Modulated Chemotherapy According to Modified Comprehensive Geriatric Assessment in 100 Consecutive Elderly Patients with Diffuse Large B-Cell Lymphoma

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Key Words. Elderly • Non-Hodgkin's lymphoma • Comprehensive geriatric assessment • Treatment

Disclosures: The authors indicated no financial relationships.

Section Editors: **Hyman B. Muss:** Pfizer, Amgen, Roche, BMS, Boehringer-Ingelheim, Sandoz, Abraxis, Eisai (C/A); **Arti Hurria:** Amgen, Genentech, GTX (C/A); Celgene (previously Abraxis Bioscience), GlaxoSmithKline (RF); **Matti Aapro:** None

Reviewer "A": Roche, Janssen (C/A)

Reviewer "B": Novartis, Allos (C/A); Novartis, Allos, Pfizer, GlaxoSmithKline (RF)

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Use a modulation of chemotherapy according to modified geriatric assessment to improve outcomes for elderly patients with diffuse large B-cell lymphoma with an acceptable level of toxicity.
2. Offer elderly patients the best tailored treatment while minimizing the dose-limiting toxicity.

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ABSTRACT

Chemotherapy is associated with toxicity in elderly patients with potentially curable malignancies, posing the dilemma of whether to intensify therapy, thereby improving the cure rate, or deescalate therapy, thereby reducing toxicity, with consequent risks for under- or overtreatment. Adequate tools to define doses and combinations have not been identified for lymphoma patients. We conducted a

prospective trial aimed to evaluate the feasibility and efficacy of chemotherapy modulated according to a modified comprehensive geriatric assessment (CGA) in elderly (aged ≥ 70 years) patients with diffuse large B-cell lymphoma (DLBCL). In June 2000 to March 2006, 100 patients were stratified using a CGA into three groups (fit, unfit, and frail), and they received a rituximab plus cyclo-

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phosphamide, doxorubicin, vincristine, and prednisone modulated in dose and drugs according to comorbidities and activities of daily living (ADL) and instrumental ADL scores.

Treatment was associated with a complete response rate of 81 % and mild toxicity: grade 4 neutropenia in 14 %, anemia in 1 %, and neurological and cardiac toxicity in 2 % of patients. At a median follow-up of 64 months, 51 patients

were alive, with 5-year disease-free, overall, and cause-specific survival rates of 80 %, 60 %, and 74 %, respectively.

Chemoimmunotherapy adjustments based on a CGA are associated with manageable toxicity and excellent outcomes in elderly patients with DLBCL. Wide use of this CGA-driven treatment may result in better cure rates, especially in fit and unfit patients. *The Oncologist* 2012;17:838–846

INTRODUCTION

Before the introduction of rituximab into clinical practice, the cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) combination regimen was considered as the standard treatment for elderly (aged ≥ 70 years) patients with diffuse large B-cell lymphoma (DLBCL) [1]. Following the introduction and widespread use of rituximab, the combination of immunotherapy plus chemotherapy in the rituximab plus CHOP (R-CHOP) regimen has become the new gold standard [2–6].

Age is one of the most important prognostic factors in DLBCL patients [7], and because it is well known that these tumors are potentially curable, particular effort should be made to improve outcomes in elderly patients. Because the number of fit elderly patients with DLBCL is increasing, chronological age can no longer be a criterion to justify or deny access to a potentially curative approach for these patients. Moreover, the vast majority of published randomized studies regard patients aged > 60 years as elderly, which means that only one third of the study population is aged > 70 years. Finally, it is clear that the results of published clinical trials cannot be extended to all elderly patients, considering that the proportion of elderly patients enrolled in these trials decreases with age (only 20 % aged > 70 years and only 10 % aged > 75 years) [8].

In the last decades, geriatricians have developed a functional assessment scoring system for elderly patients [9–12]. Despite the fact that this tool is not cancer specific, some authors have reported that it is indeed useful for the evaluation of cancer patients [13–15], and its widespread use may result in better outcomes, even for lymphoma patients, considering that most patients aged ≥ 70 years are often not amenable to standard R-CHOP because of a poor performance status and/or concomitant morbidities. Specific trials to establish the value of this functional assessment scoring system in the management of lymphoma patients should be performed.

