Leukemia & Lymphoma, February 2007; 48(2): 367 – 373

informa
healthcare

ORIGINAL ARTICLE: CLINICAL

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

F. MERLI[1], M. BERTINI[2], S. LUMINARI[3], R. MOZZANA[4], B. BOTTO[2], A. M. LIBERATI[5], L. BALDINI[6], G. CABRAS[7], F. DI VITO[8], L. ORSUCCI[2], E. NAGLIERI[9], G. POLIMENO[10], L. MARCHESELLI[3], E. PENNESE[11], U. VITOLO[2], M. FEDERICO[3], & E. GALLO[2]

[1]*Unità Operativa di Ematologia, A.O. S. Maria Nuova, Reggio Emilia, Italy,* [2]*Struttura Complessa di Ematologia, A.O. S. Giovanni Battista, Torino, Italy,* [3]*Dipartimento di Oncologia ed Ematologia, Università di Modena e Reggio Emilia, Modena, Italy,* [4]*Medicina Interna, Azienda Ospedaliera S. Antonio Abate, Gallarate, Italy,* [5]*Istituto di Medicina Interna e Sc. Oncologiche, Policlinico Monteluce, Perugia, Italy,* [6]*Unità malattie linfoproliferative, Dipartimento di Ematologia, Centro G. Marcora, Ospedale Maggiore, IRCCS, Milan, Italy,* [7]*Divisione di Ematologia, Ospedale Businco, Cagliari, Italy,* [8]*Dipartimento di Oncologia, Ospedale Regionale, Aosta, Italy,* [9]*Dipartimento di Oncologia Medica e Sperimentale, Istituto Oncologico, Bari, Italy,* [10]*U.O. Semplice di Oncoematologia, Divisione di Medicina, Ospedale "F. Miulli", Acquaviva delle Fonti (BA), Italy,* [11]*Dipartimento di Ematologia, Osp. S. Spirito, Pescara, Italy*

(Received 4 August 2006; revised 3 October 2006; accepted 18 October 2006)

Abstract

The Intergruppo Italiano Linfomi started, in 1996, a randomized trial for the initial treatment of elderly patients (older than 65 years) with Diffuse Large B-Cell Lymphoma (B-DLCL) comparing 6 courses of Mini-CEOP vs 8 weeks of P-VEBEC chemotherapy. Study objectives were survival, response and Quality of Life (QoL). Two hundred and thirty-two patients were evaluable for final analysis. Complete Response (CR) and Overall Response Rates (ORR) were 54% vs 66% ($p = 0.107$) and 90% vs 78% ($p = 0.021$) for P-VEBEC and Mini-CEOP, respectively. With a median follow-up of 72 months, the 5-year Overall Survival (OS), Relapse Free Survival (RFS), and Failure Free Survival (FFS) were 32%, 52%, and 21%, respectively. Subjects achieving a CR showed improvement of QoL regardless of treatment arm. Both Mini-CEOP and P-VEBEC determined a similar outcome for elderly patients with B-DLCL, with a third of patients alive after more than 6 years of follow-up. Both regimens can be considered equally for combination treatment with anti-CD20 monoclonal antibody.

Keywords: *elderly, B-DLCL, aggressive lymphoma, chemotherapy, Quality of Life*

Introduction

Non-Hodgkin lymphomas (NHL) are the fifth most common human neoplasm, with an incidence of 3 – 4% of all newly diagnosed cancers, and are more frequent in the elderly population.

In contrast to young patients, the presence of concomitant diseases or the frail status of elderly patients may influence treatment decisions limiting available options, and this often results in under-treatment and a reduced chance of cure [1]. However, approximately 50% of patients with Diffuse Large B-Cell Lymphoma (B-DLCL) are aged over 60 years. In the '80s and '90s several attempts were made to identify chemotherapy regimens specifically devised for elderly patients, which allowed good rates of disease remission and an acceptable toxicity profile [2 – 5].

