Diffuse large B-cell lymphoma in octogenarians aged 85 and older can benefit from treatment with curative intent: a report on 129 patients prospectively registered in the Elderly Project of the Fondazione Italiana Linfomi (FIL)

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Abstract

Octogenarian patients with diffuse large B-cell lymphoma are managed mainly with palliation, but recent improvement in their overall condition makes potentially curative treatment a possibility. Studies have shown that half of selected octogenarians may be cured using reduced-dose anthracycline chemoimmunotherapy. However, patients aged >85 (late octogenarians [LO]) were underrepresented, and selection criteria were poorly defined. We analyzed the clinical characteristics and outcomes of LO enrolled in the FIL Elderly Project in terms of the treatment received (palliative *vs*. curative) and of their simplified geriatric assessment (sGA), then compared them with early octogenarians (EO) aged 80-84 and with those aged 65-79 classified as UNFIT or FRAIL according to sGA enrolled in the same study. Of the 1,163 patients, 370 were >80 and 129 LO. Clinical characteristics were similar between LO and EO, but LO more frequently received palliation (50% *vs*. 23%; *P*=0.001) and had worse 2-year overall survival (OS) (48% *vs*. 63%; *P*=0.001) and 2-year progression-free survival (PFS) (43% *vs*. 56%; *P*=0.01). Patients receiving anthracycline did better than patients receiving palliation (*P*<0.001), without any difference between full or reduced doses. Rituximab within palliation improved outcome (2-yr OS with or without rituximab 42% *vs*. 22%; *P*=0.008). Elderly Prognostic Index (EPI) performed better than sGA in

identifying different risk categories, and high-risk EPI retained an independent unfavorable effect on OS and PFS, together with treatment without anthracycline. In conclusion, late octogenarians can benefit from a curative approach with reduced-dose anthracycline and from rituximab within palliation. EPI may help in patient selection more than sGA can.

Introduction

Diffuse large B-cell lymphoma (DLCBL) is the most common lymphoid malignancy in Western countries, with a median age of 70 years at presentation.[1,2] Given the progressive improvement in life expectancy,[3,4] octogenarians will increasingly become more represented in this patient age group.[5] Thanks to general improvement in socioeconomic conditions and in supportive care, the overall condition of octogenarian patients has become progressively better, making many of them suitable for treatment approaches with curative intent. Nevertheless, comorbidities and different limitations in daily living activities reduce the capacity of many of them to tolerate full-dose therapy. Thus, the need to tailor treatment choices for this category of patients affected by an aggressive but potentially curable disease is a growing clinical challenge for hematologists.
Several studies have recently reported on the characteristics and prognosis of non-Hodgkin lymphoma (NHL) in octogenarian patients.[6-9] The use of reduced doses of anthracycline in the rituximab-mini-CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) regimen has been proposed for patients aged >80 years by the French Lymphoma Study Association (LYSA); their favorable results represent a good compromise between efficacy and safety.[10] However, in all the above-mentioned studies, the median age was <84 years, and most of the patients were under the age of 85 years.
More recently, interest in the cohort of late octogenarians aged >85 has also been growing. Using the Swedish and Danish population-based lymphoma registers, the Nordic Lymphoma Group has recently analyzed the clinical characteristics and outcomes of 2,347 patients aged >85 years diagnosed with lymphoma, 924 of whom (39%) with DLBCL. Administration of active treatment was associated with a 2-year relative survival (RS) of 49% and a 5-year RS of 44% in patients with aggressive histology, but the lack of data regarding toxicity, dose reductions, and frailty assessment precluded more detailed analyses.[11] In a retrospective study by the LYSA, active treatment improved the survival of 234 patients over the age of 90 years (113 with DLBCL - 48%). However, the geriatric characteristics of these very old patients were not formally assessed.[12]
Comprehensive geriatric assessment (CGA) has proven useful in guiding treatment decisions in older patients with DLBCL[13] and is now recommended by international scientific societies.[14-16] In particular, the identification of patients fit for curative intent has reduced the risk of undertreating many older patients. However, the choice of therapies in octogenarians, particularly in those aged >85 years, still represents a problem in daily clinical practice. Recently, the Italian Lymphoma Foundation (FIL) conducted the Elderly Project (*clinicaltrails gov. Identifier: NCT02364050*), a large prospective study on 1,163 older patients with DLBCL. The aim of the study was to evaluate their outcome according to the treatment received and to the geriatric category defined by a simplified geriatric assessment (sGA).[17]
With the aim of potentially identifying the most appropriate match between patient characteristics and treatment intensity, the present study analyzed all patients enrolled in the Elderly Project study aged >85 years, defined as late octogenarians (LO), describing their clinical and geriatric characteristics as well as their outcome according to their fitness category and to the treatment actually received. It also compared LO with the cohorts of early octogenarians (EO) aged 80-84 years and of patients aged 65-79 years categorized as UNFIT or FRAIL according to sGA also enrolled in the Elderly Project.

