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SPECIAL ARTICLE

ESMO Consensus Conference on malignant lymphoma: general perspectives and recommendations for the clinical management of the elderly patient with malignant lymphoma

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The European Society for Medical Oncology (ESMO) consensus conference on mature B cell lymphomas and chronic lymphocytic leukaemia (CLL) was held on 20 June 2015 in Lugano, Switzerland, and included a multidisciplinary panel of 25 leading experts. The aim of the conference was to develop recommendations on critical subjects difficult to consider in detail in the ESMO Clinical Practice Guidelines. The following areas were identified: (1) the elderly patient, (2) prognostic factors suitable for clinical use, and (3) the 'ultra-high-risk' group. Before the conference, the expert panel was divided into three working groups; each group focused on one of these areas in order to address clinically-relevant questions relating to that topic. All relevant scientific literature, as identified by the experts, was reviewed in advance. During the consensus conference, each working group developed recommendations to address each of the four questions assigned to their group. These recommendations were presented to the entire panel and a consensus was reached. This consensus, which was further developed in continuous post-meeting discussions, formed the basis of three manuscripts, each covering one of the three key areas identified. This manuscript presents the consensus recommendations regarding the clinical management of elderly patients diagnosed with malignant lymphoma. Four clinically-relevant topics identified by the panel were: 1) how to define patient fitness, 2) assessing quality of life, 3) diagnostic work-up and 4) clinical management of elderly patients with lymphoma. Each of these key topics is addressed in the context of five different lymphoma entities, namely: CLL, follicular lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma and diffuse large B-cell lymphoma. Results, including a summary of evidence supporting each recommendation, are detailed in this manuscript.

Key words: lymphoma, consensus, elderly patient, quality of life, diagnosis, treatment

Introduction

Western industrial countries, as well as developing countries, are facing dramatic demographic changes in the near future, with an increasing proportion of elderly persons in these societies. In 2015, ~18.9% of the population in the European Union were ≥65 years old; specifically, 4.4% were 70–74, 3.8% were 75–79 and 5.3% were ≥80 years old [1]. Moreover, by 2060, it is estimated that the proportion of people ≥65 years old will rise to 28% and the proportion who are ≥80 years old will rise to 12% [2]. Consequently, the

number of elderly patients with haematological malignancies will rise continuously and dramatically since they are typical diseases of the elderly, with a median age at initial diagnosis of >70 years for the most common lymphoma subtypes, such as diffuse large B-cell lymphoma (DLBCL) or chronic lymphocytic leukaemia (CLL) [3, 4]. On the other hand, the number of treatment options has increased dramatically over the past years, ranging from best supportive care to haematopoietic stem cell transplantation. In more recent years, well-tolerated and effective cytostatic drugs as well as immuno-modulatory drugs, monoclonal antibodies and small molecules with favourable efficacy profiles have been developed. Based on the complexity of elderly patients with malignant lymphoma and the lack of evidence-based recommendations regarding treatment algorithms for these patients, the rational integration of this armamentarium of new drugs remains a challenge. This is particularly true given that decision making for elderly patients with lymphoma depends on aspects of the ageing process including comorbidities, malnutrition and/or impairments in functional capacities. As such, at this present time, evidence-based treatment algorithms and recommendations for elderly patients with lymphoma are rare. This is also due to the lack of integration of elderly patients into clinical trials. Indeed, clinical trials are typically limited to younger patients and those with an excellent performance status (PS) and a lack of, or only minor, comorbidities. A systematic review by Hamaker et al. [5] showed that only 5% of trials in haematological malignancies focus exclusively on elderly patients, and 69% of trials excluded older patients based on their chronological age alone. Furthermore, end points that are particularly relevant for the elderly, such as improvement or maintenance of quality of life and functional capacities, are rarely considered within clinical trials [5].

Treatment algorithms in a given elderly patient with lymphoma should be based on the individual risk and prognosis, with personalised treatment algorithms based on the integration of age-adjusted models including age-adjusted life expectancy and the evaluation of patient status by geriatric assessment [6, 7].

Based on the huge and continuously increasing numbers of elderly patients with malignant lymphoma, and the lack of recommendations on their treatment so far, the European Society for Medical Oncology (ESMO) convened a panel of experts in order to develop consensus-based recommendations regarding the clinical management of elderly patients with malignant lymphoma.

Methods

A consensus panel, comprising a multidisciplinary panel of 25 experts in the management of lymphoma, was convened by ESMO. Three consensus conference chairs (**C. Buske, M. Ladetto, M. Hutchings**) were also appointed. The consensus panel was divided into three working groups, each of which was assigned a specific subject area and a working group chair as follows:

1. The elderly patient (Chair: **C. Buske**).
2. Prognostic factors suitable for clinical use (Chair: **M. Ladetto**).
3. The 'ultra-high-risk' group (Chair: **M. Hutchings**).

The consensus conference was held on 20 June 2015 in Lugano, Switzerland. Before this consensus conference, clinically relevant questions were identified for each subject area.

A literature review was conducted by each working group before the consensus conference, with each group responsible for compiling a summary of relevant information required to develop recommendations relating to each of their questions at the conference. No systematic literature search was undertaken. During the conference, in parallel sessions, the three working groups discussed and agreed on recommendations relating to each of their assigned questions. The level of evidence and strength of each recommendation were also noted, which were defined based on the 'Infectious Diseases Society of America-United States Public Health Service Grading System', as shown in Table 1 [8]. Recommendations from each group were then presented to the entire panel of experts, where they were discussed and modified as required. Finally, a vote was conducted to determine the level of agreement amongst the expert panel for each of the recommendations. When necessary, more recent developments emerging after the consensus conference in Lugano in June 2015 were taken into account when finalising this consensus manuscript.

For working group 1, four topics were identified for discussion in terms of their potential suitability to guide physicians in the management of elderly patients with lymphoma. As such, the following topics were considered:

1. Assessing fitness in elderly patients with lymphoma.
2. Assessing 'quality of life' in elderly patients with lymphoma.
3. Diagnostic work-up in elderly patients with lymphoma.
4. Treatment of elderly patients with lymphoma.

Table 1. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System [8])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs,. . .), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

By permission of the Infectious Diseases Society of America [8].

For topics 3 and 4, the following lymphoma entities were discussed: CLL, DLBCL, follicular lymphoma (FL), mantle cell lymphoma (MCL) and peripheral T-cell lymphoma (PTCL). Results from the section of the consensus conference dedicated to the above topics related to elderly patients with lymphoma, together with a summary of evidence supporting each recommendation, are detailed in this article. Topics 3 and 4 are presented together and subdivided according to the different lymphoma entities. A summary of these recommendations is included in Table 2. Importantly, these additional recommendations should be read in conjunction with the already-published ESMO Clinical Practice Guidelines (CPGs) for the diagnosis, treatment and follow-up of the aforementioned malignant lymphoma entities [9–13].

Results

1. Assessing fitness in elderly patients with malignant lymphoma

The term 'elderly' patients is used frequently in the literature without clearly defining the criteria for 'elderly'. Although numerical or chronological age itself is not a good tool to define fitness in patients, it is well accepted that age-related changes result in decreased fitness. Increasing age is associated with a higher prevalence of comorbidities, functional decline, cognitive impairment, depressive mood and dependence in activities of daily living (ADL). In addition, increasing age is associated with increasing rates of toxicity from treatment and treatment-related mortality. According to data of the DSHNHL (Deutsche Studiengruppe Hochmaligne Non-Hodgkin-Lymphome) in patients with DLBCL within clinical trials treated with cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) or CHOP-like protocols, the treatment-related mortality increased from 4% in those aged 50–64 years to 20% in those aged 75–79 years when no antibacterial or antiviral prophylaxis was given [14].

Age-related changes occur as a gradual process, but increase substantially in patients of 70 years and older. Therefore, the authors recommend using the term 'elderly' for all patients of 70 years and older, in line with recommendations of the International Society of Geriatric Oncology (SIOG) and the European Organisation for Research and Treatment of Cancer (EORTC) [7, 15].