Correspondence: Francesco Merli, MD, Servizio di Ematologia, A.O. S. Maria Nuova, V.le Risorgimento, 80 – 42100 Reggio Emilia, Italy.
Tel: +39-522-296626, Fax: +39-522-295935. E-mail: merli.francesco@asmn.re.it

ISSN 1042-8194 print/ISSN 1029-2403 online © 2007 Informa UK Ltd.
DOI: 10.1080/10428190601078100

Before the Rituximab era, no chemotherapy combination was demonstrated to be superior to CHOP chemotherapy [6]. However, concerns regarding the tolerability of this regimen for a population of elderly patients still remained [7]. As a consequence, various chemotherapy regimens deriving from CHOP have been prepared, with the aim of reducing early and late toxicity [8–10].

In 1996 Bertini et al. published the encouraging results of a phase II trial, in which 100 patients aged over 65 years with aggressive NHL received 8 courses of the intensive multi-drug regimen P-VEBEC. Patients achieved 62% Complete Remission (CR) rate and an Overall Survival (OS) of 44% at 33 months, with severe toxicity rarely recorded and only one toxic death [11].

In 1996, Interguppo Italiano Linfomi (IIL) started a phase III randomized study comparing P-VEBEC with a newly designed CHOP derived regimen, namely Mini-CEOP, in which doxorubicin was substituted with less toxic doses of epirubicin and vincristine was replaced by vinblastine, which is likewise considered more tolerable. The two chemotherapy regimens were compared in terms of response rate, survival, and toxicity. In addition, the aim of the study was to assess the real impact of lymphoma treatment and cure on Quality of Life (QoL).

Materials and methods

Inclusion criteria and staging procedures

To be enrolled in the study patients had to be aged over 65 years and have newly diagnosed histologically confirmed Diffuse Large B-Cell Lymphoma according to REAL classification [12]. Patients also had to have advanced disease defined as Ann Arbor stage III or IV or stage II with B symptoms or any stage with bulky mass greater than 10 cm in maximum diameter. Performance Status had to be ambulatory (ECOG 0–2) and patients had to be HIV negative, without severe concomitant disorders or primary CNS lymphoma. Patients were required to have an ejection fraction of at least 50% at bidimensional echocardiogram. The presence of comorbidities was allowed if not invalidating and if well controlled with drug therapy.

All patients should have performed baseline exams including: chest, abdomen and pelvis CT scan, and bone marrow biopsy, complete liver and renal function tests, serum protein electrophoresis, serum calcium, blood cell and differential counts, serum Lactic Dehydrogenase (LDH) levels and Electrocardiogram. Age adjusted IPI was calculated for all registered patients as originally reported [13].

Study design

Eligible patients were centrally randomized in a 1:1 ratio to one of two study arms. Arm A received 6 cycles of Mini-CEOP regimen which consisted of 50 mg/m^2 epirubicin i.v., 750 mg/m^2 cyclophosphamide, 5 mg/m^2 vinblastine day 1 and 50 mg/m^2 prednisone days 1–5 every 3 or 4 weeks according to the hematologic toxicity. Arm B received 8 weeks of P-VEBEC regimen, which consisted of 50 mg/m^2 epirubicin i.v.; 300 mg/m^2 cyclophosphamide i.v.; 100 mg/m^2 etoposide in weeks 1, 3, 5, 7; 5 mg/m^2 vinblastine; and 5 mg/m^2 bleomycin in weeks 2, 4, 6, 8; and 50 mg prednisone daily per os in the first two weeks and then every other day. Clinical restaging was performed after 3 cycles of Mini-CEOP or 4 weeks of P-VEBEC and at the end of treatment. No further therapy was administered to patients in CR. Patients with a partial response (PR) or failure received different combinations of radiation and salvage chemotherapy.

Prophylaxis of bacterial and fungal infections was undertaken with ciprofloxacin and ketoconazole in the event of infection or leukopenia during the previous course. Dose reductions were allowed according to specified criteria: epirubicin, cyclophosphamide and etoposide were to be delivered at full doses if neutrophils were more than 1.0×10^9/L, at 2/3 of full dose if between 0.5 and 0.999×10^9/l. Treatment was postponed for one week if neutrophil counts were less than 0.5×10^9/l. No reduction was planned in the event of thrombocytopenia or anemia. Use of G-CSF at 5 μg/kg was not mandatory but was allowed at the discretion of the physician.

