0.372
	>1	27	25	35	31	35	28	
Symptoms	A	67	61	68	60	135	60	0.892
	B	43	39	46	40	89	40	
aaIPI*	0	20	18	14	13	34	16	0.117
	1	36	33	44	42	80	37	
	2	46	43	35	33	81	38	
	3	6	6	13	12	19	9	
IADL	Score <8	26	24	22	19	48	21	0.327
CIRS-G	Score 1–2	97	88	98	86	195	87	0.693
	Score 3	13	12	16	14	29	13	

R-CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab; R-miniCEOP, epirubicin, cyclophosphamide, vinblastine, prednisone and rituximab; AA, Ann Arbor; PS, performance status; LDH, lactate dehydrogenase; B2M, β_2-microglobulin; ENS, number of extranodal sites; aaIPI, age-adjusted International Prognostic Index; IADL, instrumental activities of daily living; CIRS-G: Cumulative Illness Rating Scale for Geriatrics; NV, normal value; UNL, upper normal limit.
*Missing data: LDH (n = 10), B2M (n = 61), bulky (n = 1), ENS (n = 2), aaIPI (n = 10).
†p-Value: from Fisher's exact test, except Mann–Whitney test for age in continuous form.

progression or recurrence; other causes of death were recorded as complications/toxicity of first-line treatment in 17 patients, myocardial infarction during follow-up in four, second cancer in four, complications of salvage treatment in two, sudden death in two and one patient each due to stroke and car accident. In two cases, the cause of death was not known. Comparing R-CHOP and R-miniCEOP, causes of death were equally distributed between study arms, with the exception of a trend toward a higher number of deaths for lymphoma relapse/progression in the R-miniCEOP group (47% vs. 66% of all deaths, respectively; $p = 0.165$).

Table III. Summary of study results by treatment arm.

	R-CHOP (n = 110)		R-miniCEOP (n = 114)		
Response	n	%	n	%	p-Value
CR	80	73	77	68	0.466
PR	15	14	15	13	—
ORR	95	87	92	81	0.284
SD/PD	8	8	16	14	—
E-W	7	7	6	5	—
Survival (%)					
5-year OS	62 (51–71)		63 (52–72)		0.702
5-year EFS	48 (37–58)		46 (36–55)		0.538
Toxicity* (grade III–IV)					
Anemia	8	9	5	5	0.392
Neutropenia	20	23	22	23	1.000
Thrombocytopenia	2	2	2	2	1.000
Infections	7	8	2	2	0.090
Arrhythmia	0	0	1	1	1.000
Nausea/vomiting	3	3	1	1	0.348

R-CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab; R-miniCEOP, epirubicin, cyclophosphamide, vinblastine, prednisone and rituximab; CR, complete remission; PR, partial response; ORR, overall response rate; SD, stable disease; PD, progressive disease; E-W, early withdrawal; OS, overall survival; EFS, event-free survival.
*Toxicity data were available in 185 patients.

With respect to initial study design and hypothesis, 2-year EFS was 55% (49–62%), being 57% and 54% in the R-CHOP and R-miniCEOP arms, respectively (two-sided χ^2 test; $p = 0.678$).

Overall the estimated 5-year EFS was 47% (95% CI: 40–54%): 48% (95% CI: 37–58%) and 46% (95% CI: 36–55%) for R-CHOP and R-miniCEOP, respectively ($p = 0.538$); the 5-year OS for the whole series was 62% (95% CI: 55–69%): 62% (95% CI: 50–71%) and 63% (95% CI: 52–72%) for R-CHOP and R-miniCEOP, respectively ($p = 0.702$) (Fig. 2).

We performed univariate analysis for EFS and OS considering aaIPI risk groups, age, bulky disease and number of extranodal sites (ENS) as covariates. Age with a cut-off at 72 years and aaIPI (0–1 vs. 2–3 risk factors) were significant predictors for EFS with the addition of bulky disease, and were the only prognostic factors for OS (data not shown). In multivariate analysis aaIPI was confirmed to be an independent prognostic factor both for EFS and for OS; age above 72 years was an independent prognostic factor for OS and borderline for EFS (Table IV). Regarding EFS, the hazard ratio calculated with proportional hazards regression analysis between R-miniCEOP and R-CHOP was 1.12 (95% CI: 0.78–1.6), with a log-rank p-value of 0.538. This result was not modified by any of the potential effect modifiers. When the analysis was performed for OS the R-miniCEOP showed a better performance compared to R-CHOP in the age group older than 72 years (Fig. 3). Thus, we created four groups and performed an OS analysis: age <72 with aaIPI 0–1 (n = 64, 30%) or aaIPI 2–3 (n = 55, 26%), and age >72 with aaIPI 0–1 (n = 50, 23%) or aaIPI 2–3 (n = 45, 21%). According to this analysis, patients with age > 72 years and low aaIPI (0–1) had a better outcome when treated with R-miniCEOP compared to those