Herein, we report the final results of a multicenter, prospective phase II trial aimed at evaluating the tolerability and efficacy of chemoimmunotherapy with doses and combinations adapted to a modified comprehensive geriatric assessment (CGA) in elderly (aged ≥ 70 years) patients with newly diagnosed DLBCL.

PATIENTS AND METHODS

Inclusion and Exclusion Criteria

Patients were enrolled if they fulfilled the following inclusion criteria: biopsy-proven CD20⁺ DLBCL according to the World Health Organization (WHO) classification [16], age ≥ 70 years, no previous chemotherapy for lymphoma, no con-

comitant or previous malignancy other than nonmelanoma skin cancer and in situ cervical carcinoma, a total bilirubin level ≤ 1.5 mg/dL, a creatinine level ≤ 2.0 mg/dL, a granulocyte count $\geq 1,500$ cells/dL, a platelet count $\geq 100,000$ cells/dL (unless the granulocyte and platelet counts were affected by bone marrow involvement), and written informed consent. Patients with a previous history of indolent lymphoma, central nervous system or meningeal involvement, HIV infection, or dementia were not enrolled.

The study was carried out by the Gruppo Oncoematologico Linfomi, an Italian cooperative group for the treatment of lymphomas. The study was approved by the institutional review boards of the four participating centers, and all patients gave written informed consent. The first patient was registered in June 2000, and the study was closed to entry as of March 2006. The evaluation of the results was made at the end of March 2011, with a minimum follow-up duration of 5 years for all registered patients. Registration on the ClinicalTrials.gov Web site was not required because the study was initiated in 2000.

Staging

All patients were evaluated with a history and physical examination, including height, weight, and WHO performance status assessment; measurement of all involved palpable lesions; a CBC; blood chemistry; chest radiography and computed tomography of the thorax, abdomen, and pelvis; bone marrow aspiration and biopsy; electrocardiogram and left ventricular ejection fraction evaluation; and gastroscopy when indicated. The Ann Arbor staging system was applied [17].

Modified CGA and Comorbidities

The functional status of enrolled patients was evaluated based on a modified CGA scale consisting of multiple domains (demographic characteristics, physical performance and disability indices, depression and cognitive status) as measured by the activities of daily living (ADL) [9] and instrumental activities of daily living (IADL) [10] scales and also by the geriatric depression [11] and mini-mental state [12] scales. For the purpose of our study, we decided to use the ADL and IADL scales. The ADL scale includes six items that assess the performance of the basic self-care activities required at least once a day: bathing, dressing, toileting, transfer, feeding, and continence [9]. Patients were scored 0–6 according to their ability on each item. The IADL scale is an eight-item scale measuring finer levels of physical and cognitive impairment, including the ability to use the phone, shopping, preparing food, housekeeping, laundry, the ability to travel on public transportation, re-

Figure 1. Chemotherapy regimens: treatment decision flow chart.

Abbreviations: ADL, activities of daily living; CEOP, cyclophosphamide, epirubicin, vincristine, and prednisone; CHO, cyclophosphamide, doxorubicin, and vincristine; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CHP, cyclophosphamide, doxorubicin, and prednisone; CVP, cyclophosphamide, vincristine, and prednisone; IADL, instrumental activities of daily living; R, rituximab.

sponsibility for taking drugs, and the ability to handle money [10]. Patients were scored 0–8 according to their ability on each item. Comorbidities were rated according to the Cumulative Illness Rating Score for Geriatricians (CIRS-G) [18] as follows: no problem, 0; current mild problem or past significant problem, 1; moderate disability or morbidity, requires therapy, 2; severe or constant significant disability or “uncontrollable” chronic problems, 3; extremely severe or immediate treatment required or end organ failure or severe impairment in function, 4. Moreover, we also rated cardiopathy according to the New York Heart Association (NYHA) classification [19, 20].

The purpose of the study was to adapt the standard CHOP and R-CHOP regimens to the functional status and comorbidities of patients with the aim of treating all diagnosed patients in order to offer them the best tailored treatment, minimizing dose-limiting toxicity.

