

Diffuse Large B-cell Lymphoma in the Elderly: A Review of Potential Difficulties

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Abstract

Half of patients with diffuse large B-cell lymphoma (DLBCL) are more than 65 years old. These elderly patients frequently have other diseases, some of them severe, which may alter their ability to receive standard curative therapy. However, these associated diseases are heterogeneous and only a few contraindicate chemotherapy treatments. We reviewed all potential difficulties, such as the evaluation of comorbidities, the heterogeneous functional status of this population, and the consequences of the aging process that might be associated with treating these patients, and now propose solutions. As standard rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy may cure the majority of patients, it must always be the first proposed option. With this approach, elderly patients with DLBCL treated with a curative intent can reach a complete remission and have a similar outcome as younger patients. Reduced dose intensity must be applied for very elderly patients or those unfit for full-dose anthracycline. The critical question for a physician is why these patients cannot be treated with the standard regimen, namely R-CHOP. *Clin Cancer Res*; 19(7); 1660–9. ©2013 AACR.

Introduction

Elderly patients are classically defined as older than 65 years. In developed countries, life expectancy has been increasing consistently over the last century and is estimated to reach 85 years for women and 80 for men by 2030 (1). People more than 65 years of age will soon represent more than 20% of the global population (2). Age is one of the major risk factors for cancer and, by the year 2020, 70% of all neoplasms are likely to occur in persons aged more than 65 years (3). Non-Hodgkin lymphoma (NHL) is the fifth most common cancer in men and the sixth in women. Diffuse large B-cell lymphoma (DLBCL) is the most frequent NHL, representing more than 40% of lymphomas in the elderly (4, 5). The probability of having a DLBCL grows with age, from 0.13% and 0.09% before 39 years to 1.77% and 1.4% after 70 for men and women, respectively (6, 7). DLBCL incidence increases in the elderly, with 45 cases per year for 100,000 inhabitants aged 60 to 64 years and 112 cases among those 80 to 84 years. Around 50% of DLBCL cases occur in patients older than 65 years, and 40% in patients more than 70 years (8).

Age has always been a major prognostic factor and, because older age is associated with the presence of con-

comitant diseases, it is a major determinant of therapeutic decisions (9). However, women aged 80 years might live 8 years and males 9 years (10). Furthermore, in the absence of concomitant disease, patients with DLBCL of more than 70 years of age survive as long as younger patients (11). Nevertheless, advanced age was a predictive parameter in many series of patients with NHL (12–14). Elderly DLBCL patients' poor outcome has been linked to their decreased ability to receive standard chemotherapy regimens, and physicians' tendency to administer weaker treatments that are better tolerated but less effective (15). Considering the continuous progress made in lymphoma treatment, age itself should not be a justification for palliative care decisions or reduced dose-intensity chemotherapy (16).

Differences in DLBCL morphology between younger patients and older patients

Studies on gene expression profiling have defined 3 DLBCL groups: the germinal center (GC) B-cell, the activated B-cell (ABC), and the mediastinal large B-cell subtype. The distribution of these groups changes with age, most elderly patients being of ABC subtype (17). The mediastinal large B-cell subtype is mostly seen in young patients. The GC subtype median age is approximately 8 years younger than that of the ABC (18).

In 2008, a new entity entered the World Health Organization classification, namely "EBV-positive DLBCL of the elderly" (19). It is defined as an EBV-positive clonal B-cell proliferation in patients older than 50 years without any other primary or secondary immune disease. Most of these cases displayed an ABC subtype (20). Diagnosis is made by showing the expression of LMP-1 and EBNA-2 within the tumor cells (21). Asian studies were the first to describe

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this entity, which occurs in 8% to 10% of elderly with DLBCL (22). Because these patients are not immunodeficient, the authors hypothesized that this lymphoma might be related to immunologic deterioration resulting from aging. German studies revealed geographic variation with a lower rate among the Western populations (23).

Initial Evaluation

Elderly patients present with similar clinicobiologic characteristics as those observed in younger patients (14, 24). The initial staging includes clinical evaluation, computed tomography and positron emission tomography scans (whenever possible), bone marrow biopsy, lumbar puncture in patients with high risk of central nervous system (CNS) relapse, and standard biologic tests. An electrocardiography and echocardiography must be conducted before using anthracycline to determine left ventricular ejection fraction (LVEF).