Methods

The cohort of patients age >85 years consecutively enrolled in the Elderly Project was considered for this analysis. These patients were defined as LO. Patients aged 80–84 years, defined as EO, were also considered and compared with LO. All patients underwent an sGA (*Online Supplementary Table S1*), as previously reported.[17] Accordingly, age >80 years precluded the classification of patients as FIT. Patients were classified as UNFIT if they had no limitations in activities of daily living (ADL) and instrumental ADL (IADL) and if they had fewer than five grade 2 comorbidities and no grade 3 according to the cumulative illness rating scale-geriatric (CIRS-G); in all the other conditions, patients were classified as FRAIL.[17] Clinical characteristics were recorded in a database, and the elderly prognostic index (EPI) score was calculated as previously described.[17] In particular, this score divides patients into three risk categories according to the International Prognostic Index, sGA, and hemoglobin levels (*Online Supplementary Table S2*). Treatment was delivered according to clinician's decision and was classified as full-dose treatment (FDT) if it contained anthracycline (either liposomal or standard formulation) at a relative dose intensity greater than 70% of the standard dose, reduced-dose

treatment (RDT) if it contained between 50% and 70% of standard dose of anthracycline, or palliative treatment (PVT), in the absence of anthracycline in the treatment program. Palliative therapies included rituximab plus either bendamustine (R-B) or cyclophosphamide, vincristine, and prednisone (R-CVP), or other chemotherapy regimens without rituximab, including metronomic regimens, corticosteroids, or radiotherapy alone.

UNFIT and FRAIL patients, aged 65–79 years, were also retrieved from the same Elderly Project database and acted as the control group.

Continuous variables are summarized as median with range; categorical variables are summarized as absolute and percentage frequencies. Comparisons between categorical variables and LO and EO groups were performed by Fisher's exact probability or Chi-square test. All statistical tests were two-sided, and a significant *P* value was determined as <0.05.

Progression-free survival (PFS) was defined as time from diagnosis to relapse or progression or death from any cause or date of the last clinical visit when the patient was known to be alive. Overall survival (OS) was defined as time from diagnosis to the last visit when the patient was known to be alive or death from any cause. PFS and OS were calculated using the Kaplan-Meier method, and Cox proportional hazards regression models were used to evaluate characteristics associated with PFS and OS. The effect was expressed as hazard ratio (HR) with 95% confidence interval (CI). Association with the PVT approach was estimated by means of logistic regression, and the effect is expressed as odds ratio (OR), with 95% CI. In order to partially remove the selection bias from the estimation, we performed an inverse probability weight (IPW) analysis on Cox proportional hazards regression conducted on OS (see the *Online Supplementary Appendix*). Discrimination power was evaluated using the Harrell's c-index, with 95% CI obtained from jackknife estimation. The median follow-up of observation was estimated by means of the reverse Kaplan-Meier method on OS.

Table 1. Clinical characteristics of late and early octogenarians.

Factor	Age groups		
	LO N=129*	EO N=241	*P*
Age in years, median	87	82	
sGA, N (%)			0.100
UNFIT	50 (39)	116 (48)	
FRAIL	79 (61)	125 (52)	
Sex, N (%)			0.126
M	52 (40)	118 (49)	
F	77 (60)	123 (51)	
Stage, N (%)			0.058
I-II	48 (38)	67 (28)	
III-IV	79 (62)	174 (72)	
B symptoms, N (%)	21 (16)	71 (29)	0.008
Bulky, N (%)	36 (28)	62 (26)	0.711
IPI score, N (%)			0.820
1	18 (16)	30 (14)	
2	28 (25)	59 (27)	
3-5	65 (59)	131 (59)	
Hb g/dL, N (%)			0.738
≥12	67 (54)	120 (52)	
<12	57 (46)	112 (48)	
EPI score, N (%)			0.982
Intermediate	38 (35)	74 (34)	
High	72 (65)	141 (66)	
Treatment approach, N (%)			<0.001
FDT	17 (13)	79 (33)	
RDT	47 (36)	107 (44)	
PVT	65 (50)	55 (23)	
PVT w/o R	30 (46**)	15 (27**)	0.038

LO: late octogenarians; EO: early octogenarians; sGA: simplified geriatric assessment; IPI: International Prognostic Index; Hb: hemoglobin; EPI: elderly prognostic index; FDT: full-dose treatment; RDT: reduced-dose treatment; PVT: palliative treatment; w/o: without; R: rituximab. *28 (22%) >90 years (yr) old; **referred to patients receiving PVT. Percentages are given in brackets and refer to the proportions of evaluable patients for each variable. *P* value: Fisher's exact probability of Chi-square test.

Results

Of the 1,163 consecutive and fully evaluable patients enrolled in the Elderly Project from December 2013 to December 2017, 370 (32%) were older than 79 years: 129 (35%) were aged >85 years (LO) and 241 (65%) were aged 80-84 years (EO). All came from 36 Fondazione Italiana Linfomi (FIL) centers throughout Italy.

Clinical characteristics

The characteristics of LO are summarized in Table 1, which also shows the characteristics of EO for comparison. The median age of the 129 LO patients was 87 years (range, 85–93 years), 22% were over 90, 40% were male, 62% had Ann Arbor Stage III-IV lymphoma, 16% had B symptoms, 59% belonged to the categories of intermediate-high or high-risk according to the IPI, and 46% were anemic. According to the sGA, 50 patients (39%) were classified as UNFIT and 79 (61%) as FRAIL, and 65% had a high EPI score. Among EO, there was a higher frequency of males (49%), stage III-IV (72%), B symptoms (29%), anemia (48%), sGA UNFIT (48%), and high EPI score (66%). However, differences between EO and LO were not statistically significant, with the exception of B symptoms. The frequency of EO patients with intermediate-high or high-risk IPI score was the same as that of LO patients (59%). Concerning treatment approach, the proportion of LO and EO patients who, based on clinical judgment, received FDT or PVT was significantly different. In LO, only 17 patients (13%) received FDT with curative intent, 47 (36%) received RDT, and 65 (50%) received PVT. In EO, FDT was given to