Less aggressive treatment may reduce the chances of cure, prolongation of life and/or symptom control, whereas too aggressive treatment may result in treatment-related morbidity and mortality, and/or compromised quality of life. Thus, a cornerstone in the decision-making process is to judge fitness for treatment. However, this is not a well-defined term in haematology. In addition, willingness to accept impairment by toxicity will depend on the aim of treatment and the likelihood of reaching this aim. Thus, if the chance for cure, or more generally speaking the likelihood of benefit, is high, as is the case in DLBCL, the readiness to accept toxicity is high and vice versa. Consideration of fitness has to include: (i) the lymphoma, as it defines the potential aim of treatment; (ii) the treatment, as it defines the risk of toxicity; and (iii) the patient, as the individual characteristics also contribute to toxicity and life expectancy. In addition, the patient's aims in life and treatment preferences are essential. However, a cut-off at which the likelihood of harm means that a patient should be defined as unfit does not exist. Ziepert et al. [16] identified the following factors as contributing to haematological toxicity of CHOP-like protocols: low weight, female gender, poor Eastern Cooperative Oncology Group (ECOG) PS, high lactate dehydrogenase (LDH), initial cytopenia and grade 4 haematological toxicity during the first cycle. A geriatric assessment was not included in this trial. In addition, the association between objective toxicity [defined according to the National Cancer Institute Common Terminology Criteria (NCI-CTC)] and subjective toxicity (defined as toxicity compromising quality of life) was not well studied. Current projects address the topic of patient-reported toxicity [17].

In the field of geriatric oncology, a number of trials have been conducted to evaluate the association between the results of geriatric assessment and patient outcomes. Some of them included lymphoma patients, but only a few trials were set up especially for elderly patients with malignant lymphoma. The only patient characteristics included in the analysis for prognostic variables in patients with DLBCL are therefore age and ECOG PS. Both are included in the new National Comprehensive Cancer Network International Prognostic Index (NCCN-IPI), with age of ~75 years considered as the most important prognostic factor [18]. As patient characteristics determined via geriatric assessment are not included, it might be that numerical age is just a surrogate for other age-related changes, such as comorbidities, functional decline, cognitive impairment, depressive mood and dependence in ADL. Poor performance according to geriatric assessment, such as limitations in ADL, has demonstrated prognostic importance for survival and toxicity, and might change the treatment decision. It is also associated with poor health-related quality of life [19]. However, data to show that assessment-based care improves outcome are still missing.

In a systematic review, Wildiers et al. [20] showed that the use of a geriatric assessment results in detection of impairment not identified in routine assessments (patient history or physical examination). Geriatric assessment was also able to predict severe treatment-related toxicity and overall survival (OS) in a variety of tumours and treatment settings, and so could help tailor the treatment choice and intensity in each individual patient [20]. Currently, judgement of fitness of elderly patients with malignant lymphoma should include some form of a geriatric assessment [20]. The Task Force for Cancer in the Elderly of the EORTC recommends the use of the G8 questionnaire. It is a very simple screening tool, which includes seven mini nutritional assessment items and age (<80, 80–85, >85) for a total score ranging from 0 (poor score) to 17 (good score). The task force recommended a cut-off value of 14 for an 'impaired' reference test score [21]. In an exploratory analysis of a prospective cohort study of 1435 assessable cancer patients accrued before treatment in 23 health-care facilities, an abnormal G8 score was an independent prognostic factor of 1-year survival. Importantly, the mean time to complete G8 questionnaire was about 5 min [22]. In a busy clinic, such a screening approach might be preferred [23, 24]. To quantify comorbidity, the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) is one of the most widely available scores and has already been used to allocate patients with CLL to less intensive treatment protocols in a large prospective clinical trial [15, 21,

Table 2. Summary of recommendations

Guidelines statement	LoE	GoR	Consensus
1. Assessing fitness in elderly patients with malignant lymphoma			
Recommendations:			
1.1 The panel suggests that geriatric assessment should be included in the diagnostic process of clinical trials in order to assess patient fitness	II	B	100% yes (23 voters)
1.2 The panel suggests that a geriatric assessment is included in the diagnostic process to assess patient fitness in routine clinical practise. In cases when geriatric assessment is not possible, geriatric screening (e.g. G-8) can be carried out	II	B	100% yes (23 voters)
2. Assessing quality of life in elderly patients with malignant lymphoma			
Recommendations:			
2.1 Quality of life should be considered as a prognostic indicator of survival	I	A	100% yes (23 voters)
2.2 Quality of life should be included as a major end point in clinical trials in the elderly, either alone (e.g. in the palliative setting) or in combination with a survival end point (as a co-primary or composite end point)	II	B	100% yes (23 voters)
2.3 Other PROs can be considered, including maintenance of functional capacity/dependence, either alone or in combination with survival end points. This type of end point is encouraged in clinical trials but methodological questions remain to be solved. Standardised instruments such as ADL and IADL are available and their use during treatment in clinical practice is encouraged	III	C	100% yes (23 voters)
3. Diagnostic work-up and treatment of elderly patients with CLL			
Recommendations:			
3.1 Similar methodology should be used in older compared with younger patients to diagnose and to stage CLL (i.e. history taking, physical examination, differential blood count, blood smear microscopy, flow cytometry of blood)	V	B	100% yes (23 voters)
3.2 Older patients with CLL should to be screened for Del(17p) and/or TP53mut whenever treatment is planned	III	B	100% yes (23 voters)
3.3 Clinical judgement supported by geriatric assessments should be used to stratify older patients with CLL for fitness and treatment goals (fit versus unfit versus terminally ill)	III	B	100% yes (23 voters)
3.4 Only a small minority of carefully selected and very fit older patients with untreated CLL not harbouring Del(17p) or TP53mut might be treated with full-dose FCR	I	B	100% yes (23 voters)
3.5 Fit older patients with untreated CLL not harbouring Del(17p) and TP53mut should be evaluated for alternative treatments such as BR or dose-attenuated FCR	II	B	100% yes (23 voters)
3.6 Vulnerable older patients with untreated CLL not harbouring Del(17p) or TP53mut should be treated with G-CLB, O-CLB or R-CLB	I	A	100% yes (23 voters)
3.7 Vulnerable older patients with untreated CLL not harbouring Del(17p) or TP53mut may be considered for alternative treatments such as BR or dose-attenuated FCR or ibrutinib	II	B	100% yes (23 voters)
3.8 Older patients with untreated CLL harbouring Del(17p) and/or TP53mut should be considered for treatment with ibrutinib	III	B	100% yes (23 voters)
3.9 Older patients with relapsed or refractory CLL should be considered for treatment with ibrutinib or idelalisib plus rituximab (irrespective of Del[17p] and TP53mut status)	I	A	100% yes (23 voters)
3.10 Older patients with relapsed or refractory CLL not harbouring Del(17p) or TP53mut could be evaluated for alternative treatments (e.g. CD20 antibody)	III	C	100% yes (23 voters)
3.11 Older patients with late relapse CLL not harbouring Del(17p) or TP53mut may be evaluated for re-administration of chemo-immunotherapy	V	B	100% yes (23 voters)
4. Diagnostic work-up and treatment of elderly patients with FL			
Recommendations:			
4.1 Elderly patients should be diagnosed based on lymph node histology whenever possible. The aim of staging is to discriminate between patients with limited disease and those with advanced stage disease. Any diagnostics that do not impact on treatment decisions should be avoided, particularly in terminally ill patients	V	A	100% yes (23 voters)
4.2 Asymptomatic elderly patients should undergo a watch and wait strategy	I	A	100% yes (23 voters)
4.3 Symptomatic patients with mild symptoms should be offered a chemotherapy-free approach such as rituximab single agent, if possible	III	B	100% yes (23 voters)
4.4 For patients with high tumour burden tolerating chemotherapy, a rituximab/chemotherapy regimen such as BR is recommended (with bendamustine dose reduction or fewer treatment cycles, if necessary. Be aware of bendamustine-associated infections; consider antibacterial/antiviral prophylaxis)	I	A	100% yes (23 voters)
4.5 For relapsed patients, rituximab/chemotherapy adjusted to the fitness of the patient is also standard in the elderly. Rituximab maintenance is optional both first line and in relapse.	III	B	100% yes (23 voters)