Treatment

The use of rituximab was allowed in all patients since it received marketing authorization in Italy in February 2002. Treatment was planned based on the presence or absence of comorbidities and the ADL and IADL scores. Patients without comorbidities received CHOP (cyclophosphamide, 750 mg/m² i.v. on day 1; doxorubicin, 50 mg/m² i.v. on day 1; vin-

cristine, 1.4 mg/m² i.v. on day 1 up to a maximum dose of 2 mg; prednisone, 100 mg/day orally on days 1–5) or R-CHOP (rituximab, 375 mg/m² i.v. on day 1; cyclophosphamide, 750 mg/m² i.v. on day 2; doxorubicin, 50 mg/m² i.v. on day 2; vincristine, 1.4 mg/m² i.v. on day 2 up to a maximum dose of 2 mg; prednisone, 100 mg/day orally on days 1–5). Patients with mild cardiopathy (NYHA class II or CIRS-G grade 2) were administered epirubicin instead of doxorubicin and they therefore were treated with the CEOP regimen (cyclophosphamide, 750 mg/m² i.v. on day 1; epirubicin, 70 mg/m² i.v. on day 1; vincristine, 1.4 mg/m² i.v. on day 1 up to a maximum dose of 2 mg; prednisone, 100 mg/day orally on days 1–5) or R-CEOP (rituximab, 375 mg/m² i.v. on day 1; cyclophosphamide, 750 mg/m² i.v. on day 2; epirubicin, 70 mg/m² i.v. on day 2; vincristine, 1.4 mg/m² i.v. on day 2 up to a maximum dose of 2 mg; prednisone, 100 mg/day orally on days 1–5). Patients with moderate or severe cardiopathy (NYHA class III or class IV or CIRS-G grade 3 or grade 4) were not given anthracyclines, so they were treated with the CVP regimen (cyclophosphamide, 750 mg/m² i.v. on day 1; vincristine, 1.4 mg/m² i.v. on day 1 up to a maximum dose of 2 mg; prednisone, 100 mg/day orally on days 1–5) or R-CVP (rituximab, 375 mg/m² i.v. on day 1; cyclophosphamide, 750 mg/m² i.v. on day 2; vincristine, 1.4 mg/m² i.v. on day 2 up to a maximum dose of 2 mg; prednisone, 100 mg/day orally on days 1–5). Moreover, in patients

with diabetes mellitus grade ≥ 3 (according to the CIRS-G grade), prednisone was omitted, whereas those with neuropathy (CIRS-G grade ≥ 3) did not receive vincristine.

The dose of each agent was reduced as a function of the ADL and IADL scores. Patients with an ADL score of 6 and/or an IADL score of 7 or 8 received the full planned dose. Patients with an ADL score of 5 and/or an IADL score of 5 or 6 received 75% of the full dose. Patients with an ADL score < 5 or an IADL score < 5 were given 50% of the full dose. G-CSF was given prophylactically (5 $\mu\text{g/kg}$ per day) from day 6 up to neutrophil recovery. The treatment decision flow chart and dose reductions are summarized in Figure 1.

Groups

Based on the results of the modified CGA, patients were stratified into three groups. The “fit” group included patients with no grade 3 comorbidities (or less than three grade 2 comorbidities), an ADL score of 6, and/or an IADL score of 7 or 8. The “unfit” group included patients with no grade 3 comorbidities (or three to five grade 2 comorbidities), an ADL score of 5, and/or an IADL score of 5 or 6. The “frail” group included patients with one or more grade 3 comorbidities (or more than five grade 2 comorbidities), an ADL score < 5 , or an IADL score < 5 .

Tumor Response and Toxicity

Treatment response was evaluated according to the criteria of Cheson et al. [21]. Toxicity was rated according to the WHO criteria [22].

Statistical Methods

The overall survival (OS) time was computed from the initiation of therapy to the last visit that the patient was known to be alive or death from any cause. The disease-free survival (DFS) interval was calculated for patients who achieved a complete response (CR) from the first CR recorded to relapse or to the last known date when the patient was disease free. The event-free survival (EFS) interval was computed from the initiation of treatment to the onset of a clinically significant event, defined as death from any cause, relapse, or progression. The cause-specific survival (CSS) time was computed from the initiation of therapy to the last visit that the patient was known to be alive or death from lymphoma or treatment-related toxicity.