Comorbidities (other cancers, diabetes, osteoporosis and arthritis, cardiovascular or pulmonary diseases, renal dysfunction, depression, Alzheimer's disease, etc.) are common in elderly patients, with more than 61% of patients older than 70 years and more than 85% of those older than 80 years presenting comorbidity, as opposed to 20% in younger patients (25). Patients with DLBCL with comorbidities have higher risk of treatment toxicity and of death (25). Hematopoietic reserve capacity is impaired with increasing age, and myelotoxicity of standard dose regimens has been shown to be more severe in the elderly (26). The Charlson index and the Cumulative Illness Rating Scale are well validated and reproducible tools frequently used to assess these comorbidities (27).

Aging is associated with a large functional heterogeneity, and other diseases are not always evident and easily identified. The comprehensive geriatric assessment (CGA) is a multidimensional diagnostic tool that evaluates the medical, functional, and psychological status, and therefore the presence of morbidity in elderly patients. The traditional assessment of patients' functional status relies on the Karnofsky or Eastern Cooperative Oncology Group (ECOG) performance status, whereas assessments conducted by a geriatrician include the assessment of ability to live in the community and instrumental activities of daily living [IADL and activities of daily living (ADL) scale, Supplementary Table S1; refs. 28, 29]. CGA predicts survival, tolerance to chemotherapy, and mortality, independently from the performance status (29, 30). In patients older than 70 years, low mini nutritional assessment (MNA) and mini mental state scores independently increase the probability of not completing chemotherapy (28). Nutritional problems in elderly patients are associated with decreased tolerance to chemotherapy, higher risks and severity of treatment complications, and shorter survival (31).

Furthermore, the aging process modifies drug pharmacokinetics and pharmacodynamics, decreasing therapeutic index and modifying tolerance, absorption, diffusion, and metabolism of drugs, and treatment responses (32). These

mechanisms are linked to decreased kidney or liver functions, which is the case for drugs involved in DLBCL treatment such as cyclophosphamide and anthracycline. In addition, concomitant medication and use of tobacco or alcohol may induce modifications in drug pharmacokinetics and pharmacodynamics. Elderly are also more likely to present compliance issues.

Prognostic indexes

The Ann Arbor staging system for Hodgkin lymphoma is not appropriate for NHL as prognosis is better described using the International Prognostic Index (IPI; ref. 9). A derivative and simplified score, the age-adjusted International Prognostic Index (aalPI), has been developed. Although other scores, such as revised International Prognostic Index (R-IPI) or Elderly International Prognostic Index (E-IPI), have been recently developed, the aalPI remains the most widely used for predicting survival and making a therapeutic decision in both the younger and elderly populations. (See the description of these indexes in Table 1; refs. 33, 34.)

Treatment

Older age correlates with lower complete remission (CR) rate, shorter progression-free survival (PFS), and shorter

Table 1. The prognostic indexes in patients with DLBCL

	IPI	aalPI	R-IPI	E-IPI
Age	+ (60 y)	–	+ (60 y)	+ (70 y)
LDH	+	+	+	+
Ann Arbor	+	+	+	+
ECOG-PS	+	+	+	+
Nodal sites	+	–	+	+
<i>n</i> of risk group	4	3	3	4

NOTE: IPI is based on 5 characteristics, namely age (≤ 60 or > 60 years), performance status (0–1 or > 1), lactate dehydrogenase (normal or elevated), Ann Arbor stage (localized or disseminated), and extranodal site number (0–1 or > 1). It identifies 4 risk categories (0–1 factor or low risk, 2 factors or intermediate-low risk, 3 factors or high-intermediate risk, and 4–5 factors or high risk). A derivative and simplified index was developed, the aalPI, relevant in the elderly and younger population. Since the use of rituximab in combination with chemotherapy in DLBCL, the R-IPI was developed on the basis of the same clinical factors (33). Advani proposed an E-IPI with 70 years as the cut-off point for age (34). This score allowed a classification into 4 risk groups, and the discrimination seemed to be better than with IPI, aalPI, or R-IPI. However, the aalPI is the most widely used in the younger and elderly population to predict survival and choose therapeutics option.