Continued

Table 2. *Continued*

Guidelines statement	LoE	GoR	Consensus
Idelalisib should be used with caution in relapsed patients not responding to rituximab/chemotherapy because of its toxicity profile			
5. Diagnostic work-up and treatment of elderly patients with MCL			
Recommendations:			
5.1 Diagnostic work-up in elderly patients should generally not differ from patients of a younger age. Histological confirmation by excisional lymph node biopsy or at least core biopsy is mandatory. Detection of cyclin D1 overexpression or chromosomal translocation t(11;14) is essential. Imaging should include at least a CT scan with iodine contrast of the neck, chest, abdomen and pelvis. The use of PET-CT imaging is considered optional for fit elderly patients. BM aspirate and biopsy should be carried out in elderly fit patients, whereas BM examination is not required in vulnerable or terminally ill patients.	V	A	100% yes (23 voters)
5.2 For elderly fit patients, the following chemo-immunotherapeutic regimens are recommended as the preferred first-line treatment options in routine clinical practice:			100% yes (23 voters)
1. R-CHOP followed by rituximab maintenance	I	A	
2. BR	I	A	
3. VR-CAP	I	A	
4. R-BAC	V	B	
5.3 For vulnerable elderly patients, dose-adapted chemo-immunotherapeutic regimens are considered appropriate. Options include dose-reduced BR, R-CVP or R-CLB	V	B	100% yes (23 voters)
5.4 For vulnerable patients with severe comorbidities, mild chemo-immunotherapeutic regimens like R-CLB, (dose-reduced) BR or PEP-C are considered appropriate	V	B	100% yes (23 voters)
5.5 While newer targeted drugs such as ibrutinib and lenalidomide might offer benefits, particularly in vulnerable patients, no data are available from clinical trials for this subset of patients and therefore clear recommendations cannot be given. For relapsed or refractory disease, treatment should be adapted to the age and PS of the patient. Besides non-cross-resistant combination regimens, treatment options include:			100% yes (23 voters)
1. Ibrutinib	II	A	
2. Lenalidomide ± rituximab	II	B	
3. Temsirolimus ± rituximab	II	B	
4. Bortezomib	V	B	
6. Diagnostic work-up and treatment of elderly patients with PTCL			
Recommendations:			
6.1 The final histological diagnosis requires full analysis and integration of the clinical context and expert haematopathological review	IV	A	100% yes (23 voters)
6.2 Whenever possible, patients should be entered into clinical trials. First-line regimes for elderly patients should be based on a CHOP induction backbone	III	B	100% yes (23 voters)
6.3 Whenever possible, patients should be entered into clinical trials testing novel agents. However, for elderly relapsed patients considered unsuitable for clinical trials, treatment options include:			100% yes (23 voters)
1. Salvage chemotherapy with gemcitabine or platinum-containing agents	IV	C	
2. Novel agents such as brentuximab vedotin monotherapy for patients with CD30+ T-cell lymphoma	III	B	
7. Diagnostic work-up and treatment of elderly patients with DLBCL			
Recommendations:			
7.1 For patients treated with curative intent, diagnosis should be carried out in an expert haematopathology laboratory with full diagnostic capabilities (immunophenotypic and molecular) and staging should be with PET-CT	V	A	100% yes (23 voters)
7.2 Cardiac assessment (LVEF) is required for patients treated with curative intent	V	A	100% yes (23 voters)
7.3 The IPI score should be calculated	I	A	100% yes (23 voters)
7.4 A CGA is recommended to guide treatment choice	III	A	100% yes (23 voters)
7.5 The aim of treatment in fully fit patients who are <80 years old should be curative, with a full-dose anthracycline-based regimen preferred. R-CHOP is the recommended first-line treatment choice	I	A	100% yes (23 voters)
7.6 For fully fit patients who are >80 years old without comorbidities, dose-attenuated R-CHOP may be appropriate	III	B	100% yes (23 voters)
7.7 For relapsed fit (no organ dysfunction, PS 0–1, no comorbidities), transplant-eligible patients, appropriate salvage treatment with R–DHAP, R-ESHAP, R-ICE or R-GDP is indicated. In the event of an adequate response, ASCT is recommended	II	A	100% yes (23 voters)

Continued

Table 2. *Continued*

Guidelines statement	LoE	GoR	Consensus
7.8 For transplant-ineligible patients, dose attenuated R-DHAP, R-ESHAP, R-ICE, or less intense regimens such as R-Gem-Ox, are appropriate	III	B	100% yes (23 voters)
7.9 For transplant-ineligible patients, single-agent chemotherapies such as bendamustine or pixantrone may be considered	I (pixantrone) II (bendamustine)	C	100% yes (23 voters)

ADL, activities of daily living; ASCT, autologous stem cell transplantation; BAC, bendamustine/cytarabine; BM, bone marrow; BR, bendamustine/rituximab; CGA, comprehensive geriatric assessment; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone; CLB, chlorambucil; CLL, chronic lymphocytic leukaemia; CT, computed tomography; CVP, cyclophosphamide/vincristine/prednisone; DHAP, dexamethasone/high-dose cytarabine/cisplatin; DLBCL, diffuse large B-cell lymphoma; ESHAP, etoposide/methylprednisolone/cytarabine/cisplatin; FCR, fludarabine/cyclophosphamide/rituximab; FL, follicular lymphoma; G, obinutuzumab; GDP, gemcitabine/dexamethasone/cisplatin; Gem-Ox, gemcitabine/oxaliplatin; GoR, grade of recommendation; IADL, instrumental activities of daily living; ICE, ifosfamide/carboplatin/etoposide; IPI, International Prognostic Index; LoE, level of evidence; LVEF, left ventricular ejection fraction; MCL, mantle cell lymphoma; O, ofatumumab; PEP-C, prednisone/etoposide/procarbazine/cyclophosphamide; PET, positron emission tomography; PRO, patient-reported outcome; PS, performance status; PTCL, peripheral T-cell lymphoma; R, rituximab; VR-CAP, bortezomib/rituximab/cyclophosphamide/doxorubicin/prednisone.

25]. Thus, it is recommended that prospective clinical trials should include a geriatric and comorbidity score as an obligatory component of the diagnostic work-up. This will be an important first step to correlate toxicity and efficacy of a treatment with fitness in patients with lymphoma in controlled clinical trials.

In the end, a precise definition of fitness based on scores of geriatric and/or comorbidity tests will be difficult to achieve, since prognosis and treatment-related toxicity differ from disease to disease, and as such, the criteria to define fit, vulnerable and terminally ill patients also varies. Different study groups have suggested different criteria, e.g. CLL, myelodysplastic syndrome, acute myeloid leukaemia and multiple myeloma [26–29]. To overcome this, we propose the following ESMO criteria, in which 'fitness' is defined in the context of treatment feasibility with three different categories discriminating between 'fit', 'vulnerable' and 'terminally ill' patients: (i) for an elderly 'fit' patient, it would be anticipated that application of the standard treatment, including more dose intense approaches, would not be associated with a high risk of treatment-related or treatment-unrelated adverse events (AEs) compared with a young 'fit' patient; in contrast (ii) a 'vulnerable' patient would carry a high risk for treatment-related AEs or treatment-unrelated AEs when receiving standard treatment. Vulnerable patients would present a continuum, ranging from those who are just at the border of not being able to tolerate standard treatment to those who are close to being considered as terminally ill. Finally, (iii) the 'terminally ill' patient is one with a short life expectancy (around three months only due to the lymphoma or competing lethal comorbidities), who will therefore not benefit from any anti-lymphoma treatment, but from best supportive care only [30] (Table 3).

Table 3. ESMO criteria to define fitness of patients

Category	
Fit patient	Application of the standard treatment, including more dose-intense approaches, is not associated with an increased risk of treatment-related or treatment-unrelated AEs compared with a young fit patient
Vulnerable patient	A high risk for treatment-related AEs or treatment-unrelated AEs when receiving standard treatment. Vulnerable patients present a continuum, ranging from those who are just at the border of not being able to tolerate standard treatment to those who are close to being considered as terminally ill
Terminally ill patient	Has a short life expectancy (around 3 months only, due to the lymphoma or competing lethal comorbidities) and will therefore not benefit from any anti-lymphoma treatment, but only from best supportive care

AE, adverse event; ESMO, European Society for Medical Oncology.

Methodological considerations.

Broad availability: Geriatric screening is available in all clinic settings caring for patients with malignant lymphoma. Geriatric assessment is a multi-professional approach; some institutions will not have a geriatrician, but most of the work-up can be done by different professional groups within a therapeutic team.

Reproducibility and standardisation: Assessment instruments are validated, standardised and reproducible.

Clarity of reporting system: In different countries, different scales [e.g. to assess ADL, or instrumental ADL (IADL), are available].