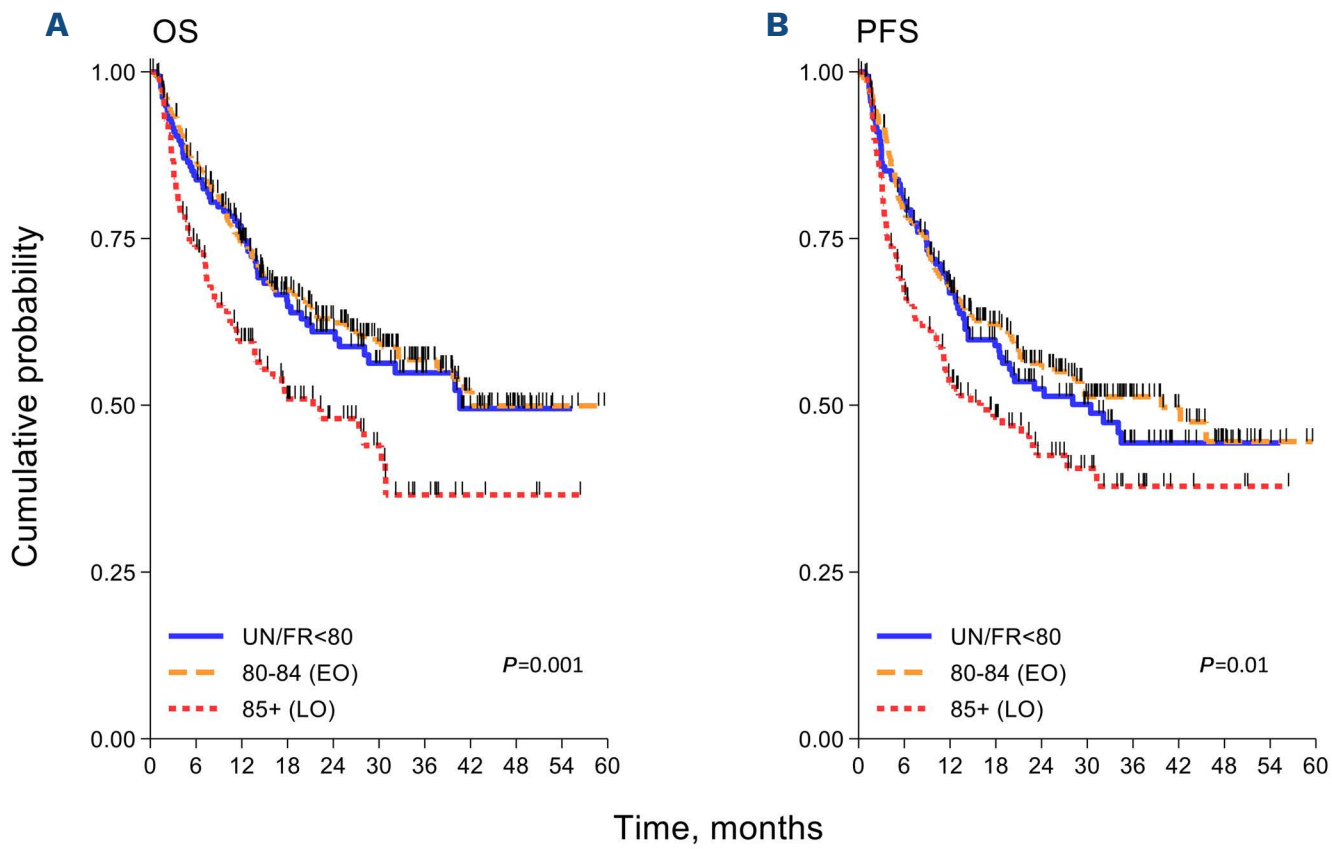

Figure 1. Kaplan-Meier curves of survival in older patients according to different age groups. Panel (A) shows overall survival (OS) and panel (B) shows progression-free survival (PFS) of different age categories: late octogenarians (LO) aged > 85 (85+), early octogenarians (EO) aged 80-84, and patients <80 years old (65-79) resulted UNFIT (UN) or FRAIL (FR) according to the simplified geriatric assessment.

33%, RDT to 44%, and PVT to 23% of patients (*P*<0.001). The proportion of patients receiving rituximab in the context of PVT was higher in EO (73%) than in LO (54%) (*P*=0.0387). Among all octogenarians, prediction of palliative treatment by means of logistic regression showed age, female sex, limitation in IADL, and some comorbidities (hypertension, heart failure, and psychiatric illness) as the most relevant variables. In the palliative group, the variables correlated with the probability of being treated without rituximab by means of logistic regression were age, limitation in ADL, and impairment of kidney and muscle function on CIRS-G evaluation (*Online Supplementary Tables S3* and *S4*).

Survival according to age

With a median follow-up of 30 months (range, 1–59 months), 2-year PFS and 2-year OS of LO were 43% and 48%, respectively, significantly lower than PFS (56%; *P*=0.01) and OS (63%; *P*=0.001) of EO (Figure 1). The most common cause of death was progressive disease in both age subgroups (67% and 76%, respectively; *P*=0.628), with no difference according to the treatment received. The cumulative incidence function (CIF) for specific cause of death is reported in the *Online Supplementary Figures S1* and *S2*. Figure 1 also reports the estimated survival of the 157 consecutive patients aged 65-79 years enrolled in the Elderly Project and classified as UNFIT or FRAIL whose 2-year PFS (52%) and OS (61%) were not significantly different from those of EO patients (*P*=0.764 and *P*=0.563, respectively). These two groups of patients had similar clinical characteristics, but they differed in terms of the treatment received (*P*<0.001): 59% of the patients aged 65–79 years received FDT, 24% received RDT, and 17% received PVT.

