Title: Comprehensive Geriatric Assessment is an essential tool to support treatment decisions in elderly patients with Diffuse Large B Cell Lymphoma: A prospective multicenter evaluation on 173 patients by the Lymphoma Italian Foundation (FIL)

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Running head: Geriatric assessment in lymphoma seniors

Key words: Lymphoma and Hodgkin disease, Chemotherapeutic approaches, Immunotherapy

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ABSTRACT

We performed a multicenter study in order to validate the concept that a simple CGA can identify elderly DLBCL non-fit patients in whom curative treatment is not better then palliation and to analyse potential benefits of treatment modulation after further subdividing the non-fit category by CGA criteria.

One-hundred-seventy-three patients aged > 69 treated with curative or palliative intent by clinical judgment only were grouped according to CGA in fit (46%), unfit (16%) and frail (38%) categories.

Two-yr OS was significantly better in fit than in non-fit patients (84% vs 47%; P <.0001). Survival in unfit and frail patients was not significantly different. Curative treatment slightly improved 2-yr OS in unfit (75% vs 44%), but not in frail patients (45% vs 39%).

CGA was confirmed as very efficient in identifying elderly DLBCL patients who can benefit from a curative approach. Further efforts are needed to better tailor therapies in non-fit patients.

INTRODUCTION

In the last few years Comprehensive Geriatric Assessment (CGA) was recognized as an essential tool for clinicians that manage elderly people affected by aggressive diseases [1]. The definition of elderly is still a matter of debate in oncology. In patients with lymphoma the age limit more frequently used to discriminate between younger and older patients is 65 [2].

It is no longer acceptable to exclude patients from intensive treatment with curative intent only on the basis of chronological age. Aging is highly individualized in terms of life expectancy, functional reserve and social support and treatment plans need to account for this diversity that can be better evaluated by a multidimensional approach [3].

Diffuse large B cell lymphoma (DLBCL) represents a typical example of neoplastic disease that can be cured with an aggressive program. The majority of these patients are over the age of 60 years and the steady improvement of life expectancy will probably further increase their number in the future [2]. Therefore, trying to improve the survival of this category of patients represents one of the major challenges for the haematologists. CGA proved to be an effective method to identify elderly DLBCL patients able to tolerate intensive treatment with curative intent, achieving an outcome similar to the one of younger patients [4].

However about one half of the elderly patients cannot benefit from a curative approach and their prognosis is still very poor independently of the treatment received.

Although broad agreement exists among oncologists on the different aspects of geriatric assessment and on the instruments to use for evaluating elderly peoples performance, the categories of elderly patients that need to be identified are still debated and the interpretation of the results of CGA tests has not been standardized yet . In particular, since new and very effective treatments with a better tolerability profile like anti-CD20 monoclonal antibodies have become available, the attempt to better define non-fit patients according to the extent of their limitations could help clinicians to better tailor treatment trying to improve the efficacy of therapies in this patient category.

Therefore the FIL launched a multicenter prospective study to verify our previous results in a broader population of DLBCL patients with the same clinical characteristics and to assess the potential usefulness of a comprehensive geriatric assessment that further divides non-fit patients in two different levels according to the severity of their unfitness.