Prognostic value. Poor performance according to geriatric assessment is associated with increased toxicity and shorter survival of elderly patients with malignant lymphoma.

Panel recommendations for assessing patient fitness in clinical trials.

Recommendation 1.1: The panel suggests that geriatric assessment should be included in the diagnostic process of clinical trials in order to assess patient fitness.

Level of evidence: II
Strength of recommendation: B
Consensus: 100% yes (23 voters)

Panel recommendations for assessing patient fitness in routine clinical practice.

Recommendation 1.2: The panel suggests that a geriatric assessment is included in the diagnostic process to assess patient fitness in routine clinical practise. In cases when geriatric assessment is not possible, geriatric screening (e.g. G-8) can be carried out.

Level of evidence: II
Strength of recommendation: B
Consensus: 100% yes (23 voters)

2. Assessing 'quality of life' in the elderly lymphoma patient

In the management of haematological malignancies, the typical dilemma faced by haematologists when making treatment decisions is to determine the balance between efficacy and toxicity. However, in the elderly, another balance between quantity and quality of life should also be considered, although this is more difficult to assess since it is highly dependent on the individual patient's views [31]. Indeed, quality of life and other patient-reported outcomes (PROs) are a routine part of treatment decision making, most strikingly for older patients, but unexpectedly are rarely included among major end points of clinical trials in the elderly. In a review of recent literature (2005–2011), among 87 randomised controlled trials conducted in patients with lymphomas, none considered quality of life as a primary end point and only 5% included it as a secondary end point [32]. This was also observed in a review of 1207 trials in haematological malignancies, with 8% of trials including quality of life as an end point; however, this paper also showed that this proportion rises to 31% in phase III trials and appears higher in the elderly (18% versus 7% in all other studies) [5]. Finally, there is strong evidence to show that quality of life may have prognostic value [33].

Other approaches to PROs should also be considered, including Q-TWIST (quality-adjusted time without symptoms of disease or toxicity of treatment) which measures quality-adjusted survival with three possible consecutive health states (time with toxicity resulting from treatment, time without symptoms of disease or toxicity, time from progression/relapse to death) [7] and evaluation of functional capacity/independence according to time, either alone or in combination with survival end points [34, 35]. However, methodological difficulties with this approach are not always easy to solve.

Methodological considerations.

Broad availability: Multiple quality of life questionnaires are available but their metrics should be evaluated cautiously. Among others, including the MOS-SF36 [36–38], the EORTC QLQ-C30 is strongly validated in multiple languages [39], and its complement for the elderly, named QLQ-ELD14, is now available [40, 41].

Reproducibility and standardisation: Recommendations have been provided for the use of EORTC QLQ-C30 in clinical trials [42], and cut-offs for significant variations have been identified through a comparison with patients' perceived changes [43].

Clarity of reporting system: Quality of life reporting has been standardised [44].

Panel recommendations for assessing quality of life in clinical trials.

Recommendation 2.1: Quality of life should be considered as a prognostic indicator of survival [33].

Level of evidence: I
Strength of recommendation: A
Consensus: 100% yes (23 voters)

Recommendation 2.2: Quality of life should be included as a major end point in clinical trials in the elderly, either alone (e.g. in the palliative setting) or in combination with a survival end point (as a co-primary or composite end point) [7].

Level of evidence: II
Strength of recommendation: B
Consensus: 100% yes (23 voters)

Panel recommendations for assessing quality of life in routine clinical practice.

Recommendation 2.3: Other PROs can be considered, including maintenance of functional capacity/dependence, either alone [7, 34, 35] or in combination with survival end points. This type of end point is encouraged in clinical trials but methodological questions remain to be solved. Standardised instruments such as ADL and IADL are available [45, 46] and their use during treatment in clinical practice is encouraged.

Level of evidence: III
Strength of recommendation: C
Consensus: 100% yes (23 voters)

3. Diagnostic work-up and treatment of elderly patients with CLL

CLL is the most common leukaemia in Western countries. Most patients newly diagnosed with CLL are of advanced age. The median age at diagnosis is over 70 years, and almost one fifth of patients are 80 years old or older when CLL is diagnosed [3]. Major comorbidities such as coronary heart disease, heart failure, peripheral artery disease, chronic obstructive lung disease or diabetes mellitus are present in approximately half of all patients newly diagnosed with CLL [47], but the prevalence of geriatric syndromes such as dementia, delirium, depression, falls, sarcopenia or frailty has not been specifically examined in older patients with CLL. There is growing evidence, however, that comorbidities and geriatric syndromes unfavourably impact on treatment feasibility and overall prognosis of such patients [48–51]. Treatment differs substantially between young and elderly patients with CLL; for example, fludarabine/cyclophosphamide/rituximab (FCR) is still the standard first-line treatment in young fit patients without a TP53 deletion/mutation [9, 52].

Diagnostic work-up of CLL in elderly patients. Procedures to diagnose and stage CLL are outlined by pre-existing guidelines [9, 53]. There are no data to suggest that methodology should

differ between younger and older patients. Diagnosis of CLL is made by history taking, physical examination, blood count including differential, blood smear microscopy and flow cytometry of the blood. Staging of CLL (i.e. Binet or Rai classification) requires a physical examination and blood count. Various studies have shown that the presence of a deletion of the short arm of chromosome 17 [Del(17p)] and/or a mutation of the tumour suppressor gene *p53* (TP53mut) is associated with poor response to conventional chemo-immunotherapy approaches and poor survival, independent of age. For proper choice of therapy, knowledge of Del(17p) and/or TP53mut status is therefore a prerequisite not just in younger but also in older patients.

Older patients with CLL differ in fitness and thus there is no uniform benefit from a given treatment regimen. In a pragmatic approach, these patients can be categorised into three groups: (i) fit patients who appear fit for full-dose standard therapy (aiming for symptom-control, complete remission (CR) of the disease and prolongation of survival); (ii) vulnerable patients who appear unfit for full-dose standard therapy but eligible for alternative therapy plus geriatric interventions (aiming for symptom-control, long-term disease-control and eventually prolongation of survival); and (iii) terminally ill patients who appear ineligible for any anti-leukaemic therapy and who should therefore receive best supportive care (aiming for symptom palliation only). Clinical judgement is the current standard to assign individual patients to one of these categories. However, additional geriatric assessment, including a systematic scoring of comorbidity, function and autonomy, is able to unmask vulnerability that otherwise may remain undetected [20, 54].

Panel recommendations for diagnostic work-up.

Recommendation 3.1: Similar methodology should be used in older compared with younger patients to diagnose and to stage CLL (i.e. history taking, physical examination, differential blood count, blood smear microscopy, flow cytometry of blood).

Level of evidence: V
Strength of recommendation: B
Consensus: 100% (23 voters)

Recommendation 3.2: Older patients with CLL should to be screened for Del(17p) and/or TP53mut whenever treatment is planned.

Level of evidence: III
Strength of recommendation: B
Consensus: 100% (23 voters)

Recommendation 3.3: Clinical judgement supported by geriatric assessments should be used to stratify older patients with CLL for fitness and treatment goals (fit versus unfit versus terminally ill).

Level of evidence: III
Strength of recommendation: B
Consensus: 100% (23 voters)

Treatment of CLL in elderly patients. Full-dose chemo-immunotherapy with FCR is the standard frontline treatment in younger patients with CLL [55]. With advancing age, however, the risk of FCR-related toxicity and treatment discontinuation generally increases [55–58]. Frontline chemo-immunotherapy with bendamustine/rituximab (BR) or dose-attenuated FCR appear less toxic than full-dose FCR and suggest preserved efficacy in fit older patients [58–61]. These regimens may therefore be considered as alternatives to full-dose FCR in this patient group. Combinations of chlorambucil with a monoclonal anti-CD20 antibody (obinutuzumab, G-CLB; ofatumumab, O-CLB; rituximab, R-CLB) have been demonstrated as feasible and beneficial in previously untreated vulnerable older patients with CLL [25, 62]. Chemo-immunotherapy with BR or dose-attenuated FCR is also feasible and efficacious in these patients [63, 64]. Yet, evidence for such treatments in vulnerable older patients is lower than in fit older patients. Irrespective of being fit or vulnerable, older patients harbouring Del(17p) or TP53mut are candidates for frontline treatment with the kinase inhibitor ibrutinib [65]. Ibrutinib may also represent a suitable frontline treatment for older patients without Del(17p) or TP53mut [66]. However, studies comparing ibrutinib with chemo-immunotherapy are lacking and short follow-up currently precludes final conclusions regarding the benefits and risks (i.e. specific toxicities, drug interactions, non-adherence) of such treatment in older patients with CLL. With advancing age, however, treatment with the kinase inhibitors ibrutinib or idelalisib (the latter in combination with rituximab) have been shown to be safe and highly efficacious as salvage therapy for fit or vulnerable older patients with refractory or early relapsing CLL.

