Current treatment options for aggressive non-Hodgkin lymphoma in elderly and frail patients: practical considerations for the hematologist

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***Abstract*:** Treatment decisions for aggressive non-Hodgkin lymphoma in elderly and frail patients still remain challenging. The heterogeneity of elderly patients consists of various physical and psychological states, coexisting comorbidities as well as frailty and socioeconomic status. Comprehensive geriatric assessment in elderly patients is efficient and necessary for risk stratification to identify fit patients without cardiac comorbidities who can tolerate curative treatment with rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) and those who are not suitable for a standard regimen. If anthracycline-containing therapy is not feasible, alternative treatment options have to be carefully evaluated and individual risk factors have to be considered.

Keywords: cardiotoxicity, comorbidity, elderly, frail, non-Hodgkin lymphoma

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most frequently diagnosed type of malignant lymphoma and accounts for 30–40% of adult non-Hodgkin lymphoma (NHL) worldwide.[1] DLBCL is an aggressive lymphoma but can be cured with standard R-CHOP immunochemotherapy in 60–70%.[2–4] For more than 25 years a chemotherapy regimen with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) has been the standard first-line treatment of patients. In 2002 the addition of rituximab, a chimeric monoclonal antibody against the CD20 B-cell antigen, changed the outcome of patients with DLBCL significantly. The randomized open-label trial by the Groupe d'Etudes des Lymphomes de l'Adulte (GELA) showed an increase in the complete response (CR) rate and overall survival (OS) without a clinically significant increase in toxicity even for elderly (60–80 years) patients.[2] Since then the combination therapy of rituximab and the CHOP rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) regimen is the absolute standard of care in the first-line treatment of DLBCL.

DLBCL is primarily a disease of elderly people and typically affects patients with a median age in the seventh decade.[5] At the same time age has proved to be one of the most important risk factors for OS of patients with DLBCL.[6] However, there are more factors contributing to the worse outcome in elderly and frail patients: impaired bone marrow function, altered drug metabolism, and the presence of comorbidity which can increase the frequency of treatment-related complications. Not least, physicians often tend to undertreat elderly patients in concern of cardiac side effects of anthracyclines or otherwise presumed poor tolerance for standard therapy with R-CHOP.[7–9] In a study with 9438 patients with DLBCL and aged 65 years or older only 42% received doxorubicin-containing therapy.[10]

In the late 1960s anthracyclines were introduced in the therapy of non-Hodgkin lymphoma, and over time clinical trials showed that doxorubicin is the most effective single agent for the treatment of NHL. Unfortunately, especially elderly patients and patients with cardiac comorbidities can suffer from severe side effects. The challenge

is therefore to decide between aggressive anthracycline-containing and potentially curative therapy with the risk of treatment-related morbidity and mortality and, in contrast, less aggressive therapy with a reduced chance for cure. Therefore, treatment options must be carefully evaluated in advance, because standard treatment with R-CHOP is not generally suitable for elderly and frail patients. Even though aged patients are the majority of people affected by DLBCL, there are only very few prospective studies available considering this patient population and therefore no clear guidelines for the treatment of these patients exist.

Definition of elderly patients

As society is getting older, the incidence of DLBCL in older individuals is also rising. Most clinical cancer studies set the cut-off between young and elderly patients at 60 or 65 years. The criterion 'older than 60 years' is used as a risk factor for the International Prognostic Index (IPI), which was developed to predict long-term survival for patients with aggressive lymphoma. But so-called 'elderly' patients are an extremely heterogeneous group and there is no clear definition of 'elderly' and 'frail' patients available. In fact, the biological age can be very different from the chronological age due to comorbidities, frailty and socioeconomic conditions. Therefore, comparing a 60-year-old patient with an 80-year-old patient especially in terms of frailty might reveal huge differences. With only very few prospective studies available for elderly patients, even less can be found for 'very elderly' patients aged 80 years or older. Unfortunately, although cancer is a disease of the elderly, this patient population is still very much under-represented in major prospective clinical trials.[11] In clinical practice, an age limit of 70 years seems to be a useful, reasonable and pragmatic criterion to define elderly patients.