Abbreviations: LDH, lactate dehydrogenase; PS, performance status.

survival in patients with DLBCL (24, 35). If the current definition of elderly is 65 years, former studies used 60 years. In elderly patients, treatment choice is based on aalPI score, CGA, and comorbidities (4, 36). Many older patients have a good performance status, allowing them to be treated with standard dose regimens. In contrast, frail patients with a loss of independence in activities of daily living may experience significant side effects and require adapted regimens. Unfortunately, and without a scientific basis, age often seems to be the only reason for decreasing chemotherapy doses (15, 37, 38). A large survey with data extracted from 4,522 patients with aggressive NHL [treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), CHOP, or cyclophosphamide, mitoxantrone, vincristine, and prednisone (CNOP)] showed that the dose was reduced compared with the minimum 6 cycles of R-CHOP in 53% of cases, in only half of them because of toxicities. Independent predictors of reduced relative dose intensity were age exceeding 60 years, advanced disease stage, poor performance status, and no prophylactic granulocyte colony-stimulating factor (G-CSF) use (38). In a Dutch retrospective study of elderly patients with DLBCL, 76% of the patients had a reduced number of cycles compared with planned treatment (39). In 77% of them, the reason was a poor performance status; however, 23% of these patients were not treated optimally because of their age despite of a good performance status. Several studies reported that optimally treated elderly patients display similar outcomes to younger patients (4, 24, 37, 39–42). Thus, given patient consent, the elderly must be treated with an effective regimen in association with active supportive care, including nutrition, neutropenia prophylaxis, and, when necessary, reduced dose intensity. The physician's major and most difficult task is choosing a regimen that allows patients to reach CR without inducing toxicities.

Treatment of fit elderly with (low-risk) localized DLBCL

Patients without adverse prognostic factors (aalPI score of 0) present localized disease. The use of radiotherapy in an elderly population was questioned by the Groupe d'Études de Lymphomes de L'Adulte (GELA) in a randomized study comparing 4 cycles of CHOP regimen with 4 cycles of CHOP followed by involved-field radiotherapy (43). Patients included were older than 60 years of age with localized disease (stage I or II) and no adverse prognostic factors. CHOP plus radiotherapy was not superior to CHOP alone. GELA confirmed this result in another study with younger patients that concluded that in stage I or II disease radiation therapy does not add to an effective chemotherapy regimen (44). Thus, 6 cycles of R-CHOP in elderly patients with localized DLBCL is the recommended regimen (41).

Treatment of fit elderly with poor-risk disease

Studies conducted when the CHOP regimen alone was the standard of care reported 40% to 50% CR in the elderly and 3-year overall survival of 30%, which was considered unsatisfactory (39). Intensified chemotherapy regimens with increasing doses, shortening cycles, or both, or autologous stem cell transplantation (ASCT), can improve out-

come in young patients but are too toxic for the elderly (45). A study conducted by the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL) in patients ages 61 to 75 showed that CR was improved with CHOP administered every 2 weeks rather than every 3 weeks (46). In this study, all patients received G-CSF, and there was no excess of toxicity in the 2-week regimen. However, the median age of the population was 65 years, with very few patients older than 70. Before the rituximab era, regimens that were better tolerated than CHOP were tested but all randomized studies agreed on the strong relationship between relative dose intensity and survival (11, 47).

In 1998, GELA conducted the first phase III study that compared CHOP plus rituximab with CHOP alone in elderly patients with stage II to IV DLBCL. The R-CHOP regimen improved CR rate (71% vs. 63%, $P = 0.005$) and duration of PFS, disease-free survival (DFS), and overall survival, with benefits still present at 10-year follow-up (48, 49). This improvement was achieved without any increase in toxic effects. Other phase III studies confirmed these results (Table 2; refs. 41, 50). In the RICOVER study, 6 cycles of R-CHOP were compared with 8 cycles every 2 weeks, with the outcome being similar in both regimens (41). On the basis of these results and others in Table 2, R-CHOP, every 3 weeks, remains the standard of care for elderly patients (51, 52).