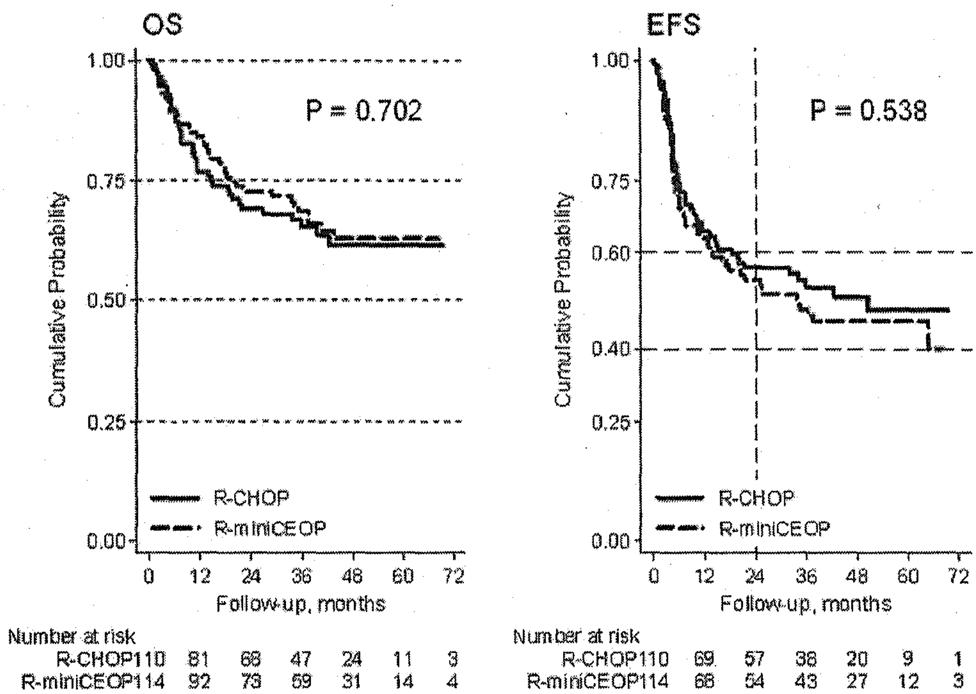

Figure 2. Overall survival (OS) and event-free survival (EFS) stratified by intention-to-treat approach. Crossing dashed lines in EFS correspond to probability at 2 years originally assumed in the trial.

treated with R-CHOP (HR = 0.13, $p = 0.011$) (Fig. 4). Also in EFS, treated patients with age > 72 and low aaIPI had a better outcome: HR 0.36 (95% CI 0.14–0.95), $p = 0.040$.

Results of comprehensive geriatric assessment

All randomized patients were defined as "fit" at CGA according to the protocol inclusion criteria. A detailed report of the CGA results is shown in Table II. Interestingly, single IADL or co-morbidity scores did not allow us to further identify prognostic subgroups in terms of EFS or OS, among randomized "fit" patients (data not shown).

Toxicity

A summary of the most common toxic events is shown in Table III. The most frequent event was neutropenia, without

Table IV. Estimates of hazard ratio from multivariate Cox proportional hazards regression for EFS and OS.

		Univariate			Multivariate		
Factor		HR	95% CI	p-Value	HR	95% CI	p-Value
EFS							
Age	>72	1.38	0.95–2.00	0.088	1.44	0.98–2.10	0.061
aaIPI	2–3	3.13	2.09–4.69	<0.001	3.19	2.12–4.78	<0.001
Bulky	+	1.57	1.05–2.36	0.029			
ENS	>1	1.45	0.98–2.15	0.063			
OS							
Age	>72	1.58	1.02–2.48	0.046	1.79	1.12–2.85	0.014
aaIPI	2–3	3.99	2.36–6.75	<0.001	4.15	2.45–7.03	<0.001
Bulky	+	1.58	0.97–2.58	0.067			
ENS	>1	1.40	0.87–2.26	0.165			