In contrast to age as a single characteristic, frailty is a multifactorial syndrome that represents a reduction in physiological resources and the ability to resist environmental stressors.[12] In cancer patients the prevalence of frailty is reported to be approximately 43%,[9] independent of age. But, as there is no clear consensus definition for elderly and frail patients, many different aspects such as physical impairment as well as psychological, cognitive and social factors have to be considered.

Pretreatment evaluation

For optimizing therapeutic decisions in the heterogeneous group of elderly people, it is crucial to evaluate carefully patients' global health status in advance. Age alone should definitely not be the only criterion for therapeutic decisions. Besides a detailed medical history of comorbidities and drug use, also renal, cardiac and pulmonary function as well as nutritional status, frailty and individual deficits in cognition and mobility must be carefully assessed. Apparatus diagnostics with echocardiography and lung function testing are indispensable and good instruments for the evaluation of cardiac and pulmonary function.

Especially good cardiac function is crucial to identify patients who can tolerate anthracycline-containing regimens with curative intention, as several factors are known to be associated with an increased risk of anthracycline-induced cardiotoxicity. Besides cumulative anthracycline dose and age >65 years also pre-existing cardiac disease or hypertension, female gender, mediastinal radiation or co-treatment with cyclophosphamide, trastuzumab or paclitaxel are individual risk factors for the development of anthracycline-related cardiotoxicity.[13] Hershman *et al.*[10] found an increase in the risk of congestive heart failure (CHF) of 29% in patients older than 65 years and treatment of DLBCL with doxorubicin-based chemotherapy. The decision of using an anthracycline-containing regimen must be based on the postulated benefit of the therapy *versus* the potential risk of short and long-term cardiac side effects, in particular CHF. Therefore, especially for elderly and cardiac frail patients frequent monitoring of left ventricular function pre, during and post-treatment is essential. In addition, cardiac biomarkers such as troponin I can help in monitoring patients.[14] Renal function can also be checked and monitored by laboratory test. In contrast, comorbidities and frailty are much more difficult to assess longitudinally.

The cumulative illness rating score (CIRS) and the Charlson comorbidity score (CCI) are instruments for measuring comorbidity before treatment initiation, and might help in the allocation of patients to appropriate therapeutic pathways.[15,16] There are also multiple instruments to identify frailty in elderly patients. Besides the phenotype model and the cumulative deficit model now especially the comprehensive geriatric assessment (CGA) seems to be the best evidence-based tool and is widely accepted in routine care.[9] It is a multidimensional

and multidisciplinary assessment process containing different domains of health: physical medical conditions, mental health conditions, functioning, social circumstances and environment.[17] However, as this detailed evaluation is very time consuming, more straightforward screening instruments have been developed. In the ONCODAGE prospective study the G8 questionnaire was validated as a sensitive tool for the screening of elderly patients with cancer in terms of frailty and the need for further geriatric assessment.[18] This tool can be performed by a trained nurse in about 15 minutes and should therefore be implemented in the evaluation of elderly and frail patients. The efficacy of CGA in detecting elderly patients with newly diagnosed DLBCL, who can be treated with curative therapy, was proved in 2009 by Tucci *et al.*[19] The authors were able to show that CGA is a more effective and objective tool than clinical decision and CGA-selected fit patients can receive an outcome similar to that of younger patients.

After pretreatment evaluation, the treating physician should first be able to categorize patients with newly diagnosed DLBCL into fit, unfit or frail. Second, he has to answer the question of whether his patient can tolerate a curative anthracycline-containing regimen. However, in addition to all options of geriatric assessment, expectations and preferences of patients must also be considered for a definite treatment decision.

Treatment options

Since the introduction of rituximab in first-line therapy there have been only modest changes in therapeutic options for DLBCL. Doxorubicin is an anthracycline and is considered to be one of the most effective components in the R-CHOP regimen.[20] Young patients without cardiac comorbidity can tolerate full doses of doxorubicin usually without major problems. In contrast, elderly and frail patients in particular can suffer from severe side effects of this agent. In addition to myelosuppression and gastrointestinal toxicity, cumulative dose-dependent cardiac toxicity is the most important side effect and can lead to severe cardiomyopathy and congestive heart failure. The risk of CHF increases with the patients' age, number of cycles, prior heart disease, comorbidities, diabetes and hypertension. That is why treatment options in elderly and frail patients have to be carefully evaluated in advance.