OS, DFS, EFS, and CSS rates were evaluated according to the Kaplan–Meier method [23], and differences between subgroups were detected by means of the log-rank test [24]. The multivariate analysis of survival was performed using the Cox proportional hazard ratio (HR) [25] and 95% confidence interval (CI), taking into account all variables that had been shown to be significantly associated with prognosis in the univariate analysis. Differences between qualitative parameters were determined using the χ^2 test and Fisher’s exact test. In all cases, statistical significance was claimed for $p \leq .05$ (two sided). A statistical evaluation for heterogeneity was performed to ascertain whether or not there was an interaction between treatment center and outcome.

RESULTS

Baseline Characteristics

From June 2000 to March 2006, 100 elderly patients with DLBCL were treated in four Italian institutions. The study group included 59 female and 41 male patients. The median age was 75 years (range, 70–89 years). When stratified by DLBCL stage, 51% had advanced disease (stage III–IV according to the Ann Arbor criteria), 49% had limited disease (stage I–II), and 55% had extranodal disease. B symptoms were recorded in 48% of patients. Based on the International Prognostic Index (IPI), patients were divided into low-risk (53%; IPI, 0 or 1), low–intermediate risk (25%; IPI, 2), intermediate–high risk (17%; IPI, 3), and high-risk (5%; IPI, 4 or 5) groups. Fifty-five percent of patients were included in the fit group, 32% were included in the unfit group, and the remaining 13% were included in the frail group. These data are reported in Table 1. Regarding the ADL score, 73% attained a score of 6, 18% scored 5, and 9% scored < 5 . Regarding the IADL score, 69% of patients achieved a score of 7 or 8, 21% attained a score of 5 or 6, and the remaining 10% scored < 5 .

Treatment

Twenty-three patients received standard R-CHOP and 16 patients received full-dose CHOP. Eleven patients were administered CEOP and four received R-CEOP. One patient received full-dose CVP. Eight patients were treated with 75% reduced-dose R-CHOP and eight were treated with 75% reduced-dose CHOP. Nine patients were treated with 75% reduced-dose R-CEOP and seven patients were treated with 75% reduced-dose CEOP. Ten patients were treated with 50% reduced-dose R-CVP and three were treated with 50% reduced-dose CVP. The chemotherapy regimens employed are summarized in Table 1. Overall, doxorubicin was used in 55 patients, epirubicin was used in 31 patients, and only 14 patients were not amenable to anthracyclines. Rituximab was used in 54 patients.

Toxicity

In total, 483 treatment cycles were administered to all 100 patients and toxicity data were available from 98 patients. In an intent-to-treat analysis, the missing data from the two patients were considered as grade 4 toxicity for all items. The median number of treatment cycles was six (range, 1–7). Nine patients discontinued treatment prematurely because of disease progression. Four toxic deaths were observed, of which two resulted from septic shock during neutropenia, one resulted from myocardial infarction, and one resulted from respiratory failure. One patient died as a result of pulmonary embolism during pretreatment staging. Two additional patients discontinued treatment because of pulmonary embolism following a femur fracture and acute systolic dysfunction, respectively. Hematological toxicity was mild, and grade 3–4 toxicity included neutropenia in 30 patients, anemia in nine patients, and thrombocytopenia in four patients. Eight patients developed febrile neutropenia, and sepsis was documented in five patients. Nonhematological grade 3–4 toxicity included mucositis in 12 patients, sensorial neurological toxicity in nine

Table 1. Patient characteristics at diagnosis

Characteristic	%
Male/females	41/59
Median age (range), yrs	75 (70–89)
Stage	
I–II	49
III–IV	51
Extranodal disease	55
B symptoms	48
International Prognostic Index score	
0–1 (low risk)	53
2 (low–intermediate risk)	25
3 (intermediate–high risk)	17
4–5 (high risk)	5
Geriatric group	
Fit	55
Unfit	32
Frail	13
Chemotherapy regimen administered	<i>n</i> of patients
R-CHOP	23
CHOP	16
CEOP	11
R-CVP, 50%	10
R-CEOP, 75%	9
CHOP, 75%	8
R-CHOP, 75%	8
CEOP, 75%	7
R-CEOP	4
CVP, 50%	3
CVP	1

