Diffuse large B-cell lymphoma in the elderly: a review of potential difficulties

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Running title: DLBCL in elderly patients

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Abstract

Half of the patients with diffuse large B-cell lymphoma are over 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 contra-indicates chemotherapy treatments. We reviewed all potential difficulties, as the evaluation of comorbidities, the heterogeneous functional status of this population and the consequences of aging process that might be associated with treating these patients and now propose solutions. As standard 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 in a curative intent can reach a complete remission and have a similar outcome than younger patients. Reduced dose intensity must be applied for very elderly or unfit patients for full dose anthracycline. The critical question for a physician is why this patient cannot be treated with the standard regimen, namely R-CHOP.
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 over 65 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 over 65 years (3). Non-Hodgkin’s 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 among 60-64-year and 112 cases among 80-84-year. Around 50% of DLBCL cases occur in patients older than 65, and 40% in patients over 70 (8).

Age has always been a major prognostic factor and, because older age is associated with the presence of concomitant diseases, it is a major determinant of therapeutic decisions (9). However, women of 80 years might live 8 years and male 9 years (10). Furthermore, in the absence of concomitant disease, DLBCL patients over 70 survive as long as younger patients (11). Nevertheless, advanced age was a predictive parameter in many series of NHL patients (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 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 and older patients

Studies on gene expression profiling have defined three DLBCL groups: the germinal centre (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 WHO 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 EBNA2 within the tumor cells (21). Asian studies were the first to describe 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 immunological deterioration resulting from aging. German studies revealed geographical variation with lower rate among the Western populations (23).

**INITIAL EVALUATION**

Elderly patients present with similar clinico-biological characteristics as those observed in younger patients (14, 24). The initial staging includes clinical evaluation, computed tomography (CT) and PET scans (whenever possible), bone marrow biopsy, lumbar puncture in patients with high risk of CNS relapse, and standard biological tests. An ECG and echocardiography must be performed 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 and more than 85% of those older than 80 presenting comorbidity, as opposed to 20% in younger patients (25). DLBCL patients 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 (CIRS) 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, psychological, and therefore risks of morbidity in elderly patients. The traditional assessment of patients’ functional status relies on the Karnofsky or Eastern Cooperative Oncology Group (ECOG) performance status, while assessments performed by a geriatrician include the assessment of ability to live in the community and instrumental activities of daily living (ADLs and IADLs scale, supplementary Table S1) (28, 29). CGA predicts survival, tolerance to chemotherapy, and mortality, independently from the PS (29, 30). In patients older than 70, low mini nutritional assessment (MNA) and mini mental state (MMS) scores independently increase the probability of not completing chemotherapy (28). Nutritional problems in elderly patients
DLBCL 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 decrease 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’s lymphoma is not appropriate for NHL as prognosis is better described using the International Prognostic index (IPI) (9). A derivative and simplified score, the aaIPI has been developed. Although other scores, such as R-IPI (revised IPI) or E-IPI (elderly IPI) have been recently developed, the aaIPI 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) (33, 34).

TREATMENT
Older age correlates with lower CR rate, shorter PFS, and shorter survival in DLBCL patients (24, 35). If the current definition of elderly is 65 years, former studies used 60 years. In elderly patients, treatment choice is based on aaIPI score, CGA, and comorbidities (4, 36). Many older patients have a good PS, allowing them to be treated with standard-dose regimens. By contrast, frail patients with a loss of independence in daily living activities may experience significant side effects and require adapted regimens. Unfortunately, and without a scientific basis, age often appears to be the only reason for decreasing chemotherapy doses (15, 37, 38). A large survey with data extracted from 4,522 aggressive NHL patients (treated with R-CHOP, CHOP, or CNOP) showed that dose was reduced compared to the minimum 6 cycle 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 G-CSF use (38). In a Dutch retrospective study of elderly DLBCL, 76% of the patients had a reduced number of cycles compared to planned treatment (39). In 77% of them the reason was a poor PS; however 23% of these patients were not treated optimally because of their age despite a good PS. Several studies reported that
optimally treated elderly patients display similar outcomes to younger patients (4, 24, 37, 39-42). Thus, given patient consent, 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 complete remission (CR) without inducing toxicities.