PATIENTS AND METHODS

All consecutive patients with diffuse large B cell lymphoma aged more than 69 years seen in 13 Hematology departments of the Italian Lymphoma Foundation (FIL) were recorded during one year. CGA was performed during staging procedures after written informed consent through the application of the following instruments: 1) age>80 years; 2) comorbidity score according to the Cumulative Illness Rating Score for Geriatrics (CIRS-G) [5] and evaluated in all the organs/systems as follows: no problem—0, mild problem (may require treatment)—1, moderate disability or morbidity (treatment required)—2, severe, constant, significant disability/''uncontrollable'' chronic problems—3, extremely severe disability, immediate treatment required/end organ failure/severe impairment in function—4; 3) activity of daily living (ADL), that is, loss in any activity, including bathing, dressing, toileting, transferring, feeding, and continence [6]; 4) instrumental activity of daily living (IADL), an indirect evaluation of functional abilities necessary for independent living through caregivers interview [7] . Patients were classified in the category of ‘‘fit’’ patients if they had all of the following conditions: age <80, no limitations in ADL and IADL scores: ADL score 6 and IADL score 8, CIRS-G: no grade 3-4 comorbidities (hematological comorbidities were not investigated) and less than 5 grade 2 comorbidities. Patients were classified as ‘‘unfit” if they had all of the following conditions: age > 79, no limitations in ADL and IADL scores: ADL score 6 and IADL score 8, CIRS-G: no grade 3-4 comorbidities and less than 5 grade 2 comorbidities. In addition patients aged <80 with ADL score of 5 and/or IADL score of 6-7, and/or CIRS-G: no grade 3-4 comorbidities and 5 to 8 grade 2 comorbidities were also classified as “unfit”. All other patients who did not meet the criteria for fit and unfit patients were classified as ‘‘frail’’ [8] (Table I). The decision to treat a patient and the choice of the type and intensity of treatment were always left to the clinical judgment of the attending physician, according to the policy of the Institution. Treatment with curative intent was defined as the use of a combination of an anthracycline-based chemotherapy (either liposomal or standard formulation), consisting of CHOP or CHOP-like regimens with rituximab, delivered at a relative dose intensity greater than 70% of the full dose as intent-to treat. Patients considered unable to tolerate such treatment received other treatments including radiation therapy only, low-dose chemotherapy without anthracyclines (cyclophosphamide, Oncovin [vincristine], and prednisone [COP], low-dose COP), rituximab as a single agent, corticosteroids alone, oral monochemotherapy or anthracycline-based cycles at a relative dose intensity less than 70%, which were all defined as palliative therapy.

The purpose of the study was to evaluate the outcome of the consecutive patients both considering the intensity of treatment received and the results of CGA assessment.

Statistical analyses were performed using Prism software (GraphPad Software, La Jolla, Calif). 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 and was evaluated according to the Kaplan–Meier method [9]. The characteristics of the subgroups of patients subdivided according to the type of treatment received and to CGA categorization were compared using Fisher exact test, Student t test, and Mann-Whitney statistics, as appropriate. Log-rank analysis was used to compare actuarial survival curves [10].The multivariate analysis of survival was performed using the Cox proportional hazard ratio (HR) [11] and 95% confidence interval (CI), taking into account all variables that had been shown to be significantly associated with survival in the univariate analysis.

RESULTS

From September 2009 to August 2010, 177 patients aged more than 69 and affected by DLBCL were consecutively registered and 173 of them had fully evaluable data to be considered for the present study. According to CGA, 79 (46%) patients were classified as ''fit'', 28 (16%) as "unfit" and 66 (38%) as "frail". Two fit, one unfit and 1 frail patients were lost to follow up. Among unfit patients, 50% were aged more than 79 without any other limitation, 15% had one or two limitation in IADL only, 23% in IADL and ADL and 12% in IADL with more than 4 comorbidities of grade 2. Among frail patients 13% were aged more than 79 and unfit, 15% had one or more comorbidities of grade 3, 2 patients had only serious limitation in IADL while all the other patients had limitations in two or more assessment scales. The main demographic and clinical characteristics of this geriatric population are reported in table II. Fit patients were significantly younger compared with unfit and frail patients ($p<0.0001$), while no significant difference concerning stage, B symptoms and International Prognostic Index (IPI) was observed. All but five fit patients (94%) received a curative treatment: one died before receiving any treatment, three patients with stage I disease received only radiation therapy and one patient with stage II disease received radiation and immunochemotherapy without antracycline because of previous treatment for breast cancer. With a median follow up of 24 months, their 2-year OS was significantly better than survival of non-fit patients (84% vs 47%) ($P <0.0001$). Among unfit and frail patients 2-year survival was 63% vs 40% respectively (p 0.13) (Figure 1).

On the basis of clinical judgment, 17 unfit patients (61%) and 18 frail patients (27%) received full-dose therapy with curative intent, and the remaining patients received palliation. Clinical characteristics of patients subdivided according to the treatment actually received are shown in table III. Patients treated with curative intent were significantly younger than patients receiving palliation (p 0.001) and had a more advanced stage (p 0.02) while no other significant differences were recorded.

Considering patients treated with curative intent overall, the survival of fit patients was significantly better than survival of non-fit patients (88% vs 56%) (p 0.0001).