Abbreviations: CEOP, cyclophosphamide, epirubicin, vincristine, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP, cyclophosphamide, vincristine, and prednisone; R, rituximab.

patients, cardiac toxicity in three patients, and cutaneous toxicity in one patient. No statistically significant differences in the occurrence of grade 3 or 4 hematological and extrahematological toxicities among the three groups (fit, unfit, and frail) were found. Severe toxicity was recorded in 31% of fit patients, 48% of unfit patients, and 58% of frail patients ($p = .11$). However, frail patients experienced more episodes of febrile neutropenia than unfit and fit patients (33% versus 13% versus 5%, respectively; $p = .02$) without any difference in toxic deaths (5%, 9%, and 11%, respectively).

Activity and Efficacy

In an intent-to-treat analysis, 81 patients achieved a CR (81%; 95% CI, 73%–89%) and six patients (6%; 95% CI, 1%–11%)

achieved a partial response, yielding an overall response rate of 87% (95% CI, 80%–94%). Thirteen patients progressed. The CR rates were similar in fit (85%), unfit (72%), and frail (85%) patients ($p = .34$).

After a median follow-up of 64 months (range, 1–127 months), 15 of 81 (19%) patients with a CR experienced relapse, whereas 50 patients from the whole study group (50%) were alive and disease free. The relapse rates were similar in fit (29%), unfit (37%), and frail (31%) patients ($p = 0.72$).

At the time of writing, 49 patients had died as a result of lymphoma ($n = 21$), toxicity ($n = 4$), and causes unrelated to lymphoma ($n = 24$) (Table 2). The 5-year OS, DFS, and EFS rates were 60% (95% CI, 50%–69%) (Fig. 2A), 80% (95% CI, 69%–88%) (Fig. 2B), and 52% (95% CI, 42%–61%) (Fig. 2C), respectively. Moreover, it is remarkable that the 5-year CSS rate was 74% (95% CI, 63%–81%) (Fig. 2D). At the time of writing, 65% of fit patients, 34% of unfit patients, and 31% of frail patients were alive ($p = .006$), with 5-year OS rates of 76%, 53%, and 29% ($p = .001$), respectively.

Prognostic Factors

On univariate analysis (Table 3), an ADL score <6 , an IADL score <7 , stratification into the geriatric groups (fit, unfit, and frail), and the IPI score were significantly associated with the OS outcome. On multivariate analysis, geriatric group and IPI score were the parameters independently associated with survival outcomes. In fact, unfit and frail patients had a significant higher risk for death than fit patients (HR, 1.96 for unfit patients and 2.55 for frail patients; $p = .01$). Similarly, patients with an IPI score of 4 or 5 and those with an IPI score of 2 or 3 had a worse outcome than patients with an IPI score of 0 or 1 (HR, 4.47 and 2.26, respectively; $p = .001$) (Table 3, Fig. 3A, 3B).

Patients Aged >80 Years

We evaluated the clinical characteristics and outcomes of patients aged >80 years. Eighteen patients, seven men and 11 women, were selected. No differences in clinical presentation of non-Hodgkin's lymphoma have been observed in comparison with younger patients. As expected, a higher number of less fit patients were included in this group than in younger patients (six of 18 [33%] versus 49 of 82 [60%]; $p = .01$). The rates of both grade 3 or 4 hematological and nonhematological toxicities did not differ in patients aged >80 years and those aged 70–80 years. Interestingly, similar CR rates were observed in both groups. In particular, patients aged >80 years achieved a CR rate of 83%, versus 80% of patients aged 70–80 years ($p = .96$). The relapse rate was 39% in patients aged >80 and 30% in younger patients ($p = .89$). Importantly, patients aged <80 years and those aged >80 years had similar survival rates (Table 4).