EFS, event-free survival; OS, overall survival; aaIPI, age-adjusted International Prognostic Index; ENS, number of extranodal sites; HR, hazard ratio; CI, confidence interval.

differences in the rate of grade III–IV events between the two arms (23%). A trend toward a higher rate of severe infections was observed in patients treated with R-CHOP (8%) compared with those treated with R-miniCEOP (2%) ($p = 0.090$). Overall four patients had a diagnosis of second cancer, including one acute myeloid leukemia (M5) at month 30, one bladder carcinoma diagnosed at month 36 and one pancreatic cancer diagnosed after 16 months, among patients randomized to R-CHOP, and one peritoneal carcinoma diagnosed after 34 months in a patient assigned to R-miniCEOP.

Discussion

This randomized trial was designed to compare the efficacy of standard R-CHOP with a less intense regimen (R-mini-CEOP) for the treatment of elderly patients with DLBCL prospectively defined as "fit" at CGA assessment. Based on our results, six courses of R-miniCEOP administered every 21 days are similarly effective to six courses of R-CHOP for the initial treatment of elderly "fit" patients with DLBCL. These results compare favorably with those achieved in other trials for the initial treatment of elderly patients with DLBCL. In particular, both the CR rate and OS achieved in our trial are comparable with those achieved in the R-CHOP arm of the Groupe d'Etude des Lymphomes de l'Adulte (GELA) trial (CR 76%; 5-year EFS 47%; 5- and 10-year OS 58% and 44%) [4,22], and in the R-CHOP arm of the intergroup US trial (CR/PR 77%; 3-year FFS 52%; 3-year OS 67%) [23]. Higher rates of CR (78%), 3-year EFS (66.5%) and OS (78.1%) could be achieved with six courses of the more intense R-CHOP14 arm of RICOVER-60, although some concerns on the feasibility of such an intense approach remain [24]. A recent study of the HAEMACARE project [25] showed that the estimated

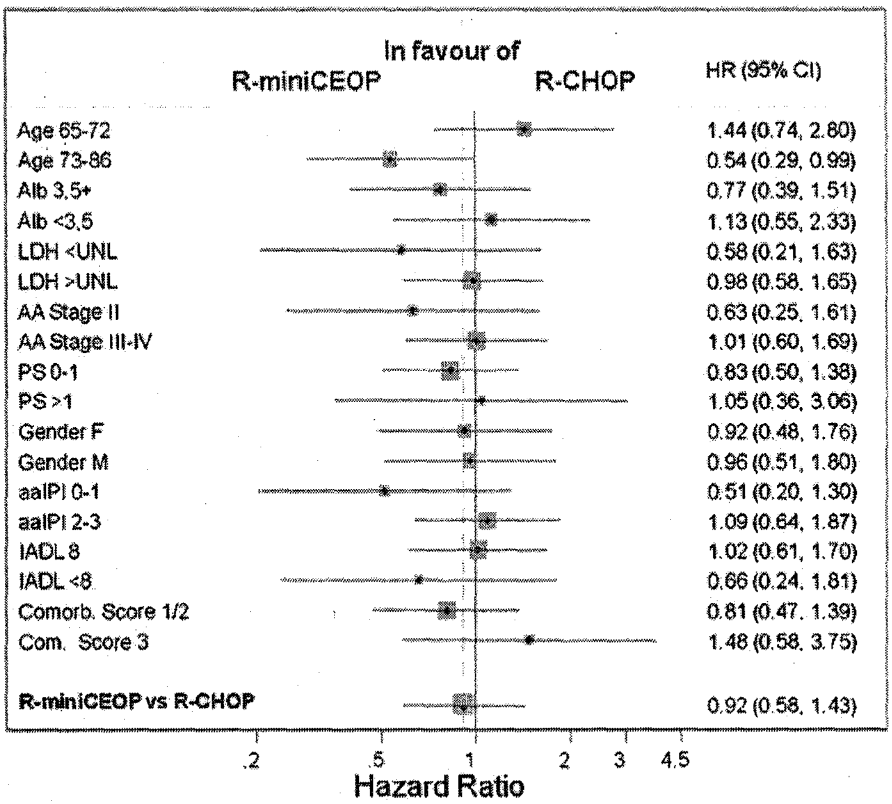

Figure 3. Effect modifier analysis. Forest plot for potentially confounding factors for overall survival (OS). Note: Continuous covariates age, erythrocyte sedimentation rate (ESR) and platelets were dichotomized at the median. Dashed vertical line: HR = 0.92, unadjusted comparison between R-miniCEOP and R-CHOP. Co-morbidity score: 1/2 fair, 3 moderate. Alb, albumin; LDH, lactate dehydrogenase; AA, Ann Arbor; PS, performance status; aaIPI, age-adjusted International Prognostic Index; IADL, instrumental activities of daily living.