Importantly, these treatments proved active in heavily pre-treated patients without Del(17p) or TP53mut and also for patients with Del(17p) or TP53mut who have failed chemo-immunotherapy [67, 68]. For patients who have failed kinase inhibitor therapy, one treatment option is the pro-apoptotic drug venetoclax (ABT-199) [69]. Other salvage therapies are available (e.g. ofatumumab, steroids plus rituximab), but evidence in older patients with CLL is generally limited. Recapitulation of chemo-immunotherapy remains a therapeutic option in older patients with late relapse of CLL and lack of Del(17p) or TP53mut.

Panel recommendations for treatment in routine clinical practice.

Recommendation 3.4: Only a small minority of carefully selected and very fit older patients with untreated CLL not harbouring Del(17p) or TP53mut might be treated with full-dose FCR.

Level of evidence: I
Strength of recommendation: B
Consensus: 100% (23 voters)

Recommendation 3.5: Fit older patients with untreated CLL not harbouring Del(17p) and TP53mut should be evaluated for alternative treatments such as BR or dose-attenuated FCR.

Level of evidence: II
Strength of recommendation: B
Consensus: 100% (23 voters)

Recommendation 3.6: Vulnerable older patients with untreated CLL not harbouring Del(17p) or TP53mut should be treated with G-CLB, O-CLB or R-CLB.

Level of evidence: I
Strength of recommendation: A
Consensus: 100% (23 voters)

Recommendation 3.7: Vulnerable older patients with untreated CLL not harbouring Del(17p) or TP53mut may be

considered for alternative treatments such as BR or dose-attenuated FCR or ibrutinib.

Level of evidence: II
Strength of recommendation: B
Consensus: 100% (23 voters)

Recommendation 3.8: Older patients with untreated CLL harbouring Del(17p) and/or TP53mut should be considered for treatment with ibrutinib.

Level of evidence: III
Strength of recommendation: B
Consensus: 100% (23 voters)

Recommendation 3.9: Older patients with relapsed or refractory CLL should be considered for treatment with ibrutinib or idelalisib plus rituximab (irrespective of Del[17p] and TP53mut status).

Level of evidence: I
Strength of recommendation: A
Consensus: 100% (23 voters)

Recommendation 3.10: Older patients with relapsed or refractory CLL not harbouring Del(17p) or TP53mut could be evaluated for alternative treatments (e.g. CD20 antibody).

Level of evidence: III
Strength of recommendation: C
Consensus: 100% (23 voters)

Recommendation 3.11: Older patients with late relapse CLL not harbouring Del(17p) or TP53mut may be evaluated for re-administration of chemo-immunotherapy.

Level of evidence: V
Strength of recommendation: B
Consensus: 100% (23 voters)

4. Diagnostic work-up and treatment of elderly patients with FL

FL occurs in the elderly with a median age of diagnosis of 61 years [70]. Registry data have shown that elderly non-Hodgkin's lymphoma (NHL) patients, including those with FL, suffer from comorbidities with increasing age, with a prevalence of serious comorbidity in 43% and 61% for patients aged 60–69 and >70 years old, respectively [71]. The vast majority of these elderly patients present at an advanced stage and are therefore in a palliative situation. Thus, the aim of treatment in this group is to control disease while maintaining the best quality of life possible. Following this approach, many patients with advanced stage FL achieve disease control with long-lasting disease-free intervals without compromising their quality of life. There are differences in management between young fit and elderly patients with comorbidities; for instance, in young fit patients with advanced-stage disease, six cycles of fully dosed (90 mg/m^2) bendamustine in combination with rituximab are standard [11], whereas in elderly patients, a reduction in both the number of cycles and dose (e.g. four cycles, 70 mg/m^2) is considered appropriate for many patients, as noted below.

Diagnostic work-up of FL in elderly patients. Diagnostic work-up in advanced stage FL is defined in the ESMO guidelines [11]. In general, diagnostics should be carried out with the same thoroughness in elderly patients as in younger patients. Whenever possible, excisional lymph node biopsy or at least a core biopsy should be carried out in patients without easily accessible lymph nodes. Fine-needle aspirations should be avoided as they are insufficient for an appropriate diagnosis. Staging should be with a view to exclude localised disease since treatment differs between localised and advanced stages of FL. This implies that as soon as advanced stage disease is confirmed, staging procedures should be avoided which do not impact treatment decisions. Initial work-up normally includes a computed tomography (CT) scan of the neck, thorax, abdomen and pelvis, and a bone marrow (BM) aspirate and biopsy. However, in individual patients with palpable lymph nodes (e.g. of the neck or axilla), physical examination combined with an ultrasound of the abdomen may be sufficient. In terminally ill patients with confirmed advanced stage disease and normal peripheral blood (PB) cell counts, BM biopsy might be omitted. Positron emission tomography CT (PET-CT) scan is not recommended on a regular basis, but can be helpful to confirm localised disease in patients for whom local radiotherapy is an option. A complete blood count, routine blood chemistry including LDH, β2-microglobulin and uric acid, as well as screening tests for human immunodeficiency virus (HIV) and hepatitis B and C, are also recommended in elderly patients. Immunophenotyping of PB and BM cytology, and detection of BCL2 rearrangements by polymerase chain reaction assay, are not routinely recommended. Prognostication by the 'Follicular Lymphoma-specific International Prognostic Index' (FLIPI) or the revised FLIPI 2 (incorporating β2-microglobulin, diameter of largest lymph node, BM involvement and haemoglobin level) is recommended, whenever possible. There are no data demonstrating the need to adjust treatment according to the prognostic scores of these indices. Geriatric assessment has not been established specifically for FL patients, but has its value to assess fitness in older lymphoma patients as demonstrated for patients with CLL [49].

Panel recommendations for diagnostic work-up.

Recommendation 4.1: Elderly patients should be diagnosed based on lymph node histology whenever possible. The aim of staging is to discriminate between patients with limited disease and those with advanced stage disease. Any diagnostics that do not impact on treatment decisions should be avoided, particularly in terminally ill patients.

Level of evidence: V
Strength of recommendation: A
Consensus: 100% (23 voters)

Treatment of FL in elderly patients.

Asymptomatic patients: For treatment-naïve patients, as well as those in relapse, the 'watch and wait' strategy is standard in the management of elderly patients with FL.

Symptomatic patients: If the elderly patient develops symptoms due to lymphoma progression, treatment should be initiated.

Patients with mild symptoms: For elderly patients with mild symptoms and low tumour burden, it is recommended to avoid chemotherapy. Rituximab has anti-lymphoma activity and is a

valid treatment option as single-agent induction (4 weekly, 375 mg/m^2) or single-agent induction followed by maintenance [72]. In relapse, dose reduced BR (50 or 70 mg/m^2 bendamustine on day 1 and day 2 of 28-day cycles) or rituximab/cyclophosphamide/vincristine/prednisone (R-CVP) are treatment options. Another possibility is to adjust rituximab/chemotherapy to the fitness of the patient in order to limit the number of cycles to three or four. Idelalisib is appropriate for patients with relapsed FL who are no longer responding to rituximab/chemotherapy. However, although this is a chemotherapy-free approach, recent data demonstrated considerable toxicity, which included diarrhoea and opportunistic infections, and so this drug should be used with caution and *Pneumocystis jiroveci* pneumonia prophylaxis and cytomegalovirus monitoring [73].