Survival according to treatment

Considering the effect of treatment intensity on patient outcome, no difference was observed between full and reduced doses of anthracycline in LO (2-year OS 64% with FDT *vs*. 67% with RDT) or in EO (2-year OS 70% with FDT *vs*. 68% with RDT). A palliative approach was associated with significantly worse 2-year survival both in LO (2-year OS 27% with PVT *vs*. 64% with FDT; *P*=0.001) and in EO (2-year OS 42% with PVT *vs*. 70% with FDT; *P*=0.003) (Figure 2). Considering the whole population of octogenarians, HR associated with PVT was 2.42 (95% CI: 1.71-3.42); after weighted Cox regression by IPW, the HR associated with PVT was 1.66 (95% CI: 1.12-2.44; *P*=0.011). Among palliative approaches, the addition of rituximab improved the outcome in all octogenarians (2-year OS with rituximab 42% *vs*. 22% without rituximab; *P*=0.008) (Figure 3). Conversely, only small differences were observed when comparing the different chemotherapy regimens employed in association with rituximab (CVP *vs*. bendamustine *vs*. other combinations or rituximab alone) (Table 2).

Survival according to geriatric parameters

The outcome of patients was significantly predicted by their

geriatric category: 2-year OS was better in UNFIT *versus* FRAIL LO patients (66% *vs*. 37%; *P*=0.006) and in UNFIT *versus* FRAIL EO patients (70% *vs*. 56%; *P*=0.024). The same difference was observed concerning 2-year PFS (58% *vs*. 33%, *P*=0.012 in LO and 59% *vs*. 53%; *P*=0.07 in EO). According to the EPI score, 2-year OS of LO was 63% in intermediate *versus* 41% in high EPI score patients (*P*=0.025), and 2-year PFS was 57% *versus* 38% (*P*=0.015). Even in EO, EPI score maintained its prognostic significance: 2-year OS was 84% *versus* 52%; *P*=0.001, in intermediate *versus* high, respectively, and 2-year PFS was 77% *versus* 45%; *P*=0.001 (Figure 4). In a multivariable analysis (MVA) of variables influencing the survival of octogenarians, age >85 years had a modest independent adverse effect on OS but not on PFS. Bulky disease and B symptoms retained a prognostic role in MVA. On the other hand, anthracycline-containing treatment, either at full or reduced doses, had a strong independent effect on both parameters compared to palliative treatment approaches. Among patients not receiving anthracycline, the inclusion of rituximab in the palliative treatment had an independent favorable effect on OS and PFS (Tables 3 and 4). Focusing on geriatric parameters, EPI score performed better than sGA in identifying different risk categories having different OS and PFS, and high EPI score retained an independent unfavorable effect on OS and PFS, together with treatment without anthracycline. We performed an internal validation, whose results are reported in the *Online Supplementary Table S5*.

Discussion

Management of octogenarian DLBCL patients is becoming an increasingly relevant problem in clinical practice. Most