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

Patients without adverse prognostic factors (aaIPI score of 0) present localized disease. The utility of radiotherapy in an elderly population was questioned by the GELA in a randomized study comparing 4 cycles of CHOP regimen to 4 cycles of CHOP followed by involved-field-radiotherapy (43). Patients included were older than 60 years 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 six cycles of R-CHOP in elderly patients with localized DLCBL 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 OS 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 outcome in young patients but are too toxic for the elderly (45). A study conducted by the German lymphoma study group (DSHLNH) in patients aged 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. Prior to 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 to CHOP alone in elderly patients with stage II to IV DLBCL. The R-CHOP regimen improved CR rate (71% versus 63%, p=0.005) and duration of progression-free survival (PFS), disease-free survival (DFS), and OS, with benefits still present at 10-year
DLBCL in elderly patients follow-up (48, 49). This improvement was achieved without any increase in toxic effects. Other phase III studies confirmed these results (Table 2) (41, 50). In the RICOVER study, six cycles of R-CHOP were compared to eight cycles every 2 weeks, with the outcome being similar in both regimens (41). Based on these results and others in Table 2, R-CHOP every 3 weeks remains the standard for elderly patients (51) (52).

One approach would be to treat these patients with regimens adapted to the CGA score. An 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 OS was 60%. Toxicity was acceptable, with grade 4 neutropenia observed in 14% of cases and grade 4 cardiac and neurological 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 OS at 31%. (54) In both studies, the number of unfit and frail patients was low, and these patients’ results 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 (over 80 years)

While the previously described studies have included patients older than 65, 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 over 60 years revealed no difference in CR and 5-year OS rates between patients over 80 years and those aged 60-69 or 70-79 (55). A French retrospective study reported that presentation and prognostic factors were the same in patients over 80 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 standard in both younger patients and those aged 60 to 80, 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 with DLBCL (Table 3) (56). Two-year OS 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
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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 >80 were compared during the pre-rituximab and rituximab eras showing 3-year OS at 41% in the rituximab era vs. 17% in the pre-rituximab 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. Due to potential preexisting heart disease, the elderly are more prone to cardiac side effects than younger patients (59). Notably, 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 OS of 49% was observed, which is shorter than the OS 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 seven CR and six 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 is 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 two 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 two 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).

Non-pegylated liposomal doxorubicin may offer greater safety with preserved efficacy. A recent Italian phase II study evaluated the activity and safety of non-pegylated liposomal doxorubicin when substituted for doxorubicin in the R-CHOP regimen (R-COMP) (63): CR rate was 57% and 3-year OS, FFS, and PFS rates were 72%, 39%, and 69%, respectively. However cardiac toxicity persisted with 21% of cardiac events, grade 3-4 in 4% of cases. A larger study with the same regimen given every two weeks showed a 4-year time to treatment failure (TTF) of only 49% (64). Another study used a reduced dose of non-pegylated liposomal doxorubicin (30mg/m2) in 35 frail elderly patients and obtained favorable results.
DLBCL in elderly patients considering this frail population with little toxicity (69% CR in intention-to-treat analysis and 2-year OS of 70%) (65).

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

The International Society of Geriatric Oncology (SIOG) has recently published recommendations for the use of anthracycline in the elderly and proposed different methods to reduce cardiac toxicity levels in daily practice (Table 4) (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 DLBCL patients 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 DLBCL patients 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 aaIPI 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 autologous stem cell transplants (ASCT). Obviously, if some young 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 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
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elderly patients at the time of relapse, palliative therapy is usually more appropriate. Consideration can be given to single agent in phase II trials.

**Standard chemotherapy**

Of 399 patients aged 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 DHAP, 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 (74): 2-year OS 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, focused 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 young elderly patients presenting a good performance status and no comorbidities, sometimes with attenuated conditioning regimens (76). A recent study of 2612 DLBCL patients receiving ASCT included 463 over 60 years, 23% of patients being in first CR and 71% in partial remission (PR) or second or higher CR (77). When compared to younger patients, non-relapse mortality was higher in the elderly. In multivariate analysis, age >60 years, two or more lines of therapy prior to ASCT, poor performance status, and refractory disease at ASCT were associated with non-relapse 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 cancer patients 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
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procedure is time-consuming and is rarely performed. 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 a reduced chemotherapy, and 42% received the best supportive care. A recent retrospective analysis performed in elderly DLBCL patients 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 old was not (78). So, while the best method for identifying non-fit 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 over 65 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 progresses in treating DLBCL patients, long-term survivors will likely increase. A recent update of the GELA phase III trial comparing R-CHOP and CHOP regimens showed that elderly DLBCL patients 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.
References