Within the single CGA categories, the 2-year overall survival of patients treated with curative or palliative intent was 88% vs 25% (p 0.0001) in fit , 75% vs 45% (p 0.32) in unfit, and 44% vs 39% (p 0.75) in frail patients respectively (Figure 2).

The rate of non hematologic toxicity of grade > 2 was not significantly different among patients treated respectively with curative or palliative intent (45% vs 38%; p 0.3). Lymphoma was the main cause of death in both treatment groups.

At univariate analysis, age, IPI, CGA, ADL, IADL, CIRS-G, treatment approach (curative vs palliative) and treatment dose-intensity (cut-off 70%) were significantly associated with overall survival. Within a multivariate analysis only IPI and CGA maintained their strong association with overall survival (Table IV).

DISCUSSION

The results of our study confirm that CGA is a strong independent predictor of overall survival [12, 13] and can be usefully applied to the treatment decision in elderly patients with DLBCL.

We adopted age 70 as the lower limit of clinical senescence since the prevalence of age-related changes is represented by an almost flat line up to this age and increases sharply with older age [3, 14].

We used a modified score originally proposed by Balducci [3] that we have validated in a small population of elderly DLBCL patients [4] and that Spina et al. already proposed in a modified version. The primary aim was to try to further divide the category of frail patients in order to modulate treatment intensity. A fully standardized geriatric assessment tool is not yet available. Therefore any choice in the subdivision of the geriatric categories is somewhat arbitrary. However the criteria we applied referred to validated rating scales and to previously published papers [4, 15].

Only short and rapid screening instruments could be widely accepted in the oncology clinical practice [16, 17].This test is easy to perform and did not require more than 15 minutes. Trained clinicians and nurses can work together according to their skills, assigning respectively the comorbidity and ADL/IADL scores. The most important warning is to avoid defining a patient as frail because of a reduced performance status depending only on his advanced and symptomatic disease. This may carry a significant risk of undertreating the patient.

More recently a great interest has been directed on the prognostic role of nutritional parameters in the outcome of geriatric cancer population. Following the observation of the close correlation between hypoalbuminemia and survival in elderly patients with DLBCL [18], sarcopenia was studied in this category of patients and was found a strong predictor of overall survival, but this approach is still not easily applicable in the worldwide clinical practice [19].

The results of this study, far from being a final recommendation to be adopted in clinical practice, represent a further step toward the development of a simple geriatric score able to define different categories of elderly DLBCL patients suitable for different treatment intensity.

According to the standard protocols for elderly patients with DLBCL [20], the combination chemotherapy with CHOP or CHOP-like regimens with rituximab was chosen as the treatment strategy with curative intent. A relative dose intensity of more than 70% of the standard dose was considered acceptable to maintain its therapeutic effect, as already demonstrated [21].

Only patients classified as fit by CGA had a very satisfactory clinical outcome using intensive curative approach . The 2-year OS rates of 88%, did not differ from the results achieved in younger patients with the same treatment [22, 23]. Moreover, major toxic effects were limited, and only 2 patients died of treatment-related toxicity. The benefit of curative versus palliative treatment was lost in non-fit patients who had a poor outcome irrespectively of the type of treatment received.

The same results were obtained in a recent study by Marchesi et al who used a similar simplified CGA [24]. In our paper frail patients had more frequently worse IPI score and stage B than fit patients, although the difference was not significant; however significant better survival of fit compared to frail intensively treated patients was evident both in the subgroup of low and high IPI score, and in the subgroup of A and B stage, eliminating possible bias (data not shown). Compared to frail patients the outcome of unfit patients was not significantly different. However, there was a clear trend to a better survival, especially in the subgroup treated with curative intent. While the small number of unfit patients identified by CGA criteria may have limited the statistical power of the study, these results suggest that efforts in modulating the treatment intensity in this intermediate category of patients might be worthwhile in order to further improve their outcome and to reduce the number of elderly patients who might benefit of palliative care only. Modulation of chemotherapy according to CGA was already proposed by different authors [8, 13]. Spina et al. obtained interesting results adjusting the single chemotherapeutic agent according to comorbidities and total doses according to ADL/IADL. Attenuated immunochemotherapy regimen (R-miniCHOP) was used by the French group in elderly patients aged over 80 years without any other CGA parameter selection, obtaining a good compromise between efficacy and safety [18]. The combination of a lower dose of immunochemotherapy with a biologic drug could also be a valid alternative to be tested in a clinical trial.