Patients with high tumour burden: For elderly patients with a high tumour burden according to the GELF (Groupe d'Etude des Lymphomes Folliculaires) criteria [74], more rapid lymphoma debulking is necessary. In this situation, BR and R-CVP are well-established and well-tolerated treatment options. However, BR was just recently associated with a higher rate of partly fatal infections, probably due to prolonged T-cell suppression. Therefore, bendamustine in combination with an anti-CD20 antibody should be given with caution and anti-bacterial/antiviral prophylaxis should be considered. In elderly fit patients, rituximab plus CHOP (R-CHOP) is also an effective treatment regimen. Rituximab maintenance in first remission has been shown to prolong progression-free survival (PFS), but it is associated with toxicities such as neutropaenia and an increased rate of infections. Although these complications are manageable in the majority of patients, rituximab maintenance should be considered optional. In relapse with a long remission duration (>18–24 months), the initial rituximab/chemotherapy can be repeated. In cases with shorter remission duration, alternate R-chemotherapies (e.g. R-CVP after BR and vice versa) should be used. Rituximab maintenance is a well-established treatment option for relapsed patients and may also be considered for patients who did not receive rituximab maintenance as part of their first-line therapy. Idelalisib is a treatment option for patients who are no longer responding to rituximab/chemotherapy combinations, but should be used with the precautions mentioned above. Radio-immunotherapy has a different mode of action compared with all other mentioned treatment approaches as it exploits the high radiosensitivity of lymphomas. Ibritumomab tiuxetan combines anti-CD20 targeting with the β-emitter Yttrium-90; it has shown high single-agent activity in relapsed FL and as consolidation therapy after first-line treatment of FL, which led to the approval of this agent in these two indications in Europe [75, 76].

Elderly vulnerable patients: A particular challenge is the management of elderly vulnerable patients in need of treatment. Treatment options correspond to the treatment options mentioned above for patients with low tumour burden and comprise rituximab single agent with or without a shortened rituximab maintenance (e.g. four infusions every 2 months). Rituximab is approved for subcutaneous application if the patient tolerates the first intravenous application. Another treatment option for elderly vulnerable patients, avoiding intravenous applications, is R-CLB.

Panel recommendations for treatment in routine clinical practice.

Recommendation 4.2: Asymptomatic elderly patients should undergo a watch and wait strategy.

Level of evidence: I
Strength of recommendation: A
Consensus: 100% (23 voters)

Recommendation 4.3: Symptomatic patients with mild symptoms should be offered a chemotherapy-free approach such as rituximab single agent, if possible.

Level of evidence: III
Strength of recommendation: B
Consensus: 100% (23 voters)

Recommendation 4.4: For patients with high tumour burden tolerating chemotherapy, a rituximab/chemotherapy regimen such as BR is recommended (with bendamustine dose reduction or fewer treatment cycles, if necessary. Be aware of bendamustine-associated infections; consider antibacterial/antiviral prophylaxis).

Level of evidence: I
Strength of recommendation: A
Consensus: 100% (23 voters)

Recommendation 4.5: For relapsed patients, rituximab/chemotherapy adjusted to the fitness of the patient is also standard in the elderly. Rituximab maintenance is optional both first line and in relapse. Idelalisib should be used with caution in relapsed patients not responding to rituximab/chemotherapy because of its toxicity profile.

Level of evidence: III
Strength of recommendation: B
Consensus: 100% (23 voters)

5. Diagnostic work-up and treatment of elderly patients with MCL

Treatment goals in elderly patients with MCL: cure versus disease control/palliation? Advanced MCL is generally considered an incurable disease. Nonetheless, even within the subgroup of older patients not eligible for intensive induction therapy and stem cell transplantation, treatment goals differ according to biological age, PS and comorbidities. A reasonable and commonly used approach is to stratify elderly patients into three categories: (i) elderly fit, (ii) elderly vulnerable and (iii) terminally ill individuals [77].

The treatment goal for elderly fit patients is similar to that for younger patients [12] (i.e. to achieve long-term remissions). Therefore, achievement of a CR by intensive immune-chemotherapy is the therapeutic goal.

For vulnerable patients with comorbidities, the aim of treatment is to control the disease. However, tolerability of standard treatment might be compromised by comorbidities and impaired organ function. Therefore, adaptation of treatment intensity is mandatory with the aim of balancing therapeutic efficacy and toxicity; thus, the therapeutic approach differs from those pursued in young fit patients [12].

In contrast, symptom control while preserving quality of life is the main goal in terminally ill patients.

How do treatment goals impact on our diagnostic work-up? Diagnostic work-up does not substantially differ in elderly

patients compared with patients of a younger age. As in younger patients, a reliable diagnosis is of major importance to distinguish MCL from other lymphoproliferative entities. Therefore, histological confirmation by excisional lymph node biopsy or at least core biopsy is mandatory. Fine-needle biopsy is considered inappropriate. In addition to immunophenotypic characterisation, detection of cyclin D1 overexpression or chromosomal translocation t(11;14) is essential to ensure an unequivocal diagnosis. In rare cyclin D1-negative cases, the use of SOX11 may help to identify at least some cyclin D1-negative MCL variants [12].

A CT scan with iodine contrast of the neck, chest, abdomen and pelvis is mandatory for all patients. The newest consensus report of the International Conference on Malignant Lymphomas Imaging Working Group recommends the use of PET-CT for staging and remission assessment at the end of therapy in 18F-fluorodeoxyglucose (FDG)-avid lymphoma in clinical practice [78]. Therefore, PET-CT scanning is considered optional for fit elderly patients. (PET)-CT is particularly useful for the minority of patients with stage I–II disease who are candidates for localised radiotherapy to confirm early-stage disease and is recommended in the latest ESMO CPG [12]. For terminally ill patients, the use of PET-CT scanning is not recommended.

BM aspirate and biopsy should be included in the diagnostic work-up of all elderly fit patients with MCL. In vulnerable patients, a BM examination is considered optional, whereas in terminally ill patients, it might be dispensable at least if the PB count is normal or only slightly altered.

Panel recommendations for diagnostic work-up in routine clinical practice.

Recommendation 5.1: Diagnostic work-up in elderly patients should generally not differ from patients of a younger age. Histological confirmation by excisional lymph node biopsy or at least core biopsy is mandatory. Detection of cyclin D1 overexpression or chromosomal translocation t(11;14) is essential. Imaging should include at least a CT scan with iodine contrast of the neck, chest, abdomen and pelvis. The use of PET-CT imaging is considered optional for fit elderly patients. BM aspirate and biopsy should be carried out in elderly fit patients, whereas BM examination is not required in vulnerable or terminally ill patients.

Level of evidence: V
Strength of recommendation: A
Consensus: 100% yes (23 voters)

Treatment of MCL in elderly patients. It is the strong belief of all authors that the best option for all elderly patients – either for first-line treatment or in relapse – is enrolment in a clinical trial.

First-line treatment: Based on the results of a large phase III trial, R-CHOP chemo-immunotherapy followed by rituximab maintenance is considered a standard first-line option for elderly fit patients outside a clinical trial [79]. The use of rituximab/fludarabine/cyclophosphamide (R-FC) as first-line treatment is discouraged due to early failures and insufficient haematopoietic recovery. BR has been reported to be at least as effective as R-CHOP in two phase III trials and is considered an alternative induction regimen for older MCL patients [80, 81]. Both trials did not include rituximab maintenance. In addition, the bortezomib-containing induction regimen, bortezomib/rituximab/cyclophosphamide/doxorubicin/prednisone (VR-CAP), has been shown to be more effective than R-CHOP in patients with newly-diagnosed MCL in a large phase III trial, but this is at the cost of increased haematological toxicity [82]. The addition of dose-adapted high-dose cytarabine to BR (i.e. R-BAC) in elderly patients has shown excellent response and PFS rates in a phase II trial, but it is also associated with considerable haematological toxicity [83]. Preliminary results from a follow-up trial using a reduced cytarabine dose have recently been presented demonstrating reduced toxicity while preserving efficacy [84]. Therefore, this regimen might be considered in very fit older patients. Currently, a large randomised phase III trial comparing R-CHOP versus alternating R-CHOP and rituximab/cytarabine/dexamethasone (R-HAD) in older patients is open for accrual [85].

For vulnerable patients with comorbidities and/or impaired organ function, dose-adapted chemo-immunotherapeutic regimens are appropriate. Options include dose-reduced BR, R-CVP or R-CLB.

For vulnerable patients with more severe comorbidities, no standard of care exists. A number of less intensive therapies are available including R-CLB, (dose-reduced) BR or the oral metronomic combination of prednisone/etoposide/procarbazine/cyclophosphamide (PEP-C) [86–88]. Rituximab monotherapy is another option for elderly patients unable to tolerate chemotherapy. However, the objective response rate with single-agent rituximab is low (27%) and, in contrast to findings in FL, patients receiving prolonged treatment did not show an improved clinical response [89].