Toxicity was evaluated during treatment and coded on a 0–4 scale according to WHO criteria.

Definition of study endpoints

Disease status was evaluated by means of clinical examination, CT scan, and any other examination that gave positive results prior to start of treatment. All masses were described, with measurement of their maximum transverse diameters. Complete response was defined as absence of any sign or symptom of lymphoma and regression to normal size of residual lymphnodes (maximum diameter less than 1.5 cm). PR was defined as a reduction of at least 50% from baseline as regards the sum of the products of the diameters of all measurable lesions, or persistence of extranodal or bone marrow infiltrate regardless of lymphnode change. Stable Disease (SD) was defined in case of a reduction in lymph node size of less than 50%. Progressive Disease (PD) was defined in case of increase of one or more

lymphoma lesions and/or the appearance of any new lymphoma-related sign or symptom.

Overall Survival (OS) was calculated for all patients from date of randomization to date of death, for whatever cause, or to date of last visit. Failure Free Survival (FFS) was calculated for all patients from date of randomization until death or progression of disease. Relapse Free Survival (RFS) was calculated for patients in CR from the end of treatment to date of relapse.

Dose intensity (DI) was calculated according to Hryniuk and Bush [14]. Actual DI is defined as the amount of drug given to a patient per unit of time, expressed as mg/m^2/week. RDI is the ratio between the DI actually received and the projected drug DIs: for P-VEBEC: vinblastine 2.5 mg/m^2/week, epirubicin 25 mg/m^2/week, bleomycin 2.5 mg/m^2/week, etoposide 50 mg/m^2/week, cyclophosphamide 150 mg/m^2/week, and prednisone 228 mg/m^2/week. The planned treatment completion time was 56 days; for Mini-CEOP: cyclophosphamide 250 mg/m^2/week, epirubicin 16.7 mg/m^2/week, vinblastine 1.7 mg/m^2/week, and prednisone 100 mg/m^2/week. The planned treatment completion time was 126 days.

For Quality of life assessment the Italian validated version of EORTC QLQ-C30 questionnaire [15] was used. The questionnaire had to be completed at diagnosis, after 63 days for Mini-CEOP and after 28 days for P-VEBEC and at the end of the two treatment programs.

Statistical methods

Data were analyzed with Statistical Package for Social Sciences (SPSS v11). Proportions were compared using the Fisher exact test. Multivariate analysis was performed according to the Cox regression model. Survival curves were plotted according to the Kaplan–Meier method and compared using the Log Rank test. All statistical tests were two-sided with a limit of significance (p value) of 0.05.

Relative survival was calculated using the maximum likelihood method of Esteve [16]. This procedure first estimates the net mortality rate for subjects, in each of a set of predefined intervals, following the initial event. Cumulative crude and relative survival rates are then calculated and tabulated for exact times after the initial event.

Relative survival is defined as the ratio of observed survival in the study group and the survival that would have been expected, had they been subject only to the population mortality rates available. Relative survival may be interpreted as survival corrected for background mortality.

Sample size

Five-year Overall survival was considered for determination of sample size considering a 5 year OS of 30% for standard arm. With the initial hypothesis that that the experimental arm could improve 5-year OS of 15% and with a power of 80% and a level of significance of 5%, the number of patients required for demonstrating such difference was 272. The planned duration of the accrual phase was 4 years.

Results

Between June 1996 and December 1999, 264 patients were registered into the trial from 3 Italian cooperative study groups of Intergruppo Italiano Linfomi and randomized. After randomization 32 patients were considered not eligible: 30 for major violation of inclusion criteria (6 due to concomitant tumor, 17 histology different from B-DLCL, 5 due to stage I disease, and 2 due to severe comorbidity) and 2 for missing data. The clinical characteristics of the remaining 232 eligible patients (125 Mini-CEOP, arm A; 107 P-VEBEC, arm B) are shown in Table I.