One approach would be to treat these patients with regimens adapted to the CGA score. An Intergruppo Italiano Lymphoma (IIL) phase II study used this approach with 100 patients evaluated by ADL and IADL scales. (53) CR was achieved in 81% of patients, and 5-year overall survival was 60%. Toxicity was acceptable, with grade 4 neutropenia observed in 14% of cases and grade 4 cardiac and neurologic toxicities in 2%. Another Italian study involving 91 patients treated according to CGA ("fit" patients with R-CHOP, patients with comorbidities with R-CHOP with liposomal doxorubicin, and frail patients with reduced doses) showed less good results with 5-year overall survival at 31% (54). In both studies, the number of unfit and frail patients was low, and the results of these patients were always inferior to those of patients treated with standard R-CHOP. In conclusion, the benefits of this adaptation are difficult to evaluate.

The very elderly patients (more than 80 years)

While the previously described studies have included patients older than 65 years, very elderly patients and those with comorbidities were traditionally excluded from participation. Therefore, for this very elderly population, the unmet medical need is high.

An Italian multicenter study involving 350 patients aged more than 60 years revealed no difference in CR and 5-year overall survival rates between patients of more than 80 years and those aged 60 to 69 or 70 to 79 years (55). A French retrospective study reported that presentation and prognostic factors were the same in patients more than 80 years of age and in younger ones (24). Lymphoma was the principal cause of death, indicating that this condition should be treated with a curative intent (24). While R-CHOP is the

Table 2. Studies in the rituximab era for fit elderly patients

References	N (Age)	Regimens	Better regimen	EFS/PFS ^a	CR/CRu ^a	OS ^a
Coiffier and colleagues (48, 49), phase III	399 (60–80)	R-CHOP vs. CHOP	R-CHOP	EFS (R-CHOP) 2-y 57% 10-y 36.5% EFS (R-CHOP) 3-y 53% (6RCHOP)	73% vs. 63% (P 0.005)	Median > 8 y 2-y 70% 10-y 43.5% 3-y 69%
Habermann and colleagues (50), phase III	632 (>60)	R-CHOP vs. CHOP +/- maintenance	RCHOP, longer EFS + maintenance if CHOP		77% vs. 76% NS	
Pfreundschuh and colleagues (41), Phase III	1222 (61–80)	6-8RCHOP vs. 6-8CHOP	6RCHOP	EFS 3-y 66.5% PFS 3-y 73%	6RCHOP 78%	3-y 78%
Delarue and colleagues (52), phase III	201 (60–80)	R-CHOP14 vs. R-CHOP-21	No	EFS 2-y 48–61% NS	–	2-y 67–70% NS
Moccia and colleagues (60), Retrospective	81 (median 73 y, 39–93)	R-CEOP vs. R-CHOP	R-CHOP	TTP 5-y 57–62% NS	–	5-y 64%
Cunningham and colleagues (51), phase III	1,080 (≥60)	R-CHOP-14 vs. R-CHOP-21 + G-CSF	No	HR-1	–	HR 0.96
Luminari and colleagues (63), phase II	75 (61–88)	R-COMP-21	–	PFS 3-y 69% 48%	57%	3-y 72%
Merli and colleagues (80), phase III	224 72 (64–86)	R-CHOP vs. R- miniICEOP	No	46%	73% 68%	5-y 62% 5-y 63%
Corazzelli and colleagues (64), phase II	41 (73 y)	R-COMP-14	–	DFS 4-y 72%	68%	4-y 67%

^aFor the phase III trial, the CR, overall survival, and PFS results are those of the better regimen. Abbreviations: EFS, event-free survival; NS, nonsignificant; R-CEOP, rituximab, etoposide, vincristine, and prednisone; R-miniICEOP: cyclophosphamide, epirubicin, vinblastine, prednisone, and rituximab.