relative survival in DLBCL in Europe (cohort of diagnosis 2000–2002) was 34.9%, after 5 years from diagnosis, in the age range 70–99.

Our study, showing a relative survival of 72% at 5 years, along with results of the other trials, highlights that there is a wide gap between the clinical trials and daily clinical practice.

Several trials investigated the role of regimens specifically designed for elderly patients with aggressive lymphoma and compared them with CHOP or CHOP-like chemotherapy in randomized trials [26–28]. All these studies demonstrated that less intense regimens achieved poorer results; however, no similar comparison has been performed in the era of chemoimmunotherapy. To our knowledge this is the first trial that was designed to assess the efficacy of a regimen less intense than CHOP and that also includes rituximab. Although it is difficult to estimate the differences in terms of dose intensity between study regimens, by applying the summation dose intensity (SDI) method proposed by Hryniuk *et al.* for comparing dose intensity of different chemotherapy regimens in advanced breast cancer [29] we can assume that miniCEOP has 30% reduction of SDI compared with CHOP. The absence of significant differences between the two study arms thus suggests that the anti-CD20 monoclonal antibody used may have acted as a treatment equalizer.

No statistically significant differences in toxicity between the two arms were observed. The main event was represented by neutropenia (23%), with lower rates compared to other studies, which can be partly explained by the prophylactic use of G-CSF. Overall the rate of treatment-related deaths was 7.6%, which may appear unexpectedly elevated, but this is still comparable to that described for the GELA trial (6%) [3] and for the US intergroup study (5%) [23]. Most deaths occurred during treatment; however, 25% of such events occurred within 3 months from the end of treatment, confirming the hypothesis that elderly patients undergoing chemotherapy may show a prolonged risk of treatment-related toxicity. Finally, 7% of patients (21% of all deaths) died during follow-up due to causes not related to lymphoma; again, no differences between the study arms were observed: myocardial infarction and second cancer were the most frequently registered causes of death, with four cases each (5% of all deaths).

One of the most relevant findings of our study is that for relatively older patients (older than 72 years) with low-risk disease (aaIPI 0–1) the less intense R-miniCEOP may be a better choice than standard R-CHOP. The trial was not powered to identify small differences of study endpoints between study arms, but our hypothesis is that R-CHOP, even if it is tolerable in elderly people, may become detrimental in relatively "frailer" patients with less aggressive disease. Looking at the study results, patients treated with R-CHOP had a trend toward a better response rate and a reduced risk of death due to lymphoma relapse or progression that was