DISCUSSION

This is the first worldwide prospective trial addressing the impact on tolerability and outcomes of a geriatric assessment score used as a parameter to modify doses and regimens of chemioimmunotherapy for elderly patients with DLBCL. The use

Table 2. Cause of death in 24 patients who died from a non-NHL or toxicity-related cause

Treatment	Months after treatment	Age at time of death	Cause of death
CHOP	93	85	Senile marasmus
CHOP, 75%	74	92	Senile marasmus
CHOP, 75%	72	92	Senile marasmus
R-CVP, 50%–75%	41	91	Senile marasmus
CEOP	26	78	Senile marasmus
R-CHOP, 75%	58	76	Myocardial infarction
CEOP, 75%	23	82	Myocardial infarction
R-CHOP, 75%	21	77	Myocardial infarction
R-CHOP, 75%	95	95	Pulmonary embolism after femur fracture
R-CEOP, 75%	11	74	Pulmonary embolism after femur fracture
CEOP	1	73	Pulmonary embolism after femur fracture
None	0 ^a	70	Pulmonary embolism
R-CEOP, 75%	48	90	Heart failure
R-CVP, 75–50%	39	87	Stroke
R-CHOP, 75%	29	78	Dementia
R-CVP, 75–50%	20	79	Dementia
R-CEOP, 75%	36	82	Liver cirrhosis
R-CHOP	32	75	Acute myeloid leukemia
CEOP, 75%	40	84	Lung cancer
R-CHOP	59	79	Pancreatic cancer
CHOP	90	84	Bladder cancer
R-CHOP	82	87	Gastric cancer
R-CHOP, 75%	45	83	Surgery complications
R-CHOP, 75%	54	86	Respiratory failure or pneumonia

^aDuring staging.

Abbreviations: CEOP, cyclophosphamide, epirubicin, vincristine, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP, cyclophosphamide, vincristine, and prednisone; NHL, non-Hodgkin's lymphoma; R, rituximab.

of CGA-tailored treatment resulted in an essential lower rate of treatment-related mortality, manageable toxicity, and better outcomes, even among patients aged >80 years. The ADL score, IADL score, and geriatric group–defining criteria were more important as efficacy-determining factors than age itself. Altogether, this trial suggests that chemoimmunotherapy should be modulated according to ADL score, IADL score, and comorbidity in elderly patients with DLBCL treated in routine practice. Because the study started before the introduction of rituximab for marketing in Italy, the major limitation of this trial was regarding the use of rituximab in half of the pa-

tients. However, the overall outcomes of both patients treated with chemotherapy alone and patients treated with chemoimmunotherapy were similar to results from previously published series.

The selection of elderly cancer patients for treatment is a very critical issue, as shown by results reported in the literature. Actually, it should be borne in mind that the age cutoff level used to define a patient as “elderly” is in the range of 60–70 years, and also that an elderly patient's clinical condition may be more limiting than in younger age groups. In other words, data reported in the literature often include elderly patients who are similar to patients aged <60 years based on their clinical condition, and therefore only a minority of patients is selected, whereas the majority of those in nonoptimal clinical condition are excluded. In the management of patients with chemotherapy-sensitive malignancies, like lymphomas, or other diseases, who may derive significant benefit from chemotherapy, with a high proportion of patients achieving a full recovery or long-term disease control, every effort should be made to offer a potentially curative approach to all patients regardless of their clinical condition and age. Currently, based on the results of the Rituximab plus Chemotherapy OVER 60 (years) (RICOVER-60) trial, the R-CHOP-14 regimen is regarded as the gold standard treatment for elderly patients with DLBCL. However, that trial enrolled patients 60–80 years of age who fulfilled the inclusion criteria, but only 36% were aged >70 years [6].

Therefore, in our opinion, we should be careful to extrapolate the results of randomized studies in this setting. In fact, even if the results of these studies [1, 2, 6] have improved the knowledge on treating aggressive lymphoma in elderly patients, the selection of enrolled patients doesn't allow us to draw any conclusions for the whole population of elderly patients.

In our study of 100 consecutive patients aged >70 years with DLBCL, the whole population was divided into three groups (fit, unfit, and frail) and each group was offered a highly individualized treatment plan, adjusted to each case, with the intent to cure the disease or attain long-term control.