Table 3. Study with reduced dose of chemotherapy or adapted regimen for elderly patients with DLBCL

References	N	Age (median)	Regimens	RDI	CR (%)	OS (%)	EFS/PFS
Zinzani (55) Prospective	350	69 (60–87)	VNCOP-B	NA	60–69: 61 70–79: 59 >80: 56	5-y: 53% 47%	
Peyrade (56) Prospective, II	149	83 (80–95)	R-miniCHOP	Doxorubicin 50% Cyclophosphamide 53%	63%	2-y: 59%	2-y: 47%
Hasselblom (57) Retrospective	70	>80 y	Pre-R: 40 pts Post-R: 30 pts	86% (toxicities)		3-y: 17% 3-y: 41%	3-y: 17% 3-y: 41%
Spina (53) Prospective	100	75 (70–89)	R-CHOP/CHOP	Fit 100% Frail 75% Unfit 50%	70–80: 83% >80: 80%	5-y 70–80: 54% >80: 61%	5-y 70–80: 67% >80: 46%
Olivieri (54) Prospective	91	74 (65–92)	R-CHOP or R-CDOP or miniCHOP	Fit: R-CHOP 100% Frail R-CDOP: NPLD 50% Unfit: cyclophosphamide 50%, doxorubicin 50%	81% 64% 50%	5-y: 46%	5-y: 31%
Gimeno (65) Prospective	35	76 (61–88)	RCMyOP	NPLD: 50% Vincristine: 24% Cycle delayed 8%	69%	2-y: 70%	2-y: 58% PFS

Abbreviations: RDI, relative dose intensity; VNCOP-B, cyclophosphamide, mitoxantrone, vincristine, bleomycine, and prednisone; R-miniCHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; Pre-R/Post-R, patients treated before the rituximab era or after the rituximab era; R-CMyOP, nonpegylated liposomal doxorubicin, cyclophosphamide, vincristine, and prednisone, rituximab.

standard of care in both younger patients and those aged 60 to 80 years, very few prospective trials on very elderly patients exist.

GELA conducted a phase II trial using an attenuated R-CHOP (R-miniCHOP) regimen in 150 patients older than 80 years of age with DLBCL (Table 3; ref. 56). Two-year overall survival was 59% and 2-year PFS was 47%. Tolerability was good, allowing for the administration of the full planned regimen in more than 72% of patients. In multivariate analysis, the serum albumin level was the only factor affecting survival (>35g/L or less), which emphasized the relevance of the nutritional status in these patients. Of the 58 deaths, 33 were related to lymphoma and 12 to treatment toxicity. In conclusion, this study showed that R-miniCHOP offered a survival benefit along with a good compromise between efficacy and safety for very elderly patients.

A Swedish retrospective study conducted between 1997 and 2009 confirmed these results (57): Outcomes of patients more than 80 years of age were compared during the prerituximab and rituximab eras showing 3-year overall survival at 41% in the rituximab era versus 17% in the prerituximab era.

Patients with a contraindication to anthracycline

Cardiotoxicity is a well-known major adverse event of anthracyclines (58). Patients with altered cardiac function (LVEF < 50%) are not eligible to receive doxorubicin or other anthracyclines. Because of potential preexisting heart dis-

ease, the elderly are more prone to cardiac side effects than younger patients (59). However, doxorubicin-free regimens are associated with shorter survival and a higher mortality rate from lymphoma (39).

The replacement of doxorubicin by etoposide was tested in a study from British Columbia: A 5-year overall survival of 49% was observed, which is shorter than the overall survival usually achieved with R-CHOP (60). A recent phase II trial selected 14 patients ineligible for R-CHOP to be treated with a combination of rituximab and bendamustine. The results were disappointing with 7 patients reaching CR and 6 patients (43%) alive without disease at 20 months (61). Other approaches to attenuate doses based on the CGA score have been developed but the benefits of this adaptation are difficult to evaluate as the studies failed to improve survival and have often generated inferior results (53, 54). Pirarubicin (THP), an analog of doxorubicin, was used in 2 Japanese studies, a phase III study comparing CHOP, THP-COP, and THP-COPE (with etoposide) in the elderly and a retrospective analysis of 467 patients with aggressive NHL comparing THP-COP and CHOP (62). In these 2 studies, no difference in outcomes was observed between the different regimens with less cardiac toxicity observed with pirarubicin. However, the CR rates were lower than in other studies conducted worldwide with R-CHOP (48, 62).