Treatment program was completed in all but 21 (9%) cases because of toxicity (10 patients in arm A, 11 in arm B). One hundred and ninety-six patients were available for final response assessment (Table II). The Overall Response Rate (ORR = CR + PR) was 78% and 90% for arm A and B ($p = 0.021$), with a CR rate of 66% and 54% for arm A and arm B, respectively ($p = 0.107$). A higher rate of SD or PD was observed in the Mini-CEOP arm.

Table I. Patients' characteristics according to treatment arm.

Characteristics	No. of patients (%) Mini-CEOP ($N = 125$)	P-VEBEC ($N = 107$)	p value
Median age (range)	73 (66–87)	74 (65–86)	n.s.
Male gender	47 (38)	47 (44)	n.s.
Performance Status 2–4	33 (27)	32 (30)	n.s.
Ann Arbor stage III–IV	94 (75)	76 (71)	n.s.
Bulky disease	29 (23)	36 (34)	n.s.
Extranodal involvement $\geq$2 sites	38 (31)	24 (23)	n.s.
Bone Marrow involvement	29 (24)	21 (20)	n.s.
Elevated LDH	66 (55)	71 (68)	
Age Adjusted IPI			
Low	17 (15)	10 (10)	n.s.
Low-Intermediate	39 (33)	29 (28)	
Intermediate-High	38 (32)	48 (47)	
High	23 (20)	16 (15)	
NA	8	4	

IPI, International Prognostic Index; NA, Not Assessed; WF, Working Formulation; ALCL, Anaplastic Large Cell Lymphoma.

The RDIs for cyclophosphamide and epirubicin were not significantly different in the two arms (data not shown); however RDI for epirubicin was similarly reduced in both arms (74%). G-CSF use was admitted by the protocol in both arms and was used in 43% of patients treated with Mini-CEOP and 29% of those treated with P-VEBEC.

After a median follow-up for living patients of 72 months (range 9–104), 57 patients out of 119 responding patients relapsed, resulting in a 5-year RFS of 48% and 57% for Mini-CEOP and P-VEBEC, respectively ($p = 0.375$) (Figure 1).

One hundred and eighty-six failures were registered among the 232 eligible patients. As a consequence the 5-year FFS was 21% for both study arms with no differences in median ($p = 0.370$).

Overall, 165 patients died, 93 in the Mini-CEOP and 72 in the P-VEBEC arm. Lymphoma was the most frequent cause of death, with similar rates between the two study arms (73% and 68% respectively). Treatment-related deaths occurred in 17 cases (10 cases for arm A and 7 cases for arm B; $p =$ ns). Five years OS was 32% without differences between the two study arms; median OS was 18 months for Mini-CEOP and 20 months for P-VEBEC (Figure 2). No differences in terms of cause-specific survival were observed (data not shown).

RFS, FFS, and OS curves for the whole series are shown in Figure 3. Toxicity was evaluated in all patients, with higher rates of grade III/IV neutropenia (27% vs 39%; $p = 0.049$) in patients treated with P-VEBEC. No significant difference was observed for other toxicities; cardiac events were observed in 6% of arm A and 7% of arm B; nausea and vomiting in 5% of arm A and 9% of arm B; severe infections in 10% of arm A and 13% of arm B (NS). Neurological problems were present in 4% and 6% of arm A and B respectively.

Table II. Response to treatment.

	No. of patients (%)		
	Mini-CEOP ($N = 104$)	P-VEBEC ($N = 92$)	p value
CR	69 (66)	50 (54)	0.107
PR	12 (12)	33 (36)	
ORR	81 (78)	83 (90)	0.021
SD/PD	23 (22)	9 (10)	
Patients with response data	104	92	
Stop for toxicity	2 (2)	4 (4)	
Toxic deaths	9 (7)	8 (7)	
Total with available data*	122	106	

*4 patients without response data (3 in arm A; 1 in arm B). CR, Complete Remission; PR, Partial Remission; ORR, Overall Response Rate; NR, No Remission; PD, Progressive Disease.