Comparing our study with the Groupe d'Etude des Lymphomes de l'Adulte (GELA) and RICOVER-60 studies, patients had similar baseline characteristics except for more patients in our study with a performance status score >1 (26%, versus 20% in the GELA study and 14% in the RICOVER-60 study) and fewer patients in our study with an IPI score >2 (22%, versus 54% and 41%, respectively). A comparison of the most relevant toxicities in the GELA, RICOVER-60, and current trials suggests that the use of CGA-driven treatment may be associated with fewer treatment-related deaths, fewer episodes of fever and infection, and a lower incidence of hematological toxicity.

Interestingly, the CR rate in the present trial is not inferior to that observed in the other two studies: 81% in our series versus 69% in the GELA study and 74% in the RICOVER-60 trial. Moreover, patient outcomes were comparable even though 33% of the patients in our study group were unfit or frail. Furthermore, 19 of these patients were aged >80 years, and they

Figure 2. Patient survival outcomes.

Table 3. Univariate and multivariate analyses on overall survival

Factor	<i>n</i> of patients	Univariate HR (95% CI)	<i>p</i> -value	Multivariate HR (95% CI)	<i>p</i> -value
ADL score					
6	73	1		1	
<6	27	3.01 (1.71–5.30)	.0001	1.41 (0.88–3.42)	.44
IADL score					
>6	69	1		1	
≤6	31	2.04 (1.14–3.62)	.01	1.37 (0.73–2.56)	.32
Geriatric status					
Fit	55	1		1	
Unfit	32	2.38 (1.28–4.43)		1.96 (1.04–3.70)	
Frail	13	3.12 (1.40–6.93)	.001	2.55 (1.14–5.73)	.01
IPI score					
0 or 1	53	1		1	
2 or 3	42	2.59 (1.43–4.69)		1.95 (1.04–3.66)	
4 or 5	5	5.93 (1.97–17.82)	.0001	4.93 (1.55–15.64)	.005

Abbreviations: ADL, activities of daily living; CI, confidence interval; HR, hazard ratio; IADL, instrumental activities of daily living; IPI, International Prognostic Index.

therefore would not have been enrolled in the GELA or RICOVER-60 studies.

In conclusion, treatment selection for elderly patients with DLBCL based on a standardized geriatric assessment is asso-

ciated with survival and toxicity rates similar to those seen in the overall DLBCL population.

This positive effect was obtained even among patients aged >80 years, which is of remarkable value considering that most

Figure 3. Overall survival times according to prognostic factors. Abbreviation: IPI, International Prognostic Index.

Table 4. Comparison of outcome between patients aged >80 years and patients aged 70–80 years			
Outcome	>80 yrs	70–80 yrs	p-value
Complete response rate	83%	80%	.96
Relapse rate	39%	30%	.49
5-yr overall survival rate	54%	61%	.24
5-yr disease-free survival rate	67%	84%	.11
5-yr event-free survival rate	46%	67%	.06
5-yr cause-specific survival rate	68%	75%	.91

elderly patients with DLBCL or cancer could be undertreated in everyday practice because of their age [26, 27]. A CGA-driven approach to treating patients with DLBCL may result in better cure rates, especially in frail patients, for whom palliative treatment is associated with a very poor outcome [28]. Our results confirm the recently published data showing that a CGA is able to well stratify patients into different groups with different outcomes [29]. However, a strong effort should be reserved to better stratify unfit and frail patients in order to understand whether similar or different approaches should be reserved for these two groups. Moreover, in the last few years, other instruments have been validated to identify frailty in

older patients [30, 31]. However, their application in cancer patients is still under investigation.

Our results confirm that the IPI score is the most important prognostic factor for survival in elderly patients with DLBCL, with a significantly higher risk for death for patients with an IPI score of 4 or 5 than for patients with a lower IPI score at diagnosis. Finally, the use of a CGA as strata criterion in future randomized trials may result in consistent therapeutic progress in the treatment of elderly patients with DLBCL, with more accurate assessments of safety and efficacy of new drugs and combinations.