Recently, chemotherapy-free regimens (e.g. lenalidomide plus rituximab) have shown promising results as a first-line regimen for MCL, with good tolerability [90]. In addition, high response rates and long-lasting remissions have been reported with the bruton tyrosine kinase inhibitor, ibrutinib, in relapsed or refractory MCL, with a favourable safety profile [91, 92]. It is tempting to speculate whether vulnerable patients may particularly benefit from these new drugs. Unfortunately, to-date no data are available from clinical trials for this subset of patients and therefore clear recommendations cannot be made.

Relapsed/refractory disease: As with first-line treatment, the choice of second-line and subsequent treatment should be adapted to the age and PS of the patient with relapsed or refractory disease. After a long-lasting remission, repetition of the first-line treatment can be considered. Otherwise, in elderly fit patients, non-cross-resistant drugs and combination regimens should be preferred as salvage treatment. In subsequent relapse or in elderly vulnerable patients, monotherapies with targeted drugs (in particular ibrutinib [91, 93], lenalidomide ± rituximab [94], temsirolimus ± rituximab [95] or bortezomib [96]) as well as well-tolerated, dose-adapted chemotherapy combinations and palliative radiotherapy should be considered.

Panel recommendations for treatment in routine clinical practice.

Recommendation 5.2: For elderly fit patients, the following chemo-immunotherapeutic regimens are recommended as the preferred first-line treatment options in routine clinical practice:

1. R-CHOP followed by rituximab maintenance
   Level of evidence: I
   Strength of recommendation: A
2. BR
   Level of evidence: I
   Strength of recommendation: A
3. VR-CAP
   Level of evidence: I
   Strength of recommendation: A
4. R-BAC
   Level of evidence: V
   Strength of recommendation: B

Consensus: 100% yes (23 voters)

Recommendation 5.3: For vulnerable elderly patients, dose-adapted chemo-immunotherapeutic regimens are considered appropriate. Options include dose-reduced BR, R-CVP or R-CLB.
Level of evidence: V
Strength of recommendation: B
Consensus: 100% yes (23 voters)

Recommendation 5.4: For vulnerable patients with severe comorbidities, mild chemo-immunotherapeutic regimens like R-CLB, (dose-reduced) BR or PEP-C are considered appropriate.
Level of evidence: V
Strength of recommendation: B
Consensus: 100% yes (23 voters)

Recommendation 5.5: While newer targeted drugs like ibrutinib and lenalidomide might offer benefits, particularly in vulnerable patients, no data are available from clinical trials for this subset of patients and therefore clear recommendations cannot be given. For relapsed or refractory disease, treatment should be adapted to the age and PS of the patient. Besides non-cross-resistant combination regimens, treatment options include:

1. Ibrutinib
   Level of evidence: II
   Strength of recommendation: A
2. Lenalidomide ± rituximab
   Level of evidence: II
   Strength of recommendation: B
3. Temsirolimus ± rituximab
   Level of evidence: II
   Strength of recommendation: B
4. Bortezomib
   Level of evidence: V
   Strength of recommendation: B

Consensus: 100% yes (23 voters)

6. Diagnostic work-up and treatment of elderly patients with PTCL

PTCL comprises a very heterogeneous group of diseases and the incidence rates of each subtype varies by geographical region. In Europe, the top three subtypes are PTCL not otherwise specified (34.3%), angioimmunoblastic (28.7%) and anaplastic large-cell lymphoma (ALCL) (15.8%) [97]; treatment recommendations in this article refer to these three subgroups, which are largely the most common forms and, importantly, are treated similarly in the elderly population. The median age of presentation of these diseases is typically over 60 years [97], the only exception being anaplastic lymphoma kinase (ALK)+ ALCL. Treatment goals for elderly patients with PTCL may be stratified according to fitness at presentation and thus often differ from treatment of young fit patients, for whom dose intensification and transplant play a major role [13]. In elderly fit patients, the aim of treatment is to induce a CR with induction therapy since attainment of a CR correlates with the best outcomes for PTCL [98]. For vulnerable patients, the aim of treatment is to control disease using treatment-adapted regimens according to end organ deficit and comorbid conditions. For terminally ill patients, it may be appropriate to offer palliative control to maintain a reasonable quality of life.

Diagnostic work-up for elderly patients with PTCL. Due to the heterogeneity in disease subtypes of PTCL, histological confirmation by excision biopsy is mandatory, and in some circumstances, incisional core biopsy may be sufficient. The histological diagnosis of PTCL should be made according the World Health Organization (WHO) Classification 2008 [99] and requires an expert haematopathologist to gather the histological, immunophenotypical and molecular (if required in difficult cases) results and combine these with the clinical presenting features to categorise the final diagnosis. Recently, advances in our understanding of the biology of some specific subtypes have revealed unique hallmark identifications, such as expression of CD10, CXCL13 and programmed cell death ligand-1 (PD-L1), suggesting a follicular helper T-cell of origin [100, 101].

The diagnostic work-up requires full staging investigations, including CT with iodine staging scans of the neck, chest, abdomen and pelvis. PET-CT scanning should be considered for elderly fit patients when curative intent is considered possible, since PET appears to be particularly useful for identifying extranodal disease such as in the gastrointestinal tract which is often observed in PTCL [102]. The recent consensus guidelines recommend PET-CT for FDG-avid lymphomas which encompass the three most common PTCL subtypes [78]. BM examination should only be undertaken in those patients for whom the treatment approach is curative. For all patients where anthracycline therapy is being considered, a baseline electrocardiogram and left ventricular ejection fraction (LVEF) assessment are recommended.

Panel recommendations for diagnostic work-up.

Recommendation 6.1: The final histological diagnosis requires full analysis and integration of the clinical context and expert haematopathological review.
Level of evidence: IV
Grade of recommendation: A
Consensus: 100% (23 voters)

Treatment of elderly patients with PTCL. Unlike high-grade B-cell lymphomas, PTCL is characterised by a higher incidence of early relapse and refractory disease. Although several trials have addressed the need to optimise CHOP, this regimen still remains the first-line treatment of choice for elderly PTCL [103], although remissions may not be durable. In order to maintain dose intensity, all patients should receive growth factor support. Agents such as etoposide and alemtuzumab have been added to the CHOP-21 backbone, but were proven to be either too toxic

[104] or non-beneficial [105] for more elderly patients. New trials are urgently required to test less toxic agents either in addition to the CHOP backbone or as a maintenance strategy to prevent relapse, and the authors strongly recommend entering patients into clinical trials whenever possible. In the younger population, consolidation with autologous stem cell transplantation (ASCT) in patients achieving a CR has been shown to improve long-term outcomes [106]; however, the applicability of this approach, although desirable, is seldom achieved in the elderly population except for in the fittest patients. The assessment of elderly patients for suitability to a more intensive approach based on optimal organ function and the presence of comorbid disease is key to decision making. In these circumstances, dose attenuation of chemotherapy or entry into a clinical trial should be considered. To aid treatment decision making, the conventional International Prognostic Index (IPI) may be helpful in selecting high-risk patients for more intensive approaches if fit enough [97, 105, 107]. Although most patients with PTCL present with advanced disease, for patients who present with early stage disease, an attenuated chemotherapy schedule followed by local radiotherapy may be appropriate. For terminally ill patients, management should be with a view to preserving quality of life and symptomatic control.

The occurrence of relapse or refractory disease in the elderly patient is associated with a very poor prognosis, and the subsequent treatment decision is dictated by patient fitness to receive a salvage regimen with gemcitabine or platinum-containing agents. In the rare instances when patients are considered fit enough, ASCT may be appropriate providing a satisfactory response is attained, ideally a CR. Patents unsuitable for this intensive approach should be offered novel agents when appropriate, such as brentuximab in ALCL [108] or other CD30+ T-cell lymphomas, or be entered into clinical trials testing novel agents.

Panel recommendations for first-line treatment in routine clinical practice.

Recommendation 6.2: Whenever possible, patients should be entered into clinical trials. First-line regimes for elderly patients should be based on a CHOP induction backbone.

Level of evidence: III
Strength of recommendation: B
Consensus: 100% (23 voters)

Panel recommendations for salvage treatment in routine clinical practice.