Interestingly, the ESMO and NCCN guidelines stratify treatment strategies for DLBCL patients not by complex scoring indices but only according to age, the international prognostic index (IPI) and feasibility of dose-intensified approaches.[21] The cut-off to young patients in the guidelines is set at 60 years of age and, in addition, elderly patients are categorized into three subgroups. The first group contains all fit patients aged 60–80 years who can tolerate standard R-CHOP immunochemotherapy. Especially judging in this regard, the feasibility of a patient for treatment with R-CHOP might be heavily influenced by the experience of the responsible physician. In the second group, there are patients aged >80 years without cardiac dysfunction included who can be treated with attenuated regimens such as R-miniCHOP. The third group contains unfit or frail patients and patients >60 years with cardiac dysfunction. This group is supposed to be treated with protocols substituting doxorubicin with gemcitabine, etoposide, liposomal doxorubicin or with other already palliative regimens.

In the guidelines of the National comprehensive cancer network (NCCN) the recommendations for treatment are quite similar to those of the European Society for Medical Oncology (ESMO). They also support first-line therapy with R-CHOP as standard treatment. For patients with poor left ventricular function they recommend substitution of doxorubicin with gemcitabine, etoposide or liposomal doxorubicin and in very frail patients and elderly patients >80 years of age R-miniCHOP is recommended additionally.

Curative regimens: R-CHOP and reduced-intensity regimen (R-miniCHOP)

Since 2002 R-CHOP is the undisputed standard in treatment for fit patients without comorbidities up to 80 years.[2] In 2005 a randomized study compared the efficacy of the CHOP regimen with R-CHOP in previously untreated DLBCL patients aged 60–80 years and showed in a 5-year follow-up improved outcomes with better event-free survival (EFS), progression-free survival (PFS), and OS.[3] However, the anthracycline contained in R-CHOP can cause significant toxicity in frail older patients or those with pre-existing cardiac dysfunction. Replacement of doxorubicin in the CHOP regimen with mitoxantrone, an anthracenedione derivative, in the so-called CNOP protocol was suggested, with better tolerance and a lower rate of cardiomyopathy.[22] However, a randomized trial

with 455 elderly patients aged 60–86 years with newly diagnosed DLBCL showed that CNOP is inferior with regard to OS, time to treatment failure (TTF) and complete remission (CR) rate compared to CHOP.[23] Another two randomized studies comparing CNOP with CHOP also showed inferior results in efficacy for mitoxantrone but a similar rate of cardiotoxicity.[24,25] Thus, there is no recommendation for the CNOP regimen and six to eight cycles of R-CHOP is standard treatment for fit elderly patients up to 80 years.

In the case of limited-stage DLBCL there is some evidence for the combination of rituximab with only three cycles of CHOP followed by involved-field radiation.[26] Especially in elderly patients and in concern for anthracycline-mediated side effects this approach can be considered.

For fit elderly patients older than 80 years and advanced stage DLBCL, reduced-intensity regimens are a useful option of adapting the R-CHOP regimen and consequently to minimize the toxicity of R-CHOP. R-miniCHOP was in 2011 prospectively analyzed in patients older than 80 years of age without severe comorbidities with newly diagnosed DLBCL. Patients received six cycles of R-miniCHOP (50% dose reduction of CHOP) at 3-week intervals and showed a 2-year PFS of 47% and an OS rate of 59%.[8] New data from the combination therapy with obinutuzumab-miniCHOP (O-miniCHOP) could show activity and good tolerability for older and unfit adult patients, but the study hypothesis of improved results to historical data obtained with R-mini-CHOP could not be proved.[27] Therefore, especially fit elderly patients aged more than 80 years and without cardiac comorbidity are eligible for this regimen and can also be cured with this treatment option.