ACKNOWLEDGMENTS

Supported by Alleanza Contro il Cancro (ACC), grant no. ACC1-WP3/1. Presented in part at the 51st Annual Meeting of the American Society of Hematology. New Orleans, LA, December 5–8, 2009.

Mrs. Daniela Furlan and Mrs. Paola Favetta were involved in the editing of the manuscript.

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REFERENCES

1. Tirelli U, Errante D, Van Glabbeke M et al. CHOP is the standard regimen in patients ≥ 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.
2. Coiffier B, Lepage E, Briere J et al. CHOP and chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 2002;346:235–242.
3. 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.
4. Sehn LH, Donaldson J, Chhanabhai M 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.
5. 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.
6. 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.
7. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med* 1993;329:987–994.
8. Mora O, Zucca E. Management of elderly patients with hematological neoplasms. *Ann Oncol* 2007;18(suppl 1):i49–i53.
9. Katz S, Akpom CA. A measure of primary sociobiological functions. *Int J Health Serv* 1976;6:493–508.
10. Lawton MP, Brody EM. Assessment of older people: Self-maintaining and instrumental activities of daily living. *Gerontologist* 1969;9:179–186.
11. Brink TL, Yesavage JA, Lum O et al. Screening tests for geriatric depression. *Clin Gerontol* 1982;1:37–44.
12. Folstein MF, Folstein SE, McHugh PR. "Mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiat Res* 1975;12:189–198.
13. Repetto L, Fratino L, Audisio RA et al. Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients: An Italian Group for Geriatric Oncology Study. *J Clin Oncol* 2002;20:494–502.
14. Balducci L. Aging, frailty, and chemotherapy. *Cancer Control* 2007;14:7–12.
15. 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.
16. Harris NL, Jaffe ES, Diebold J et al. The World Health Organization classification of hematological malignancies report of the Clinical Advisory Committee Meeting, Airlie House, Virginia, November 1997. *Mod Pathol* 2000;13:193–207.
17. Carbone PP, Kaplan HS, Musshoff K et al. Report of the Committee on Hodgkin's Disease Staging Classification. *Cancer Res* 1971;31:1860–1861.
18. Miller MD, Towers A. A manual of guidelines for scoring the cumulative illness rating scale for geriatricians (CIRS-G). Pittsburgh, PA: University of Pittsburgh, 1991:1–12.
19. The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis, Ninth Edition. Little, Brown, 1994:253–256.
20. Fleg JL, Piña IL, Balady GJ et al. Assessment of functional capacity in clinical and research applications: An advisory from the Committee on Exercise, Rehabilitation, and Prevention, Council on Clinical Cardiology, American Heart Association. *Circulation* 2000;102:1591–1597.
21. 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.
22. Miller AB, Hoogstraten B, Staquet M et al. Reporting results of cancer treatment. *Cancer* 1981;47:207–214.
23. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–481.
24. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966;50:163–170.
25. Cox DR. Regression models and life tables. *J R Stat Soc B* 1972;34:187–202.
26. Fentiman IS, Tirelli U, Monfardini S et al. Cancer in the elderly: Why so badly treated? *Lancet* 1990;335:1020–1022.
27. Bernardi D, Errante D, Tirelli U et al. Insight into the treatment of cancer in older patients: Developments in the last decade. *Cancer Treat Rev* 2006;32:277–288.
28. Monfardini S, Aversa SM, Zoli V et al. Vinorelbine and prednisone in frail elderly patients with intermediate-high grade non-Hodgkin's lymphoma. *Ann Oncol* 2005;16:1352–1358.
29. Tucci A, Ferrari S, Bottelli C et al. A comprehensive geriatric assessment is more effective than clinical judgment to identify elderly diffuse large cell lymphoma patients who benefit from aggressive therapy. *Cancer* 2009;115:4547–4553.
30. Gobbens RJ, van Assen MA, Luijckx KG et al. The Tilburg Frailty Indicator: Psychometric properties. *J Am Med Dir Assoc* 2010;11:344–355.
31. de Vries NM, Staal JB, van Ravensberg CD et al. Outcome instruments to measure frailty: A systematic review. *Ageing Res Rev* 2011;10:104–114.