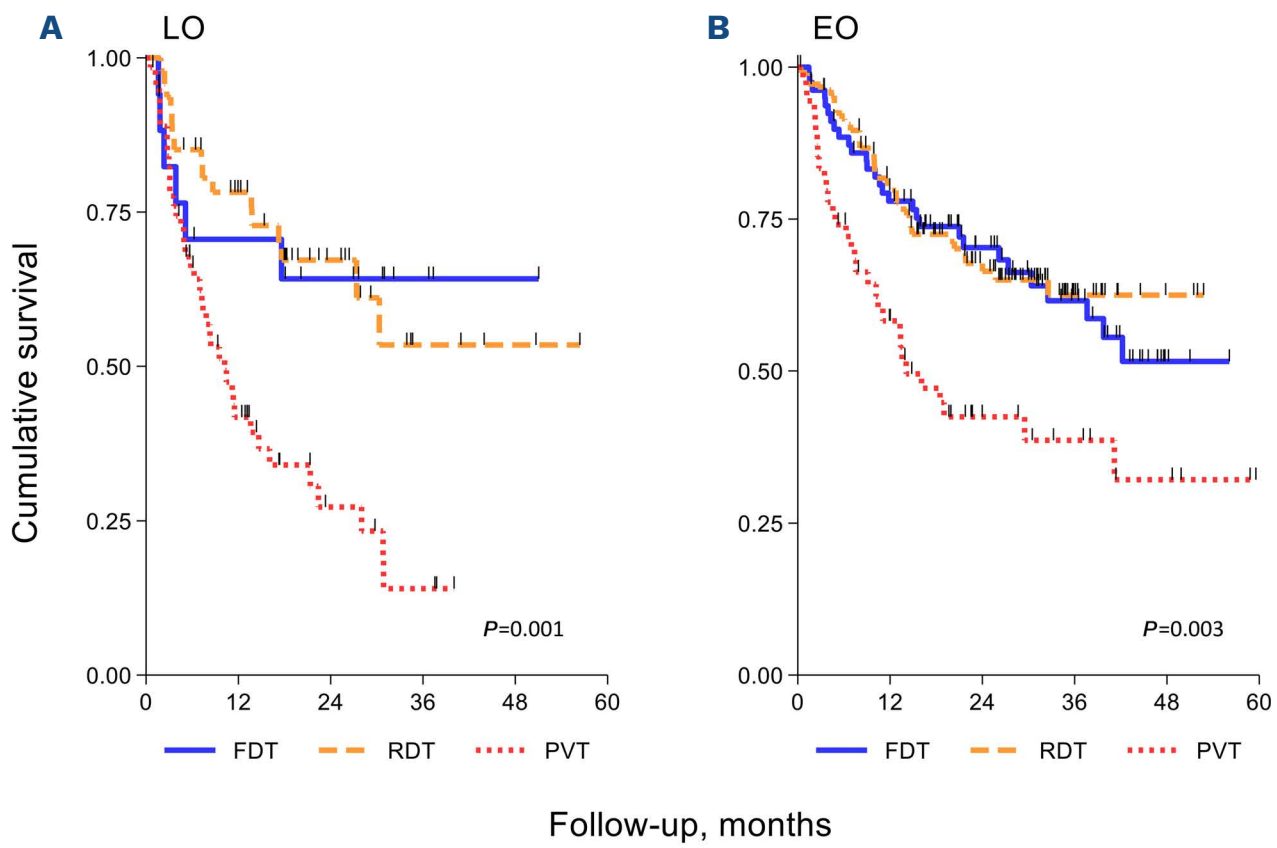

Figure 2. Kaplan-Meier curves of overall survival in octogenarian patients according to treatment received. Panel (A) shows overall survival (OS) of late octogenarians (LO) and panel (B) shows OS of early octogenarians (EO), both according to different treatment received: full-dose treatment (FDT), reduced-dose treatment (RDT), or palliative treatment (PVT).

Table 2. Different palliative treatments with or without rituximab in patients aged ≥80 years.

Treatment	N (%)	2-year OS % (95% CI)	HR (95% CI)	*P*
R-CVP	34 (28)	41 (22-59)	1.00	
RB	12 (10)	50 (21-74)	0.77 (0.32-1.87)	0.562
R-other*	29 (24)	38 (18-38)	1.14 (0.58-2.25)	0.700
No R	45 (37)	22(9-38)	1.88 (1.05-3.35)	0.034
Total	120	35 (25-44)	-	-

OS: overall survival; HR: hazard ratio; CI: confidence interval; R-CVP: rituximab, cyclophosphamide/vincristine/prednisone; RB: rituximab/bendamustine; R: rituximab. *5 R-monotherapy.

of the studies available have analyzed early octogenarians (age <85 years), whereas LO aged >85 years have largely been underrepresented. The growing interest in these patients derives from the progressive improvement in their general condition, which makes considering treating at least some of them with curative intent a possibility. In a recent study from the Danish and Swedish lymphoma registers, the 2-year survival of patients who received active treatment was significantly better than that in the untreated group (49% *vs*. 12%, respectively). However, the geriatric characteristics of the two patient groups were not reported.[11] The prospective Elderly Project study included all patients with DLBCL aged over 64 years and consecutively seen in 36 FIL centers. In the present study, we performed a detailed analysis of the LO enrolled in the Elderly Project, who accounted for more than 10% of the patients registered and for one-third of the patients over age 80. Their estimated 2-year OS was 48%, and the study confirmed a significantly better prognosis of those patients treated with curative intent with anthracycline-containing regimens (64%) than that of those receiving other regimens with palliative purpose (27%). Furthermore, in this latter group, the 2-year OS was significantly improved (37% *vs*. 15%) by including rituximab in the palliative treatment. The further improvement seen in our patients over the already remarkable survival reported in the Nordic Registry study may be explained by the fact that our patients were treated in experienced centers and cannot therefore be considered fully representative of the entire population of LO. The fact that all the participating centers used the FIL criteria to evaluate patient fitness using sGA may have also contributed.

The OS of LO (2-year OS: 48%) was significantly shorter than of that of EO (2-year OS: 63%), despite the fact that the two cohorts had very similar clinical and geriatric characteristics. In addition to age and to a higher frequency of B symptoms among EO, the only difference between EO and LO was the proportion of patients treated either with full or reduced dose of anthracycline, which was 49% in LO and 77% in EO. On the other hand, the dose of anthracycline did not affect outcome, since survival was similar in patients receiving more or less than 70% of the full anthracycline dose. These data strongly support the advisability of using a reduced dose of anthracycline in all octogenarian patients and confirm the results reported by the LYSA group using a R-mini-CHOP regimen.[10] The same group has recently reported a randomized study showing that the addition of lenalidomide to R-mini-CHOP did not improve survival of octogenarians, which was 66% at 2 years in both groups.[18] By showing a 2-year OS of 67% in LO treated with reduced anthracycline doses, our study confirms this figure and extends it to LO.

In our study, sGA made it possible to subdivide octogenarian patients into one of two groups: those without any limitations in ADL and IADL and with limited comorbidities (UNFIT), or those with limitations and major comorbidities (FRAIL). These two groups had significantly different survival among both LO and EO, confirming the validity of this geriatric tool. In addition, the recently developed EPI score, which refines the sGA by adding two important clinical parameters, the International Prognostic Index and anemia, also proved able to predict both 2-year OS and 2-year PFS, confirming that the EPI score maintains its validity in these groups of very old patients as well.