Following R-CHOP therapy there is only a risk of 2–5% for the development of a central nervous system (CNS) relapse.[28] Therefore, no general recommendation for CNS prophylaxis exists. However, various risk factors for CNS recurrence are known, such as double-hit lymphoma and CNS-IPI score,[29,30] which can be addressed with high-dose methotrexate (HD-MTX). Nevertheless, despite a high CNS relapse risk most of the elderly patients are certainly not good candidates for CNS prophylaxis with HD-MTX. As no clear benefit has been reported for intrathecal MTX[31] in elderly patients either, a patient individual treatment decision needs to be taken in this matter.

Treatment options for cardiac frail patients (replacement of cardiotoxic doxorubicin)

In elderly patients cardiac contraindications for anthracycline-based chemotherapy are much more frequent than in younger patients and there is a need for the replacement of doxorubicin in therapeutic regimes. Careful pretreatment evaluation is necessary to decide whether elderly patients can tolerate anthracycline-based chemotherapy or not. The ESMO and NCCN guidelines suggest the substitution of doxorubicin in R-CHOP with etoposide, gemcitabine or liposomal doxorubicin in cardiac frail patients.

A retrospective analysis by Moccia *et al.*[32] in 2009 reported that the substitution of doxorubicin with etoposide in the so called R-CEOP regimen can be a curative treatment option in patients with DLBCL who were unable to receive anthracycline-containing chemotherapy. Using a similar population treated with R-CHOP as a historical control they showed a lower 5-year OS rate in the R-CEOP group than in the R-CHOP group (49% *versus* 64%) but a similar 5-year time to progression (TTP) in both groups (57% *versus* 62%). These results suggest that R-CEOP might be a curative alternative in the treatment of cardiac frail patients; however, until now these data are only published in abstract form, so further careful evaluation and detailed analysis of these important data is not possible. Another small retrospective analysis suggested that the effectiveness of etoposide depends on the histopathological subtype of DLBCL. Etoposide seems to be more effective in DLBCL of germinal-center B-cell like (GCB) type than in non-GCB.[33] Overall, the data are very limited for the use of R-CEOP in cardiac frail patients.

Non-pegylated liposomal doxorubicin (NPL-doxorubicin) was designed in the hope of reduced cardiotoxic side effects compared to conventional doxorubicin. Liposomes cannot escape blood vessels with a tight capillary junction such as in the heart muscle and the gastrointestinal tract, but can escape in sites with loose capillary junctions such as bone marrow, tumor and areas of inflammation.[34] Indeed, studies with animal models and in patients with metastatic breast cancer confirmed a less cardiotoxic character with preserved antitumor efficacy of NPL-doxorubicin compared to conventional doxorubicin due to a lower peak level in the heart and also in the gastrointestinal mucosa.[35,36] Substitution of doxorubicin with NPL-doxorubicin in the R-CHOP regimen, so-called

Table 1. Combination therapies for cardiac frail patients.

Reference	Therapy	*n*	Age	CHF/red LVEF	CR (%)	PFS	OS	LVEF
Moccia *et al.*[32]	R-CEOP	81	73 (34–93)	–	–	(5 years TTP 57%)	5 years 49%	–
Luminari *et al.*[37]	R-COMP	50	76 (53–90)	7 (12%) Median LVEF: 60%	56	3 years 38%	3 years 50%	Dec: 6% Median unchanged
Rohlfing *et al.*[38]	R-COMP	25	73 (24–85)	14 (56%) Median LVEF: 51%	44	3 years 66%	3 years 73%	Dec: 28% Inc: 12% Median unchanged
Oki *et al.*[39]	R-COMP	80	69 (61–92)	None Median LVEF: 63%	78	3 years 60%	3 years 74%	Dec: 14% Median unchanged
Corazzelli *et al.*[40]	R-COMP	41	73 (62–82)	Median LVEF: 57%	68	4 years 77%	4 years 67%	Dec: 32% Median unchanged
Gimeno *et al.*[41]	R-COMP	35	76 (61–88)	4 (11%) Median LVEF: 63%	69	2 years 58%	2 years 70%	Dec: 26% Median unchanged
Rigacci *et al.*[51]	R-COMP	21	70 (54–76)	Median LVEF: 60%	76	–	–	Dec: 0% Median unchanged
Fields *et al.*[43]	R-GCVP	62	76.5 (52–90)	LVEF ⩽50%: 27 (43.5%) Borderline-LVEF >50% + comorbid cardiac risk factor: 35 (56.5%)	38.7	2 years 49.8%	2 years 55.8%	–
Strüssmann *et al.*[45]	R-CPOP	10	72.4 (61–84)	Median LVEF: 37%	62	2 years 64%	–	–