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Table 1: The prognostic indexes in DLBCL patients. IPI is based on 5 characteristics, namely age \((\leq 60 \text{ or } > 60 \text{ years})\), PS \((0-1 \text{ or } >1)\), LDH (normal or elevated), Ann Arbor stage (localized or disseminated), and extra-nodal site number \((0-1 \text{ or } >1)\). It identifies 4 risk categories \((0-1 \text{ factor or low risk}, 2 \text{ factors or intermediate-low risk}, 3 \text{ factors or high-intermediate risk}; \text{ and } 4-5 \text{ factors or high risk})\). A derivative and simplified index was developed, the aaIPI (age adjusted IPI), relevant in the elderly and younger population. Since the use of rituximab in combination with chemotherapy in DLBCL, the R-IPI (Revised IPI) was developed, based on the same clinical factors.\(^{33}\) Advani proposed an Elderly 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, aaIPI or R-IPI. However, the aaIPI is the most widely used in the younger and elderly population to predict survival and choose therapeutics option.

<table>
<thead>
<tr>
<th></th>
<th>IPI</th>
<th>aaIPI</th>
<th>R-IPI</th>
<th>E-IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>+ (60 y)</td>
<td>-</td>
<td>+ (60 y)</td>
<td>+ (70 y)</td>
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<tr>
<td>LDH</td>
<td>+</td>
<td>+</td>
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<td>+</td>
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<td>Ann Arbor</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>ECOG-PS</td>
<td>+</td>
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<tr>
<td>Nodal sites</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
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<td>N of risk group</td>
<td>4</td>
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Table 2: Studies in the rituximab era for fit elderly patients

<table>
<thead>
<tr>
<th>References</th>
<th>N (Age)</th>
<th>Regimens</th>
<th>Better Regimen</th>
<th>EFS/PFS*</th>
<th>CR/CRu*</th>
<th>OS*</th>
</tr>
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<tbody>
<tr>
<td>Coiffier 48,49 Phase III</td>
<td>399 (60-80)</td>
<td>RCHOP vs CHOP</td>
<td>RCHOP</td>
<td>EFS (R-CHOP) 2-y 57% 10-y 36.5%</td>
<td>73% vs. 63% (p 0.005)</td>
<td>Median &gt; 8 y 2-y 70% 10-y 43.5%</td>
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<td>Habermann 50 Phase III</td>
<td>632 (&gt;60)</td>
<td>RCHOP vs CHOP +/- maintenance</td>
<td>-RCHOP</td>
<td>EFS (R-CHOP) 3y 53%</td>
<td>77% vs. 76% NS</td>
<td>2y-95%</td>
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<td>Pfreundschuh 41 Phase III</td>
<td>1222 (61-80)</td>
<td>6-8RCHOP vs 6-8CHOP</td>
<td>6RCHOP</td>
<td>(6RCHOP) EFS 3y 66.5 PFS 3y 73%</td>
<td>6RCHOP 78%</td>
<td>3-y 78%</td>
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<tr>
<td>Delarue 52 Phase III</td>
<td>201 (60-80)</td>
<td>RCHOP14 vs RCHOP21</td>
<td>Non</td>
<td>EFS 2-y 48-61% NS</td>
<td>-</td>
<td>2-y 67-70% NS</td>
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<tr>
<td>Moccia 62 Retrospective</td>
<td>81 (median 73y 39-93)</td>
<td>RCEOP vs RCHOP</td>
<td>RCHOP</td>
<td>TTP 5-y 57-62% NS</td>
<td>-</td>
<td>5-y 64%</td>
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<tr>
<td>Cunningham 51 Phase III</td>
<td>1080 (≥60)</td>
<td>RCHOP14 vs RCHOP21 + GCSF</td>
<td>Non</td>
<td>HR 1</td>
<td>-</td>
<td>HR 0.96</td>
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<tr>
<td>Luminari 67 Phase II</td>
<td>75 (61-83)</td>
<td>R-COMP21</td>
<td>-</td>
<td>PFS 3y 69%</td>
<td>57%</td>
<td>3y-72%</td>
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<tr>
<td>Merli 57 Phase III</td>
<td>224 72 (64-86)</td>
<td>RCHOP vs R-miniCEOP</td>
<td>Non</td>
<td>48% 46%</td>
<td>73% 68%</td>
<td>5y: 62% 5y: 63%</td>
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<tr>
<td>Corazzelli 58 Phase II</td>
<td>41 (73y)</td>
<td>R-COMP14</td>
<td>-</td>
<td>DFS 4y 72%</td>
<td>68%</td>
<td>4y 67%</td>
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</table>
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*For the phase III trial, the CR, OS and PFS results are those of the better regimen