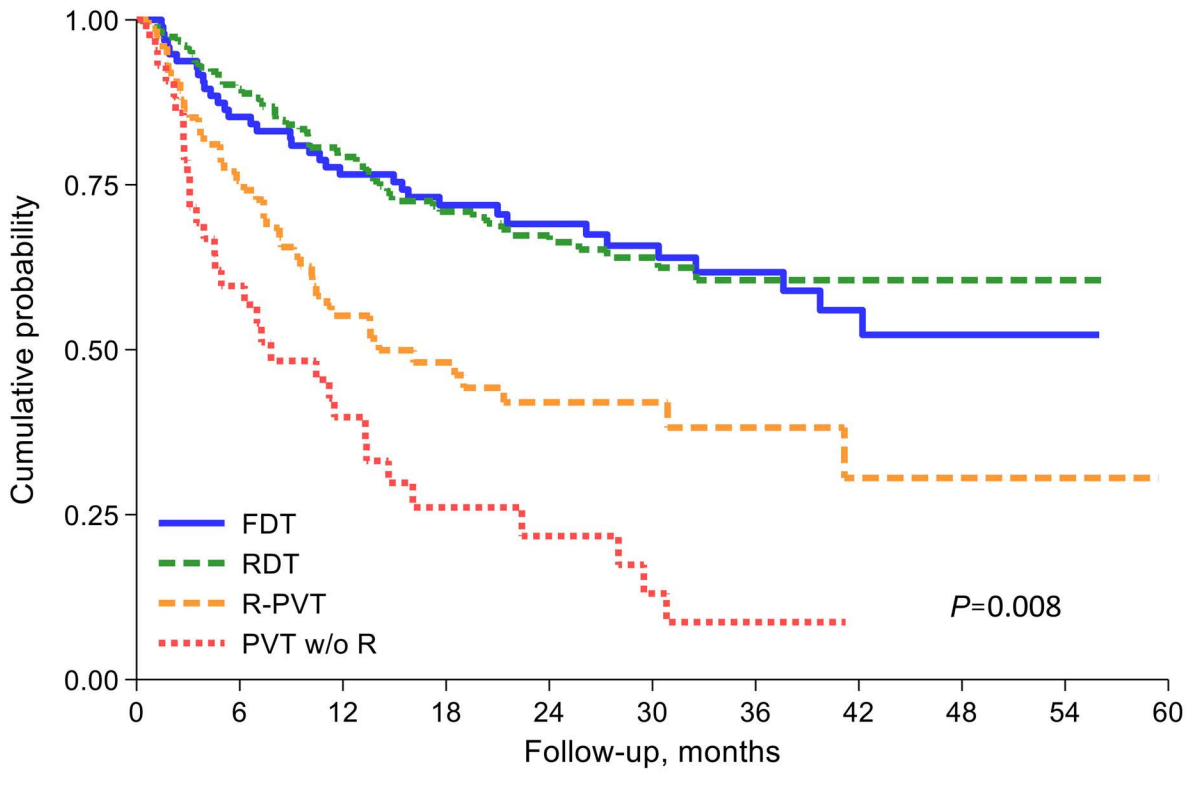

Figure 3. Overall survival of the whole octogenarian population according to different treatment received. Full-dose treatment (FDT), reduced-dose treatment (RDT), palliative treatment with rituximab (R-PVT) or without rituximab (PVT w/o R).

Indeed, on multivariable analysis, the EPI score and the use of an anthracycline-containing treatment were the only two variables retaining an independent effect for predicting both OS and PFS in octogenarians, while age lost its significance, and the sGA performed less efficiently.

In particular, EPI score identified a high-risk group whose needs are clearly unmet and who should be the subject of future investigations based on target molecules rather than standard chemotherapy regimens.

Furthermore, these data suggest that in very advanced-age patients such as LO, the geriatric criteria commonly used to define patient fitness in older DLBCL patients may not be completely adequate and may need further refinements by exploring different geriatric domains.

The most frequent comorbidities observed in patients undergoing palliative treatments may suggest carefully evaluating kidney impairment, sarcopenia, and/or more subtle cognitive functions.

Rosko *et al*. recently underlined the need to carefully evaluate disease and patient-specific characteristics to define specific guidelines that incorporate GA measures. This would guide treatment choices better among the increasingly wide range of options and supportive care available for older patients.[19]

Furthermore, as fitness and frailty are dynamic factors that can improve or deteriorate during the course of a disease and its treatment, repeated geriatric assessments are encouraged, especially in this very old population.[20]

An important observation is that the inclusion of rituximab in palliative regimens or its use as a single agent significantly improved survival compared with rituximab-free palliative regimens, regardless of age and patient fitness. The important gain in life span and the relatively good tolerability of this drug makes its use suitable when anthracyclines are not indicated, while the choice of the anthracycline-free chemotherapy regimen seems less important. Immunotherapy is an effective and well-tolerated approach that allows dose-intensity modulation of chemotherapy regimens. A recent study showed promising results obtained with a bispecific antibody used as a monotherapy in unfit patients with previously