In conclusion the CGA used in our study proved to be an efficient method to identify elderly DLBCL patients who can benefit from a curative approach with anthracycline-containing immuno-chemotherapy. It further suggests the potential usefulness of identifying different risk groups in the category of non-fit patients, by showing that a proportion of unfit patients exists who could obtain significant benefit when treated with curative intent. Therefore, new risk adapted strategies of treatment through modulated-intensity programs could reduce the difference of survival between fit and unfit patients and clinical trials in this setting should be planned. Palliation seems the best choice for frail patients and improvement of the supportive care is the only effort that could be proposed in this category of patients.

DISCLOSURES

No financial disclosures, no conflicts of interest, no funding sources for the manuscript, no acknowledgements for all the authors.

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Table I: Definition of three geriatric risk categories according to age, comorbidities and functional abilities of daily living

CGA Categories	Fit	Unfit	Frail
ADL	6	5*	≤ 4*
IADL	8	7 – 6*	≤ 5*
CIRS-G	no comorbidity score 3-4 and <5 comorbidities score 2	no comorbidity score 3-4 and 5-8 comorbidities score 2	≥1 comorbidity score 3-4 or > 8 comorbidities score 2
Age		≥ 80 fit	≥ 80 unfit

NOTE. * number of residual functions

Table II: Characteristics of patients classified according to CGA

CGA category	All	Fit	Unfit	Frail	P
N° of evaluable patients (%)	173	79 (46%)	28 (16%)	66 (38%)	
M/F	91/82	52/27	13/15	26/40	
Median age	77	74	79	81	<0.0001
Ann Arbor stage III-IV (%)*	57	57	58	58	NS
Stage B (%)**	32	25	24	37	NS
IPI risk class Interm-high – high (%)***	43	41	44	54	NS

NOTE. Data were available for 100% of patients in analysis except * Stage: missing data in 3%; **B stage: missing data in 30%; **IPI index: missing data in 6%.

Table III: Characteristics of unfit and frail patients subdivided according to the type of treatment actually received based on clinical judgement

TREATMENT	CURATIVE		PALLIATIVE		P
CGA categories	UNFIT	FRAIL	UNFIT	FRAIL	
N° of patients	17	18	11	48	
Median age	78	78	83	82	0.001*
Ann Arbor stage III-IV	69%	78%	45%	49%	0.02*
Stage B	33%	45%	10%	32%	NS
IPI risk class Interm high/high	56	58	30	52	NS
ORR (CR + PR)	14 (82%)	13 (72%)	7 (64%)	25 (52%)	NS
Relapse Rate	2/14	4/13	2/7	5/25	
Lymphoma death	60%	80%	80%	84%	NS
Non hematologic toxicity >2	40%	50%	40%	33%	NS

NOTE. * Comparison between all patients who received curative vs palliative treatment

Abbreviations: ORR, overall response rate; CR, complete remission; PR, partial remission

Table IV: Overall survival time according to patient and treatment characteristics (univariate and multivariate Cox-regression analysis)

Variables	Univariate HR (95% CI)	p-value	Multivariate HR (95% CI)	p-value
Age <80 vs ≥80 years	2.67 (1.61-4.44)	p 0.0002		
Stage I-II vs III-IV	1.59 (0.92-2.74)	P 0.09		
IPI (Interm low/low vs Interm high/high)	3.72 (1.80-7.68)	p 0.0003	4.60 (1.35-15.64)	p 0.008
CGA	5. 61 (2.95-10.64)	P 0.0001	3.69 (1.09-12.51)	P 0.03
ADL (≤ 5 vs 6)	0.3 (0.17-0.51)	P 0.0001		
IADL (≤ 6 vs ≥ 7)	0.24 (0.14-0.41)	P 0.0001		
CIRS-G grade 2 (< 5 vs ≥ 5)	2.89 (1.04-8.03)	P 0.04		
CIRS-G grade 3-4 (0 vs ≥ 1)	2.14 (1.22-3.73)	P 0.007		
Curative vs palliative treatment approach	0.27 (0.16-0.46)	P 0.0001		
Treatment dose: <70% vs ≥70%	0.38 (0.17-0.86)	P 0.02		

Abbreviations: HR, hazard ratio; CI, confidence interval