CR, complete remission; CHF, congestive heart failure; LVEF, left ventricular ejection fraction; OS, overall survival; PFS, progression free survival; R-CEOP, rituximab, cyclophosphamide, etoposide, vincristine, prednisone; R-COMP, rituximab, cyclophosphamide, vincristine, non-pegylated liposomal doxorubicin, prednisone; R-CPOP,rituximab, cyclophosphamide, pixantrone, vincristine, prednisone; R-GCVP, rituximab, gemcitabine, cyclophosphamide, vincristine, prednisolone; TTP, time to progression.

R-COMP regimen, was evaluated in several studies for patients with newly diagnosed DLBCL.[37–42] Comparison of these studies (Table 1) suggests that quite a few patients experience a complete response (44–78%), but the investigated study populations did not reflect cardiac frail patients. The median left ventricular ejection fraction (LVEF) in these studies was stable, but there also occurred relevant cardiac events during treatment with R-COMP and a decline in left ventricular function was noted.

Another option for the substitution of doxorubicin in R-CHOP for cardiac frail patients is gemcitabine in the so-called R-GCVP regimen. In a phase III multicenter trial in 2014 Fields *et al.*[43] were able to show promising results. This protocol seems to be an active and reasonably well-tolerated treatment option for patients with DLBCL and coexisting cardiac disease. The study population with an indeed poor cardiac status could achieve a 2-year PFS of 49.8% and a 2-year OS of 55.8%.

Another option for patients with cardiac comorbidities is the substitution of doxorubicin in R-CHOP with pixantrone, so-called R-CPOP. Pixantrone is an aza-anthracenedione, which was designed in order to reduce anthracycline-related cardiotoxic effects without compromising antitumor activity. Herbrecht *et al.*[44] assessed the activity and safety of R-CPOP compared to R-CHOP in first-line therapy of patients with DLBCL. Although they investigated only a small group of patients, R-CPOP turned out to be an effective regimen with moderately lower response rates than R-CHOP but similar PFS and event-free survival and especially less severe cardiac events. In our institution we could show the feasibility of R-CPOP in first-line treatment for patients with DLBCL with congestive

Table 2. Combination therapies for elderly and frail patients.

Reference	Therapy	*n*	Age	ECOG ⩾2 (%)	CR (%)	Median PFS	Median OS
Peyrade *et al.*[8]	R-miniCHOP	149	83 (80–95)	34	63	21 months 2 years 47%	29 months 2 years 59%
Merli *et al.*[27]	O-miniCHOP	34	82 (68–89)	6	42	2 years 49%	2 years 68%
Laribi *et al.*[46]	R-CVP	43	83 (80–93)	88.4	37.2	11.2 months	12.6 months 2 years 31.9%
Storti *et al.*[47]	R-bendamustine	45	81 (71–89)	36	53	10 months 2 years 38%	30 months 2 years 51%
Park *et al.*[48]	R-bendamustine	23	80 (65–89)	52	52	5.4 months	10.2 months
Weidmann *et al.*[49]	R-bendamustine	14	85 (80–95)	28.5	54	7.7 months	7.7 months
Monfardini *et al.*[50]	Vinorelbine + Prednisone	30	83 (70–96)	60	10	CR: 29 months PR: 1 months	10 months

CR, complete remission; ECOG, Eastern cooperative oncology group performance status; O-miniCHOP, obinutuzumab, rituximab, dose reduced CHOP; OS, overall survival; PFS, progression free survival; R-bendamustine, rituximab, bendamustine; R-miniCHOP, rituximab, dose reduced CHOP; R-CVP, rituximab, cyclophosphamide, vincristine, prednisone.

heart failure or at risk of anthracycline-induced cardiotoxicity. In a group of 10 patients with a median age of 72.4 years and a median left ventricular ejection fraction (LVEF) of 37% eight patients responded to R-CPOP, with confirmed complete remission in five patients (62%).[45] These results are quite promising and R-CPOP is a serious treatment option for cardiac frail patients.