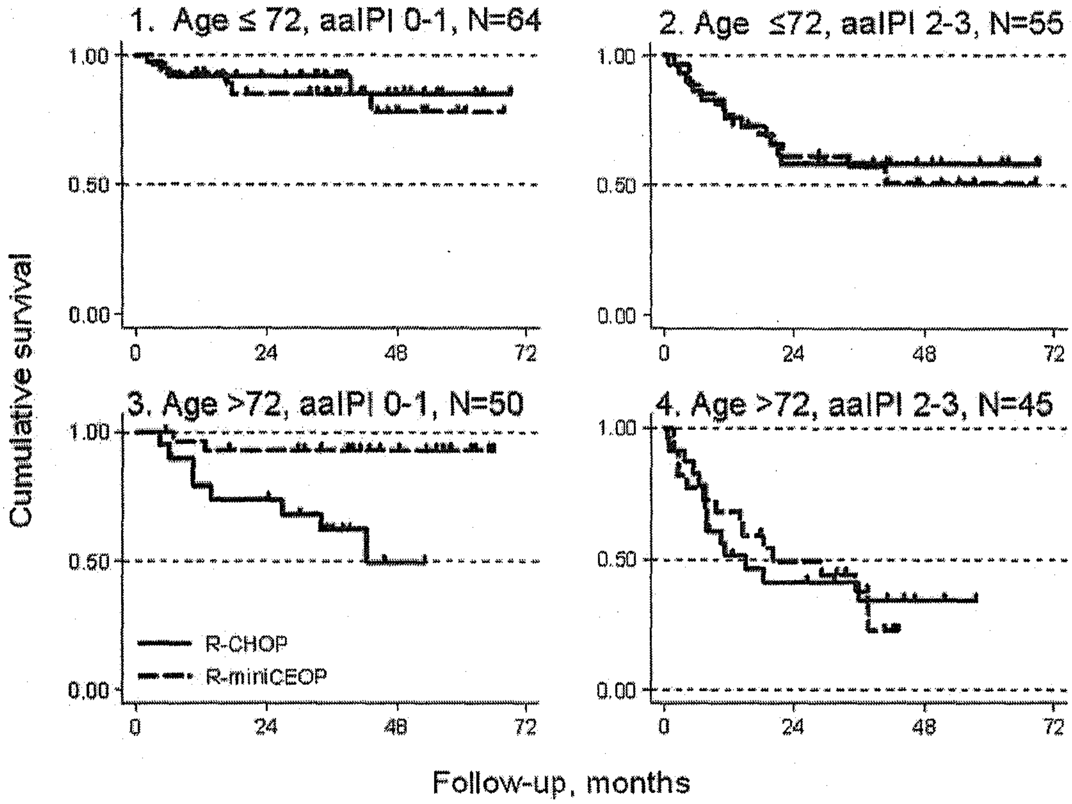

Figure 4. Overall survival estimated with Kaplan-Meier method stratified by age and aaIPI. Comparison R-miniCEOP (dashed line) vs. R-CHOP (solid line). 1. HR = 1.57, p = 0.501; 2. HR = 1.11, p = 0.803; 3. HR = 0.13, p = 0.011; 4. HR = 1.04, p = 0.923.

counterbalanced by a non-statistically significant increase in the rate of severe infections and of treatment-related deaths. For very old patients with low-risk disease, less intense regimens such as R-miniCEOP may then be a better strategy, as they are more focused on preserving the patient from unnecessary toxicity, compared with R-CHOP. The use of age as a prognostic variable to further discriminate elderly patients at different risk of failure or death has been recently confirmed by Advani *et al.* [30]; however, additional trials specifically powered to verify our hypothesis are warranted.

Prospective assessment of patient "status" was one of the most important features of this study, and was introduced to avoid subjective evaluation of a patient's ability to receive full-dose therapy. Currently used criteria for registering patients are usually limited to the assessment of performance status and/or to non-validated criteria generally referred to as: "in the opinion of the investigator the general status of the patient did permit the administration of 8 courses of CHOP" [3]; or "if patient is able to comply with study requirements" [24]. In our study unfit patients had an HR of 3.03 (95% CI, 2.17–4.23) compared to fit patients for the risk of death, and showed a poorer outcome also if treated with a rituximab-containing regimen (HR 2.34; 95% CI, 1.43–3.83) [23]. These data support the use of CGA as a good tool to select "fit" patients, confirming previous reports [10,31]. Indeed, the adoption of such an approach makes our results more reproducible, as patient selection was not left to subjective assessment. Moreover, even though the present trial was not designed to verify the effectiveness of CGA to identify patients who can receive full-dose treatment, considering the elevated median age and the inclusion of very old patients in our trial, we hypothesize that this is the result of a better selection of patients. CGA is then a tool that extends the possibility of adopting full-dose chemotherapy in elderly patients with DLBCL and ultimately improving curability. Further improvement in the approach to elderly patients undergoing systemic chemotherapy may be achieved in future studies by investigating patients' functionality and quality of life during treatment and follow-up.

In conclusion, based on our results, we confirm that a good proportion of elderly patients with DLBCL can be cured with immunochemotherapy. The choice of the optimal therapy for each individual patient should be based on an accurate assessment of disease risk and of the patient's status through the adoption of validated tools to identify "fit" patients, such as CGA. Finally, our results also suggest that availability of the anti-CD20 monoclonal antibody can allow the use of less-intense chemotherapy regimens such as mini-CEOP, and that this can an acceptable option for the treatment of relatively older patients with low-risk disease.