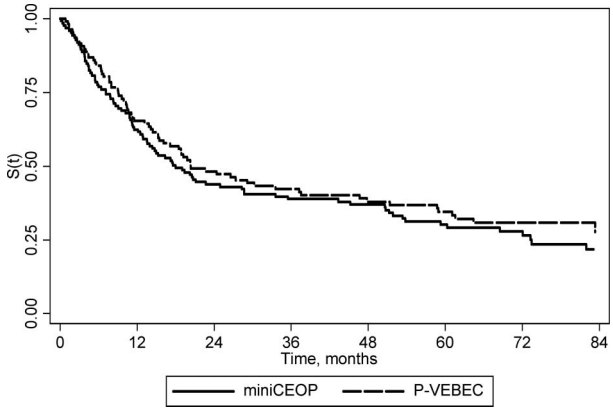

Figure 2. Overall Survival (OS) according to treatment arm (Mini-CEOP, solid line; P-VEBEC, dashed line).

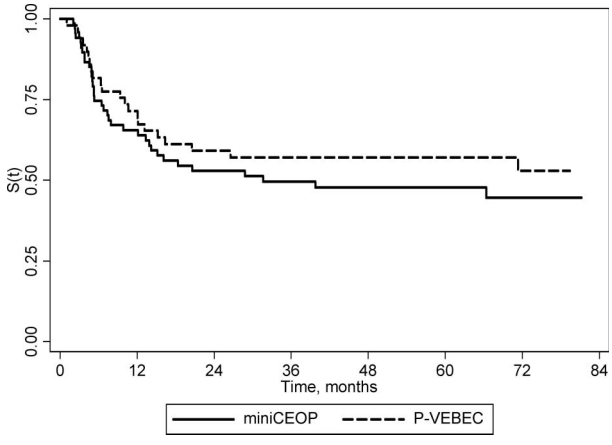

Figure 1. Relapse Free Survival (RFS) according to treatment arm (Mini-CEOP, solid line; P-VEBEC, dashed line).

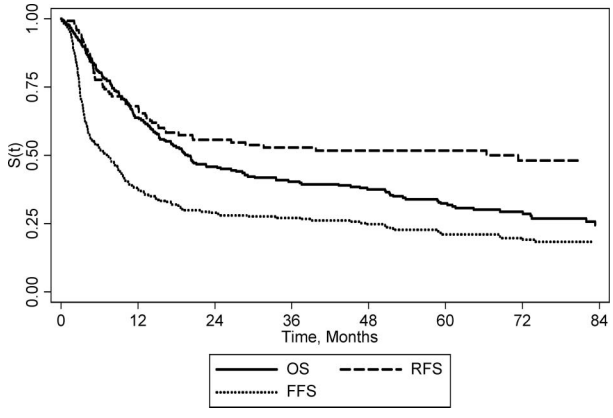

Figure 3. Overall Survival (OS), Relapse Free Survival (RFS), and Failure Free Survival (FFS) for all 232 patients (OS, solid line; RFS, dashed line; FFS, dotted line).

Univariate analysis of survival for the whole group showed a correlation with a shorter OS for age as a continuous variable ($p < 0.001$), bone marrow involvement ($p = 0.04$) and elevated LDH ($p < 0.001$), and with age adjusted International Prognostic Index (aaIPI) ($p = 0.004$); shorter RFS was associated with bone marrow involvement ($p < 0.001$).

Cox multivariate analysis of OS confirmed an independent prognostic role only for age ($p = 0.001$) and elevated LDH ($p < 0.001$). Bone marrow involvement confirmed its role as an independent prognostic factor for RFS ($p < 0.001$).

Actual survival rates were compared with relative survival, calculated on the basis of data from the Italian National Institute of Statistics (http://www.mortalita.iss.it). The results of our analysis showed that the Standardized Mortality Ratio (SMR) was 5.38 for the whole study population, without differences between the two study arms. SMR was higher for patients aged less than 70 years (SMR 12.7) and tended to stabilize after 75 years (Figure 4a). The excess in mortality rate was highest during the first two years of follow-up, and then become more stable and comparable to that of the general population (Figure 4b).