Palliative regimens

Anthracycline-containing R-CHOP is problematic in elderly and frail patients. R-CHOP without doxorubicin, the so-called R-CVP regimen, is an alternative option for frail patients. Laribi *et al.*[46] showed effectiveness and safety in patients aged 80 years or over and unable to receive treatment with anthracyclines. The median OS was 12.6 months. However, compared to the curative R-miniCHOP regimen with a median OS of 29 months R-CVP must be named as a palliative therapy option.

Bendamustine has similarities to alkylating agents as well as to purine analogs and first alone or in combination with rituximab (RB) was frequently used for the treatment of chronic lymphocytic leukemia (CLL) and indolent NHL. Over time, bendamustine was also studied in aggressive lymphoma, but there are conflicting study results (Table 2). Storti *et al.*[47] prospectively analyzed RB in a phase II study as a front-line therapy in frail elderly patients aged 70 years or over with newly diagnosed DLBCL. The study showed quite promising 2-year OS of 51% and 2-year PFS of 38%, with manageable side effects of bendamustine. Two further phase II studies, however, showed significantly lower survival rates for RB as a front-line therapy.[48,49] However, the side effects of this therapy are heavily dependent on the selected dose of bendamustine. The frequently used dose of 120 mg/m^2 in the study protocols for aggressive lymphomas is significantly less well tolerated in elderly and frail patients than 90 mg/m^2. In the end the combination of rituximab and bendamustine is a possible but non-curative treatment option in frail patients.

The combination therapy of vinorelbine and prednisone showed low therapeutic activity but was a relatively well tolerated combination and can only be used for temporary palliation.[50]

Salvage strategies

However, about one-third of patients develop refractory or relapsed disease[52] and then the only curative option left is intense salvage chemotherapy followed by high-dose chemotherapy with autologous stem-cell transplantation (ASCT). In view of the significant risks of morbidity and mortality, an even more careful selection of patients is mandatory than in patients with newly diagnosed DLBCL. In the end, only a few patients are eligible for this

potential curative therapeutic option. Typically used salvage regimens are R-ICE (rituximab, ifosfamide, carboplatin, and etoposide) or R-DHAP/DHAOx (rituximab, dexamethasone, cytarabine, and cisplatin/oxaliplatin).[51,53,54] Moreover, gemcitabine-containing regimens such as R-GDP (rituximab, gemcitabine, dexamethasone, and cisplatin) or R-GemOx (rituximab, gemcitabine, and oxaliplatin) are also available and showed promising results with acceptable toxicity.[55–57] Although there is a curative intention of treatment, prognosis of refractory and relapsed DLBCL is poor. Patients with relapsed DLBCL and a median age of 55 years who received rituximab-containing salvage regimen followed by ASCT reached only a 3-year OS of less than 50%.[58] Therefore, there is a sustained need for effective salvage therapies without severe side effects for elderly and especially frail patients.

Recently, chimeric antigen receptor (CAR) T-cell therapy revolutionized salvage strategies for relapsed and refractory DLBCL and promised to improve complete response rates compared to conventional therapies. Axicabtagene ciloleucel (Yescarta) and tisagenlecleucel (Kymriah) are chimeric antigen receptor modified T cells targeting CD19, approved in refractory and relapsed DLBCL after at least two lines of systemic therapy.[59,60] Indeed, this new therapeutic option can go along with severe side effects, such as potentially life-threatening cytokine-release syndrome and remarkable neurotoxicity. Therefore, elderly patients have to be carefully selected as in consideration of ASCT and frail patients seem not to be eligible for this therapeutic option.