Nonpegylated liposomal doxorubicin may offer greater safety with preserved efficacy. A recent Italian phase II study

Table 4. SIOG proposals for the management of anthracycline cardiotoxicity risk

Recommendations	SIOG proposal for the physician
Rigorous screening to exclude patients at unacceptably high cardiac risk (Level 1a)	Comprehensive patient history: <ul style="list-style-type: none"> – Current signs or history of CHF – Cardiovascular comorbidity (i.e., hypertension, diabetes, or coronary artery disease) – Prior exposure to anthracyclines for current or previous malignancy (Level 1a)
Not exceeding the recommended upper cumulative dose (Level 1a)	Reduction in maximum cumulative dose (Level 5)
Use of less cardiotoxic therapy (Level 1a)	<ul style="list-style-type: none"> – Use of continuous infusion (Level 1a) – Epirubicin but less efficacy (Level 1a) – Dexrazoxane (elderly, Level 5) – Liposomal anthracycline formulation (elderly, Level 5)
Regular monitoring of cardiac function, signs, and symptoms (Level 1a)	<ul style="list-style-type: none"> – Measure of LVEF by ultrasound (preferred, level 5) or MUGA scan, every 2 or 3 cycles with anthracyclines (Level 1a) – Special attention needed if drop in LVEF exceeded 10%, even if remaining within normal range (Level 5) – Long-term follow-up (Level 1a)
Cardiovascular risk reduction interventions (Level 1a)	<ul style="list-style-type: none"> – Early management of dysfunction (Level 1a) – Lifestyle modifications (i.e., smoking cessation, regular exercise, weight loss where appropriate; Level 1a) – Beta blockers and ACE inhibitors (Level 1a) – Reduced lipid levels (Level 1a)

NOTE: The recommendations of SIOG are on the left side of the table with proposed daily practice for the physician on the right side. Adapted from Aapro and colleagues (68) by permission of Oxford University Press.

Abbreviations: CHF, congestive heart failure; MUGA, multiple uptake gated acquisition; ACE, angiotensin-converting enzyme.

evaluated the activity and safety of nonpegylated liposomal doxorubicin when substituted for doxorubicin in the R-CHOP regimen [rituximab, cyclophosphamide, non-pegylated liposome-encapsulated doxorubicin, vincristine and prednisone (R-COMP); ref. 63]: CR rate was 57% and 3-year overall survival, failure-free survival, and PFS rates were 72%, 39%, and 69%, respectively. However, cardiac toxicity persisted with 21% of cardiac events, grade 3 to 4 in 4% of cases. A larger study with the same regimen given every 2 weeks showed a 4-year time-to-treatment-failure of only 49% (64). Another study used a reduced dose of nonpegylated liposomal doxorubicin (30 mg/m²) in 35 frail elderly patients and obtained favorable results considering this frail population with little toxicity (69% CR in intention-to-treat analysis and 2-year overall survival of 70%; ref. 65).

The risk of congestive heart failure associated with anthracycline has been shown to decrease with the use of dexrazoxane, an iron chelator (66). However, there are concerns over its efficacy, safety, and possibility of altering anthracycline antitumor activity (67).

The International Society of Geriatric Oncology (SIOG) has recently published recommendations for the use of anthracycline in the elderly and proposed different meth-

ods to reduce cardiac toxicity levels in daily practice (Table 4; ref. 68).

Prevention of febrile neutropenia

Several studies indicated that the risks of neutropenia and infection were increased in older patients (69), possibly affecting 40% of cases (18% in younger patients), and was associated with higher hospitalization and mortality rates. Whether prophylactic G-CSF might decrease the mortality during treatment and improve survival in elderly patients with DLBCL is still a matter of debate (70). However, based on pharmacoeconomic considerations, prophylactic G-CSF is recommended where the risk of febrile neutropenia exceeds 20% (71). Therefore, recent guidelines recommend using G-CSF in elderly patients with DLBCL from the first R-CHOP cycle (72).

Central nervous system prophylaxis

The incidence of CNS relapse in DLBCL is not high enough in elderly patients to recommend prevention in every patient. The R-CHOP study concluded that rituximab did not reduce CNS relapse incidence and confirmed that CNS relapse was associated with high aalPI scores (73). When there

is no initial CNS involvement, prophylaxis should be reserved for patients with high risk of CNS relapse.