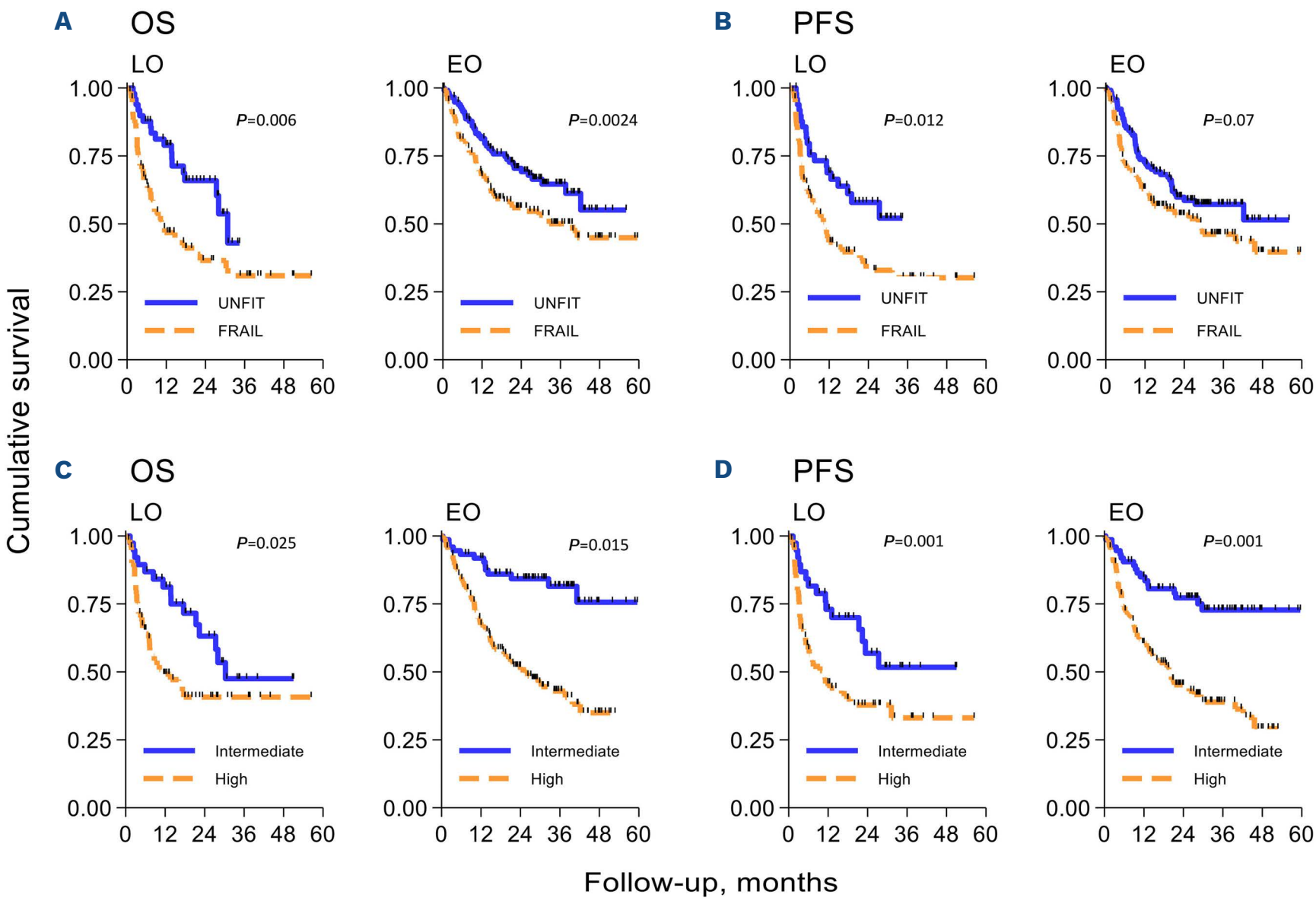

Figure 4. Kaplan-Meier curves of overall survival and progression-free survival in octogenarian patients according to simplified geriatric assessment and Elderly Prognostic Index. Panel (A) shows (OS) and panel (B) shows progression-free survival (PFS) in late octogenarians (LO) and early octogenarians (EO) according to geriatric category (UNFIT and FRAIL); panel (C) shows OS and panel (D) PFS in LO and EO according to EPI (Elderly Prognostic Index) score (Intermediate and High).

untreated aggressive B-cell lymphoma,[21] opening the way to a chemotherapy-free approach in this very old population. A careful use of supportive care is another important way to improve outcome and quality of life in this group of patients.[16,19,20]

Although the reported results come from a large number of octogenarians consecutively treated in specialized centers, this study has some limitations. Patients in very compromised clinical conditions or with very advanced disease may be lost as they are often not referred to second-level centers. Furthermore, details on patient follow-up, including reports on exact treatment modalities, treatment-related toxicities, and/or the appearance of new comorbidities may have been incomplete. Moreover, the predictive capability of sGA and of EPI need to be formally tested using an external validation dataset. Overall, the impact of the type of treatment on survival in the presence of many confounding factors is difficult to determine; only a randomized study can answer this question.

In conclusion, while chronological age still has a negative impact on older patients' survival, this study highlights the risk of undertreating patients solely because of their very advanced age. We demonstrate that late octogenarians can achieve long-term survival; a curative intent approach, with reduced anthracycline dose, is the best choice in this group of patients, and the choice may be effectively guided by considering the EPI score. The inclusion of rituximab in palliative treatment programs should always be considered, even in frail and very old patients.

Table 3. Multivariable Cox proportional hazards regression on overall survival with Elderly Prognostic Index or simplified geriatric assessment in patients aged ≥80 years.