EFS: event free survival; PFS: progression free survival; CR: complete remission; OS: overall survival; TTP: time to progression; HR: Hazard Ratio; NS: Non significant

R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CEOP: rituximab, cyclophosphamide, etoposide, vincristine, and prednisone; R-COMP: rituximab, cyclophosphamide, non-pegylated liposome-encapsulated doxorubicin, vincristine and prednisone; R-miniCEOP: cyclophosphamide, epirubicin, vinblastine, prednisone, and rituximab; G-CSF: Granocyte colony stimulating factor
Table 3: Study with reduced dose of chemotherapy or adapted regimen for elderly patients with DLBCL.

<table>
<thead>
<tr>
<th>References</th>
<th>N</th>
<th>Age (median)</th>
<th>Regimens</th>
<th>RDI</th>
<th>CR (%)</th>
<th>OS (%)</th>
<th>EFS/ PFS</th>
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<td>Peyrade</td>
<td>149</td>
<td>83 (80-95)</td>
<td>RminiCHOP</td>
<td>Doxorubicin 50%</td>
<td>63%</td>
<td>2y: 59%</td>
<td>2y: 47%</td>
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<td>Cyclophosphamide 53%</td>
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<td>Hasselblom</td>
<td>70</td>
<td>&gt;80y</td>
<td>Pre-R: 40pts</td>
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<td>3y: 17%</td>
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<td>Post-R: 30pts</td>
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<td>3y: 41%</td>
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<td>Spina</td>
<td>100</td>
<td>75 (70-89)</td>
<td>RCHOP/CHOP</td>
<td>Fit 100%</td>
<td>70-80: 83%</td>
<td>5y:</td>
<td>5y:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Frail 75%</td>
<td>&gt;80: 80%</td>
<td>70-80: 54%</td>
<td>70-80: 67%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unfit 50%</td>
<td>&gt;80: 61%</td>
<td>&gt;80: 46%</td>
<td></td>
</tr>
<tr>
<td>Olivieri</td>
<td>91</td>
<td>74 (65-92)</td>
<td>RCHOP or</td>
<td>Fit: RCHOP 100%</td>
<td>81%</td>
<td>5y 46%</td>
<td>5y 31%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RCDO or</td>
<td>Frail RCDOP: NPLD 50%</td>
<td>64%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>miniCHOP</td>
<td>Unfit: cyclophosphamide 50%, doxorubicin 50%</td>
<td>50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gimeno</td>
<td>35</td>
<td>76 (61-88)</td>
<td>RCMyOP</td>
<td>NPLD: 50%</td>
<td>69%</td>
<td>2y: 70%</td>
<td>2y: 58% PFS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Vincristine: v%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cycle delayed 8%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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: non-pegylated liposomal doxorubicin, cyclophosphamide, vincristine, and prednisone, rituximab
Table 4: SIOG proposals for the management of anthracycline cardiotoxicity risk (adapted from Aapro et al. (68), Permission granted from Oxford University Press). The recommendations of SIOG are on the left side of the table with proposed daily practice for the physician on the right side.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>SIOG proposal for the physician</th>
</tr>
</thead>
</table>
| Rigorous screening to exclude patients at unacceptably high cardiac risk (Level 1a) | Comprehensive patient history:  
- 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 continuous infusion (Level 1a)  
- Epirubicin but less efficacy (Level 1a)  
- Dexrazoxane (elderly, Level 5)  
- Liposomal anthracycline formulation (elderly, Level 5) |
| Use of less cardiotoxic therapy (Level 1a) | - 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) |
| Regular monitoring of cardiac function, signs and symptoms (Level 1a) | - 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) |

CHF: congestive heart failure; MUGA: multiple uptake gated acquisition; ACE: angiotensin-converting enzyme
Clinical Cancer Research

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Clémentine Sarkozy and Bertrand Coiffier

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