At Relapse

At relapse, young patients who respond to salvage chemotherapy were shown to benefit from high-dose therapy and ASCT. Obviously, if some younger elderly patients may tolerate such an intensive regimen, the majority of them do not. Although very few series have focused on the outcomes of elderly patients in relapse, it is generally recognized that the outcome is very poor, with only few therapeutic possibilities available. Therefore, there is a high unmet medical need for tolerable and efficient salvage in elderly patients. While consideration should again be given for curative therapy in some elderly patients at the time of relapse, palliative therapy is usually more appropriate. Consideration can be given to a single agent in phase II trials.

Standard chemotherapy

Of 399 patients, ages 60 to 80 years, entered in an upfront GELA study, 204 (51%) experienced relapse or progression, and all but 17 received salvage therapy, consisting mainly of dexamethasone, high-dose aracytin, and cisplatin (DHAP), etoposide, Solu-Medrol, aracytin, and cisplatin (ESHAP); or ifosfamide plus etoposide, with 2-year survival between 26% and 31% (49). Interestingly, survival rate was improved in patients receiving a rituximab-containing regimen at time of salvage (49). Another study evaluated the R-DHAOx regimen (DHAP where oxaliplatin is substituted for cisplatin) in 91 cases of relapse or refractory NHL with a median age of 60 years (74): 2-year overall survival was 75% and EFS 43%. R-GemOx, which combines rituximab, gemcitabine, and oxaliplatin, was well tolerated when given every 2 weeks, with good efficacy (75). These studies, focusing on individuals who were not candidates for transplant, did not directly assess the impact of age on salvage therapy.

Autologous stem cell transplantation

ASCT is feasible and effective in younger elderly patients presenting a good performance status and no comorbidities, sometimes with attenuated conditioning regimens (76). A recent study of 2,612 patients with DLBCL receiving ASCT included 463 patients more than 60 years of age, 23% of patients being in first CR and 71% in partial remission or second or higher CR (77). When compared with younger patients, nonrelapse mortality was higher in the elderly. In multivariate analysis, age more than 60 years, 2 or more lines of therapy before ASCT, poor performance status, and refractory disease at ASCT were associated with nonrelapse mortality (77). In conclusion, while salvage ASCT is possible in a selected group of elderly patients, a higher treatment-related mortality underlies the necessity of carefully selecting eligible patients.

Conclusion

Advances in DLBCL therapy with immunochemotherapy have improved long-term survival in young and

elderly patients (48, 49). All the prospective studies have clearly shown that elderly patients must be treated similarly to young patients provided that their functional status allows it. However, the thinking that elderly patients with cancer are more fragile exerts a negative impact on medical practice, and, therefore, the elderly patients with DLBCL do not always receive the right treatment (31). Although physicians generally agree that evaluating the status of the elderly using a CGA score prior initiating treatment is essential, this procedure is time consuming and is rarely conducted. Currently, prospective studies are ongoing to evaluate the impact of the different indexes. In a recent study, male sex, poor MNA, advanced disease stage, and poor mobility were found to be the 4 independent factors associated with early death (31). In this study, 44% of the patients received a full-dose regimen, 14% received reduced chemotherapy, and 42% received the best supportive care. A recent retrospective analysis conducted in elderly patients with DLBCL showed that high scores in the Charlson Comorbidity Index were an independent factor associated with low dose-intensity regimen and worse outcome, whereas age exceeding 80 years was not (78). So, while the best method for identifying nonfit patients is not known, it is important to use one of the available indices before treatment, and to include them in clinical trials in which patients more than 65 years of age are enrolled. The assumption that an elderly individual will do poorly must be avoided to prevent the occurrence of a "self-fulfilling prophecy" in the treatment of these patients.

With the regular increase in elderly population and the progress in treating patients with DLBCL, long-term survivors will likely increase. A recent update of the GELA phase III trial comparing R-CHOP with CHOP regimens showed that elderly patients with DLBCL had a greater risk of developing a secondary cancer than the general population (79). The question of whether we should or can treat such new cancers must soon be addressed.

Disclosure of Potential Conflicts of Interest

B. Coiffier is a consultant/advisory board member of Roche and Celgene. No potential conflicts of interest were disclosed by C. Sarkozy.

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Conception and design: C. Sarkozy, B. Coiffier

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