QoL was investigated in 156/232 patients (67%), although only 91 patients completed both pre-therapy and post-therapy questionnaires. Baseline QoL assessment showed a strong correlation of poor values of QoL with anemia and high risk according to the International Prognostic Index. At the end of treatment no functional scales showed worse values. A significant improvement was observed for pain ($p = 0.003$), appetite ($p = 0.006$), sleep ($p = 0.015$), and global health ($p = 0.027$). Considering only the 50 patients who achieved a CR, an improvement was also recorded for emotional state ($p = 0.10$), role ($p = 0.05$), constipation ($p = 0.04$), and global QoL ($p = 0.05$). No significant differences in terms of QoL changes were found between patients treated with P-VEBEC and those treated with Mini-CEOP (data not shown).

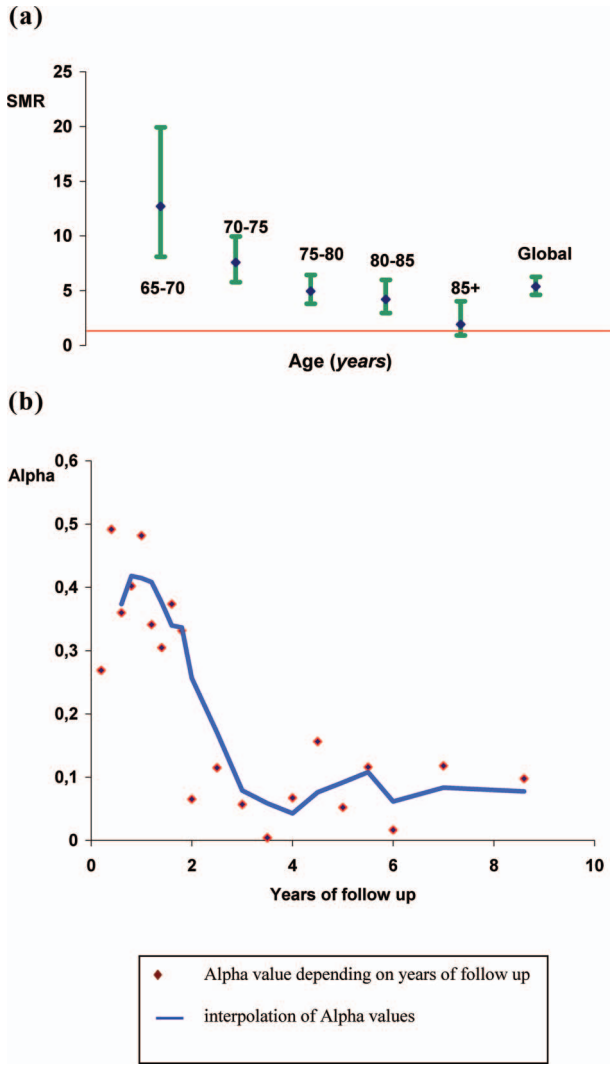

Figure 4. (a) Median Standardized Mortality Rate (SMR) for the 232 patients according to age group (reference line for SMR = 1 is represented at the bottom of the graph). (b) Excess of relative mortality rate expressed as Alpha index for the study population by duration of follow-up (diamonds indicate single Alpha values; solid line represents interpolation of single values).

Discussion

Management of elderly B-DLCL patients requires special attention because of the increased risk of toxicity and treatment-related death and comorbidity. In recent years the addition of Rituximab to standard dose CHOP has completely modified our approach to elderly patients with B-DLCL and it has been demonstrated that the cure of lymphoma is a realistic goal for this subset of patients too [17]. However, the addition of monoclonal antibodies to chemotherapy does not answer the question of which chemotherapy regimen can offer the best results. This is particularly true for the subset of elderly patients with comorbid conditions, which may represent a contraindication to the administration of standard dose CHOP. Moreover, it is not only the effectiveness of treatment that should be evaluated in elderly patients, but also the type of life they are offered during and after chemotherapy.

In 1996, IIL started a prospective trial, which compared a CHOP-derived regimen (Mini-CEOP) to a MACOP-B-derived therapy (P-VEBEC) for the treatment of elderly patients with aggressive NHL. In addition to the traditional endpoints relating to treatment efficacy, the study also evaluated the issue of QoL following chemotherapy. The aim of our

study was basically to compare two different strategies for the treatment of elderly patients with lymphoma. On one side we chose to treat patients with a CHOP-derived regimen specially designed for the elderly (epirubicin instead of doxorubicin and vinblastine instead of vincristine).