If patients are not eligible for salvage chemotherapy and ASCT or CAR T-cell therapy, there are according to the ESMO and NCCN guidelines other non-curative options left. For those patients, of course, the outlook is very poor, the goal of the therapy becomes palliative and there is a sustained need for good tolerance to therapy. Moreover, treatment options in this setting are limited because patients often already received anthracycline-containing regimens in the first line. Rituximab together with bendamustine, which is also used in palliative intention in first-line therapy, also has a place in salvage regimens for elderly and frail patients who are not eligible for autologous stem-cell transplantation. Ohmachi *et al.*[61] was able to show an overall response rate of 62% with a CR rate of 37.3%. According to Pettengell *et al.*[62] another effective option is using pixantrone as a single-agent salvage therapy for heavily pretreated patients with refractory or relapsed aggressive NHL. In that study pixantrone was quite well tolerated and 20% who received pixantrone were able to achieve a complete or unconfirmed complete response at the end of treatment compared to 5.7% in the comparator group with investigator's choice of a single-agent therapy. Very promising results have recently been shown with the combination therapy of the antibody–drug conjugate polatuzumab vedotin, targeting the B-cell receptor component CD79 together with bendamustine. In contrast to bendamustine alone the combination therapy with polatuzumab doubled the rate of complete remissions (40% *versus* 17.5%), prolonged median PFS (9.5 *versus* 3.7 months) and also improved OS (12.4 *versus* 4.7 months).[63]

Non-GCB subtype DLBCL has a worse cure rate with available therapies than the GCB subtype.[64] Ibrutinib, an inhibitor of B-cell receptor (BCR) signaling, shows especially in non-GCB activity. In a phase I/II trial that involved 80 subjects with relapsed or refractory DLBCL, ibrutinib produced complete or partial responses in 37% of those with non-GCB DLBCL but only in 5% of patients with GCB DLBCL.[65]

Oral lenalidomide monotherapy or in combination with rituximab are other well-tolerated regimens which are associated with some efficacy in these patients.[66,67] Recently the US Food and Drug Administration (FDA) approved tafasitamab, a humanized Fc-modified cytolytic CD19 targeting monoclonal antibody, in combination with lenalidomide for the treatment of adult patients with relapsed/refractory DLBCL who are not eligible for ASCT. This decision was based on results of the phase II L-MIND trial with an overall response rate of 60%.[68] However, in that study the median age of patients was 72 (range 62–72) years with only 9% of them with an Eastern cooperative oncology group (ECOG) score ≥ 2. With an occurrence of serious adverse events in 51% in this cohort, the value of this therapy for elderly and frail patients has still to be established.

For patients with relapsed or refractory DLBCL after at least two lines of systemic therapy selinexor, a selective inhibitor of nuclear export, also recently received FDA approval.[69] This single-drug and orally available therapy with manageable side effects might indeed also be a new treatment option for elderly and frail patients.

In addition, in the palliative care setting patients with relapsed/refractory lymphoma who are not able

to tolerate intensive therapies might benefit from metronomic therapy consisting of oral prednisone, cyclophosphamide, etoposide and procarbazine.[70]

Whenever possible, of course, clinical trials should be offered for patients for testing new approaches and therapies in this special cohort.

Conclusion

The management of elderly patients with aggressive lymphoma still remains challenging due to the enormous heterogeneity of this patient population. Chronological age definitely should not be the only feature for therapeutic decisions. In the end it is crucial to go through a detailed pretreatment assessment and evaluate patients' frailty prior to therapeutic decisions. Unfortunately, there is no uniform screening tool which concerns all aspects of this heterogeneous patient population and results in a clear treatment decision. Rather, it is a complex decision based on screening for frailty by different screening tools and if necessary further geriatric assessment. Oncogeriatric assessment will be much more important in future.

Fit patients with aggressive lymphoma and no contraindication to anthracycline-based chemotherapy should receive standard treatment with the R-CHOP regimen, in the case of patients aged 80 years or over R-mini-CHOP. However, there is not such a clear recommendation for unfit and frail patients. For these patients you rather have to perform a careful assessment and benefit–risk evaluation, consider the different therapeutic options and create an individualized treatment plan.

Conflict of interest statement

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