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References

[1] Swerdlow SH, Campo E, Harris NL, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon: IARC; 2008.
[2] 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.
[3] 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.
[4] 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.
[5] Merli F, Bertini M, Luminari S, et al. Long term results of a randomized study performed by Intergruppo Italiano Linfomi comparing mini-CEOP vs P-VEBEC in elderly patients with diffuse large B-cell lymphoma. Leuk Lymphoma 2007;48:367-373.
[6] Zinzani PL, Gherlinzoni F, Storti S, et al. Randomized trial of 8-week versus 12-week VNCOP-B plus G-CSF regimens as front-line treatment in elderly aggressive non-Hodgkin's lymphoma patients. Ann Oncol 2002;13:1364-1369.
[7] Luminari S, Montanini A, Caballero D, et al. Nonpegylated liposomal doxorubicin (MyocetTM) combination (R-COMP) chemotherapy in elderly patients with diffuse large B-cell lymphoma (DLBCL): results from the phase II EURO18 trial. Ann Oncol 2010;21:1492-1499.
[8] Peyrade F, Jardin F, Gisselbrecht C, et al. Rituximab and reduced dose CHOP (R-mini-CHOP) for patients over 80 years with diffuse large B-cell lymphoma (DLBCL) - Groupe d'Etude Des Lymphomes De l'Adulte (GELA) Study LNH03-7B. Blood 2010;116(Suppl. 1): Abstract 853.
[9] Balducci L, Beghe C. The application of the principles of geriatrics to the management of the older person with cancer. Crit Rev Oncol Hematol 2000;35:147-154.
[10] Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. J Clin Oncol 2007;25:1824-1831.
[11] Miller MD, Towers A. A manual of guidelines for scoring the cumulative illness rating scale for geriatrics (CIRS-G). Pittsburg, PA: University of Pittsburg; 1991.
[12] 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.
[13] Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol 1999;17:1244.
[14] Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.
[15] Hryniuk WM. Average relative dose intensity and the impact on design of clinical trials. Semin Oncol 1987;14:65-74.
[16] Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-481.
[17] Cox DR. Regression models and life tables. J R Stat Soc B 1972;34:187-202.
[18] Armitage P, Berry G. Statistical methods in medical research. Oxford, UK: Blackwell; 1987.
[19] Wang R, Lagakos SW, Ware JH, et al. Statistics in medicine—reporting of subgroup analyses in clinical trials. N Engl J Med 2007;357:2189-2194.
[20] Shoenfeld D. Partial residuals for the proportional hazard regression model. Biometrika 1982;69:239-241.
[21] Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood 2010;116:2040-2045.
[22] 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.
[23] Pfreundschuh M, Schubert J, Ziepert M, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20 + B-cell lymphomas: a randomised controlled trial (RICOVER-60). Lancet Oncol 2008;9:105-116.
[24] Marcos-Gragera R, Allemani C, Tereanu C, et al. Survival of European patients diagnosed with lymphoid neoplasms in 2000-2002: results of the HAEMACARE project. Haematologica 2011;96:720-728.
[25] Sonneveld P, de Ridder M, van der Lelie H, 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.
[26] Tirelli U, Errante D, Van Glabbeke M, et al. CHOP is the standard regimen in patients > or = 70 years of age with intermediate-grade and high-grade non-Hodgkin's lymphoma: results of a randomized study of the European Organization for Research and Treatment of Cancer Lymphoma Cooperative Study Group. J Clin Oncol 1998;16:27-34.
[27] Bastion Y, Blay JY, Divine M, et al. Elderly patients with aggressive non-Hodgkin's lymphoma: disease presentation, response to treatment, and survival—a Groupe d'Etude des Lymphomes de l'Adulte study on 453 patients older than 69 years. J Clin Oncol 1997;15:2945-2953.
[28] Hryniuk W, Frei E 3rd, Wright FA. A single scale for comparing dose-intensity of all chemotherapy regimens in breast cancer: summation dose-intensity. J Clin Oncol 1998;16:3137-3147.
[29] Advani RH, Chen H, Habermann TM, et al. Comparison of conventional prognostic indices in patients older than 60 years with diffuse large B-cell lymphoma treated with R-CHOP in the US Intergroup Study (ECOG 4494, CALGB 9793): consideration of age greater than 70 years in an elderly prognostic index (E-IPI). Br J Haematol 2010;151:143-151.
[30] Monfardini S, Ferrucci L, Fratino L, et al. Validation of a multidimensional evaluation scale for use in elderly cancer patients. Cancer 1996;77:395-401.