Overall survival	**With EPI N=322**	
Variable	**HR (95% CI)**	***P***
Age 85+ years	1.59 (1.11-2.30)	0.012
EPI		
Intermediate	1.00	
High	2.43 (1.59-3.74)	<0.001
B symptoms	1.58 (1.09-2.29)	0.015
Bulky	1.59 (1.10-2.29)	0.013
Treatment		
R-CHOP/COMP/R-mini-CHOP	1.00	
Others with R	1.99 (1.37-2.88)	<0.001
Others w/o R	3.92 (2.36-6.52)	<0.001
Others w/o R *vs.* with R	1.97 (1.18-3.29)	0.009
c-Harrell	0.717 (0.673-0.760)	
Overall survival	**With sGA N=322**	
Variable	**HR (95% CI)**	***P***
Age 85+ years	1.52 (1.06-2.19)	0.023
sGA		
UNFIT	1.00	
FRAIL	1.16 (0.81-1.67)	0.416
B symptoms	1.83 (1.27-2.64)	0.001
Bulky	1.79 (1.24-2.58)	0.002
Treatment		
R-CHOP/COMP/R-miniCHOP	1.00	
Others with R	2.06 (1.41-3.02)	<0.001
Others w/o R	3.99 (2.36-6.74)	<0.001
Others w/o R *vs.* with R	1.94 (1.16-3.24)	0.012
c-Harrel	0.686 (0.638-0.734)	

EPI: Elderly Prognostic Index; HR: hazard ratio; CI: confidence interval; R-CHOP/COMP: rituximab-cyclophosphamide, doxorubicin hydrochloride, vincristine, prednisone/ cyclophosphamide, liposomal doxorubicin, vincristine, prednisone; sGA: simplified geriatric assessment; R: rituximab. Comparison c-Harrel: model with EPI – model with sGA =0.031 (95% CI: 0.001-0.060); *P*=0.041. The discriminant index Harrell's C refers to Cox model.

Table 4. Multivariable Cox proportional hazards regression on progression-free survival with Elderly Prognostic Index or simplified geriatric assessment in patients aged ≥80 years.

Progression-free survival	**With EPI N=322**	
Variable	**HR (95% CI)**	***P***
Age 85+ years	1.36 (0.96-1.93)	0.084
EPI		
Intermediate	1.00	
High	2.21 (1.49-3.29)	<0.001
B symptoms	1.62 (1.14-2.30)	0.008
Bulky	1.67 (1.19-2.35)	0.003
Treatment		
R-CHOP/COMP/R-mini-CHOP	1.00	
Others with R	1.81 (1.27-2.57)	0.001
Others w/o R	3.57 (2.17-5.89)	<0.001
Others w/o R *vs.* with R	1.97 (1.19-3.27)	0.007
c-Harrell	0.696 (0.653-0.739)	
Progression-free survival	**With sGA N=322**	
Variable	**HR (95% CI)**	***P***
Age 85+ years	1.32 (0.93-1.87)	0.115
sGA		
UNFIT	1.00	
FRAIL	1.05 (0.75-1.48)	0.761
B symptoms	1.83 (1.29-2.60)	0.001
Bulky	1.87 (1.33-2.63)	<0.001
Treatment		
R-CHOP/COMP/R-mini-CHOP	1.00	
Others with R	1.91 (1.33-2.74)	<0.001
Others w/o R	3.84 (2.29-6.44)	<0.001
Others w/o R *vs.* with R	2.01 (1.21-3.34)	0.007
c-Harrel	0.664 (0.618-0.711)	

EPI: Elderly Prognostic Index; HR: hazard ratio; CI: confidence interval; R-CHOP/COMP: rituximab-cyclophosphamide, doxorubicin hydrochloride, vincristine, prednisone/ cyclophosphamide, liposomal doxorubicin, vincristine, prednisone; w/o: without; R: rituximab; sGI: simplified geriatric assessment. Comparison c-Harrel: model with EPI – model with sGA =0.031 (95% CI: 0.004-0.059), *P*=0.024. The discriminant index Harrell's C refers to Cox model.

Disclosures

AT has a consultancy or advisory role at Janssen, Gentili, MSD, Takeda, Kiowa kyrin and Sanophi. FM has a consultancy or advisory role at Janssen, Gilead Sciences, MSD, Takeda and Roche; he has received travel and accommodation expenses from Janssen, Gilead Sciences, EUSA Pharma, Celgene, Roche and Takeda. LF has received travel and accommodation expenses from Roche and Janssen. AA has a consultancy or advisory role at Janssen-Cilag and has received travel and accommodation expenses from Janssen-Cilag and Takeda; AF has a consultancy and advisory role at Roche, Takeda, Incyte, Servier and Kyowa Kirin. FC is on the advisory board of Roche, he has received speaker fees from Servier and Gilead; he consults for Incyte and has an advisory role at Roche, Incyte and Janssen. GM has a consultancy and advisory role at Janssen Oncology and Servier. SL has a consultancy and advisory role at Roche, Gilead Sciences and Celegne; he has received travel and accommodation expenses from Janssen and Celgene. MS is employed by Bristol-Myers Squibb/Medarex and Sanofi; he has a consultancy or advisory role at Gilead Sciences and Incyte. All other authors have no conflicts of interest to disclose.

Contributions

AT, FM, LM, SL, GR, and MS conceived and designed the study; AT, FM, AF, CP, BP, DM, MZ, EP, LF, AA, BB, MC, AR, AT, VRZ, EC, RS, CB, MM, LP, GG, MB, FC, GM, SL, GR, and MS provided study materials and patients; AT, FM, LM, SL, GR, and MS performed data analysis and interpretation; AT and GR wrote the manuscript. All authors performed data collection and assembly and approved the final version of the manuscript.

Data-sharing statement

The authors will make their original data available to future researchers upon request directed to the corresponding author.

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