The alternative treatment was chosen on the basis of the results of a previous phase II study investigating P-VEBEC regimen, which consisted of weekly administration of lower single doses of drugs over a shorter period of time.

Our results did not demonstrate differences between the two study arms. Although patients treated with P-VEBEC had a better ORR than those treated with mini-CEOP, similar CR rate RFS and OS were observed. Toxicity rate was comparable between arms and similar to that observed in other studies: neutropenia and anemia were more frequent in patients treated with P-VEBEC ($p = 0.01$ and $p = 0.05$, respectively), whereas the incidence of infections was similar in the two groups. No differences were observed for neurological, gastrointestinal, and cardiac complications.

In our study, evaluation of patients' QoL was also included among study endpoints. QoL evaluation acquires greater significance in cancer trials, since it may well be preferred to quantity of life by the elderly [18,19]. Based on study results no functional scale showed worse values at the end of therapy than at diagnosis. More importantly, patients who responded to therapy had an improvement in global health, global QoL, pain, sleep, appetite loss, emotional state, role, and constipation. These data demonstrate that the symptoms of the disease have a greater negative influence on patient's life than do treatment-related side effects [20].

Based on prolonged follow-up of our study, the observation that one third of patients are alive after 5 years provides a realistic picture of the curability of elderly patients with aggressive NHL in the pre-Rituximab era. Interestingly, from the analysis of relative survival the excess of mortality rate was more relevant for patients aged from 65 to 75 years and during the first two years of follow-up. These data suggest that analysis of relative survival is important to understand the real impact of lymphoma and treatment in a population of patients characterized by frequent comorbidities and shorter life expectancy. Our results also indicate the need for more effective treatment, in particular for patients less than 70 years of age. On the basis of recently published data we know that the addition of Rituximab to conventional chemotherapy or dose dense CHOP regimens is able to improve the outcome of elderly patients with NHL [21–23]. However, available data on R-CHEMO in the elderly population did not investigate the issue of patients' frailty sufficiently, and this is still a matter of concern in daily clinical practice. Our results with P-VEBEC arm are substantially superimposable to those obtained in the phase II study with only slight differences in terms of CR rate (62% vs 54%) that could be explained with a higher median age in the current series (74 vs 71 years), with a higher rate of patients with elevated LDH in the randomized study (78% vs 37%) and with the inclusion of intermediate aggressiveness lymphomas (Working Formulation D and E) in the phase II trial. Even if results of P-VEBEC are worse than those obtained with R-chemo in elderly patients with aggressive B-cell NHL, the good tolerability and the short duration of our experimental arm may be considered, in combination with Rituximab, as a treatment option for frail patients, not eligible to full-doses R-CHOP chemotherapy that is the standard for the elderly patients who can tolerate full dose regimens. We then believe that the definition of patient's status is a fundamental aspect of future studies in pre-treatment selection and management of elderly patients. A clinical randomized trial by our group, comparing R-CHOP and R-miniCEOP regimens for elderly B-DLCL patients, that includes a prospective selection of cases on the basis of a comprehensive geriatric assessment [24] is currently ongoing.

Acknowledgements

We thank Lina De Masi for computing assistance and Antonella Montanini for supporting the manuscript preparation. This work was partially supported by GRADE (Gruppo Amici dell'Ematologia), Reggio Emilia, and Associazione Angela Serra per la Ricerca sul Cancro, Modena.

References

1. Vose JM, Armitage JO, Weisenburger DD, Bierman PJ, Sorensen S, Hutchins M, et al. The importance of age in survival of patients treated with chemotherapy for aggressive non-Hodgkin's lymphoma. J Clin Oncol 1988;6: 1838–1844.
2. O'Reilly SE, Klimo P, Connors JM. Low-dose ACOP-B and VABE: weekly chemotherapy for elderly patients with advanced-stage diffuse large-cell lymphoma. J Clin Oncol 1991;9:741–747.
3. Tirelli U, Zagonel V, Errante D, Serraino D, Talamini R, De Cicco M, et al. A prospective study of a new combination chemotherapy regimen in patients older than 70 years with unfavorable non-Hodgkin's lymphoma. J Clin Oncol 1992; 10:228–236.
4. Martelli M, Guglielmi C, Coluzzi S, Avvisati G, Amadori S, Giovannini M, et al. P-VABEC: a prospective study of a new weekly chemotherapy regimen for elderly aggressive non-Hodgkin's lymphoma. J Clin Oncol 1993;11:2362–2369.

5. Zinzani PL, Storti S, Zaccaria A, Moretti L, Magagnoli M, Pavone E, et al. Elderly aggressive-histology non-Hodgkin's lymphoma: first-line VNCOP-B regimen experience on 350 patients. Blood 1999;94:33–38.
6. Fisher RI, Gaynor ER, Dahlberg S, Oken MM, Grogan TM, Mize EM, 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.
7. Doorduijn JK, van der Holt B, van Imhoff GW, van der Hem KG, Kramer MH, van Oers MH, et al. CHOP compared with CHOP plus granulocyte colony-stimulating factor in elderly patients with aggressive non-Hodgkin's lymphoma. J Clin Oncol 2003;21:3041–3050.
8. Sonneveld P, de Ridder M, van der Lelie H, Nieuwenhuis K, Schouten H, Mulder A, 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.
9. Meyer RM, Browman GP, Samosh ML, Benger AM, Bryant-Lukosius D, Wilson WE, et al. Randomized phase II comparison of standard CHOP with weekly CHOP in elderly patients with non-Hodgkin's lymphoma. J Clin Oncol 1995;13:2386–2393.
10. Osby E, Hagberg H, Kvaloy S, Teerenhovi L, Anderson H, Cavallin-Stahl E, et al. CHOP is superior to CNOP in elderly patients with aggressive lymphoma while outcome is unaffected by filgrastim treatment: results of a Nordic Lymphoma Group randomized trial. Blood 2003;101:3840–3848.
11. Bertini M, Freilone R, Vitolo U, Botto B, Ciotti R, Cinieri S, et al. The treatment of elderly patients with aggressive non-Hodgkin's lymphomas: feasibility and efficacy of an intensive multidrug regimen. Leuk Lymphoma 1996;22:483–493.
12. Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994;84:1361–1392.
13. 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.
14. Hryniuk W, Bush H. The importance of dose intensity in chemotherapy of metastatic breast cancer. J Clin Oncol 1984;2:1281–1288.
15. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–376.
16. Esteve J, Benhamou E, Croasdale M, Raymond L. Relative survival and the estimation of net survival: elements for further discussion. Stat Med 1990;9:529–538.
17. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, 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.
18. Yellen SB, Cella DF, Leslie WT. Age and clinical decision making in oncology patients. J Natl Cancer Inst 1994;86:1766–1770.
19. Effect of age on the characteristics and clinical behavior of non-Hodgkin's lymphoma patients. The Non-Hodgkin's Lymphoma Classification Project. Ann Oncol 1997;8:973–978.
20. Merli F, Bertini M, Luminari S, Mozzana R, Berte R, Trottini M, et al. Quality of life assessment in elderly patients with aggressive non-Hodgkin's Lymphoma treated with anthracycline-containing regimens. Report of a prospective study by the Intergruppo Italiano Linfomi. Haematologica 2004;89:973–978.
21. Feugier P, Van Hoof A, Sebban C, Solal-Celigny P, Bouabdallah R, Ferme 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.
22. Pfreundschuh M, Trumper L, Kloess M, Schmits R, Feller AC, Rube C, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL. Blood 2004;104:634–641.
23. Sehn LH, Donaldson J, Chhanabhai M, Fitzgerald C, Gill K, Klasa R, et al. Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia. J Clin Oncol 2005;23:5027–5033.
24. Monfardini S, Balducci L. A comprehensive geriatric assessment (CGA) is necessary for the study and the management of cancer in the elderly. Eur J Cancer 1999;35:1771–1772.