Recommendation 6.3: Whenever possible, patients should be entered into clinical trials testing novel agents. However, for elderly relapsed patients considered unsuitable for clinical trials, treatment options include:

1. Salvage chemotherapy with gemcitabine or platinum-containing agents
   Level of evidence: IV
   Strength of recommendation: C
2. Novel agents such as brentuximab monotherapy for patients with CD30+ T-cell lymphoma
   Level of evidence: III
   Strength of recommendation: B

Consensus: 100% (23 voters)

7. Diagnostic work-up and treatment of elderly patients with DLBCL

DLBCL is the most common subtype of NHL, with an incidence of 45 per 100 000 in persons aged 60–64 years, rising to 112 per 100 000 in those of 80–84 years [109]. In contrast to the other lymphoma subtypes discussed so far, DLBCL is a curative disease. The treatment of elderly patients with DLBCL is unsatisfactory, with decreasing OS rates observed with increasing age [110, 111]. Reasons for this are multifactorial and include an increased incidence of comorbid conditions, decreased physiological reserve and decreased functional capacity, all of which are associated with advancing age. Given this, in contrast to young fit patients, dose intense regimens are often not feasible in this elderly population [10]. Recent seminal publications have confirmed that R-CHOP is the gold standard in patients aged 60–80 years [112], but it should be noted that these studies did not include patients of >80 years. Optimal categorisation of elderly patients who are fit to receive curative regimens is required to ensure a consistent approach to decision making for the elderly patient diagnosed with DLBCL.

Diagnostic work-up for elderly patients with DLBCL. The diagnosis of elderly patients with DLBCL who are fit for curative treatment should follow standard diagnostic guidelines used for younger patients [10]. This requires resource from a haematopathology laboratory with expertise in morphology and the ability to carry out immunophenotypic [immunohistochemistry (IHC) or fluorescence-activated cell sorting (FACS)] and molecular investigations, should they be required [level of evidence (LoE) V, grade of recommendation (GoR) A]. A minimum set of B-cell IHC markers should be carried out to include CD20, CD22, CD79a and CD10. A cell of origin phenotype may be obtained based on IHC, but it is not recommended to base clinical decisions on these results. Epstein–Barr virus (EBV) confirmation by EBER-1 staining is helpful to confirm a diagnosis of EBV-positive DLBCL. The concurrent IHC expression of both MyC and BCL-2 is associated with a poor prognosis [113].

Patients should be carefully examined for evidence of comorbid illnesses, impaired PS and functional deficits. A comprehensive geriatric assessment (CGA) is desirable and recommended to aid categorisation into fit, vulnerable and terminally ill patients. Routine haematological and biochemical blood investigations, including LDH assessment, are required. Serology screening should be carried out for hepatitis B [hepatitis B core antibody (anti-HBc) and hepatitis B surface antigen (HBsAg)], hepatitis C and HIV status. Vitamin D level evaluation could be taken into consideration, since low levels may result in an inferior treatment outcome.

Staging should be carried out according to the Ann Arbor classification [I, A]. PET-CT should be carried out in patients who are candidates for curative treatment. If the PET-CT demonstrates BM involvement, BM biopsy is not required. However, if the PET-CT fails to demonstrate this, in cases of early stage disease, a BM biopsy may be appropriate. Further imaging with magnetic resonance imaging is indicated if central nervous system disease is suspected, and a lumbar puncture may be carried out, if feasible, to detect leptomeningeal disease. All patients who are candidates for anthracycline-based treatment require

baseline LVEF estimation. Prognostic index scoring should be carried out, and the IPI should be calculated [I, A], but it should be recognised that this index allocates one point for an age of >60 years, but does not stratify the very elderly (>80 years). The recently devised NCCN-IPI, as well as other elderly prognostic indexes [114, 115], have refined their categorisation according to age, with higher weighting allocated according to advanced age [18]. This is important as newer trials focussing specifically on elderly patients will require more refined risk scoring to aid stratification to more intensive treatment approaches.

Panel recommendations for diagnostic work-up.

Recommendation 7.1: For patients treated with curative intent, diagnosis should be carried out in an expert haematopathology laboratory with full diagnostic capabilities (immunophenotypic and molecular) and staging should be with PET-CT.

Level of evidence: V
Strength of recommendation: A
Consensus: 100% yes (23 voters)

Recommendation 7.2: Cardiac assessment (LVEF) is required for patients treated with curative intent.

Level of evidence: V
Strength of recommendation: A
Consensus: 100% yes (23 voters)

Recommendation 7.3: The IPI score should be calculated.

Level of evidence: I
Strength of recommendation: A
Consensus: 100% yes (23 voters)

Panel recommendations for treatment in routine clinical practice.

De novo disease: Six to eight cycles of R-CHOP-21 are a widely used standard treatment of elderly fit patients aged 60–80 years. However, there are no prospective data to show that six cycles of R-CHOP-21 are as effective as eight cycles.

A large randomised phase III trial demonstrated equivalent efficacy and similar toxicity with eight cycles of R-CHOP-21 and eight cycles of R-CHOP-14 in treatment-naïve elderly patients of this age group [116]. In the German RICOVER-60 trial, six cycles of R-CHOP-14 were superior to eight cycles of R-CHOP-14 in patients of the same age group [112]. Six cycles of R-CHOP-14 has the advantage of a shorter duration of chemotherapy compared with eight cycles R-CHOP-21 (71 versus 149 days) and reduced exposure (only three quarters of the total chemotherapy dose). Thus, six cycles of R-CHOP-14 with eight doses of rituximab are an alternative treatment regimen for elderly patients who tolerate this dose dense regimen.

All patients above 65 years should receive prophylactic granulocyte-colony stimulating factor since the highest incidence of treatment-related mortality occurs within the first two cycles [117]. Emerging data in the fit very elderly (>80 years) patients with no existing comorbidities suggest that full-dose-intensity R-CHOP may be detrimental [118, 119], with reports suggesting inferior results in this age group. This is supported by the encouraging results for the >80-year-old group treated with the mini R-CHOP regimen, who achieved a 2-year OS rate of 59% with mini R-CHOP [120], and 2-year OS rate of 64.7% with ofatumumab and reduced-dose CHOP (OFA-mini-CHOP) [III, B] [121]. However, carefully selected patients could still receive full-dose CHOP.

Regarding the group of vulnerable elderly patients with comorbidities, especially cardiac, which may contraindicate anthracycline use, substitution of doxorubicin by drugs such as gemcitabine, etoposide or a liposomal formulation of doxorubicin may be beneficial [III, C] [122, 123]. In cases where a high tumour load is evident, a steroid pre-phase is recommended to optimise PS and decrease the risk of tumour lysis syndrome [I, A]. The use of radiotherapy to sites of bulky disease (>7.5 cm) should also be considered, since a recent study has shown that it improves outcomes for elderly patients in this setting [II, C] [124].

In clinical practice, it is often difficult to discriminate who should receive full-dose curative approaches. CGAs are helpful in the decision-making process regarding who should receive full-dose R-CHOP, and their use is recommended [III, C] [125, 126]. Further prospective studies are required to test and optimise these strategies, preferably with time-efficient assessments to inform DLBCL risk stratification, both within the clinical trial setting and in routine clinical practice. Repletion with vitamin D is generally recommended in patients with vitamin D deficiency, as rituximab-mediated cellular cytotoxicity is reduced in vitamin D deficient patients [IV, B] [127].

Further emerging reports regarding the mechanisms of treatment failure with chemo-immunotherapy have been described, with enhanced drug clearance of rituximab observed in elderly male patients [128]; however, there is currently insufficient evidence to modify rituximab dosage for these patient subgroups until further prospective data are available. For terminally ill patients, the goal of treatment is to achieve a response and control of symptoms in a palliative approach, and to maintain quality of life as much as possible.

Relapsed DLBCL: For rare cases of patients who are <70 years old and fit enough to be considered for stem cell transplant, salvage treatments should be selected with the best chance of inducing remission, such as rituximab/dexamethasone/high-dose cytarabine/cisplatin (R-DHAP), rituximab/etoposide/methylprednisolone/cytarabine/cisplatin (R-ESHAP), rituximab/gemcitabine/dexamethasone/cisplatin (R-GDP) or rituximab/ifosfamide/carboplatin/etoposide (R-ICE) [129, 130]. If such patients cannot tolerate full doses, dose attenuation may be necessary. For patients who are transplant ineligible, salvage treatment may be offered with similar regimens as above, or other regimens which may be administered in the outpatient setting, such as rituximab/gemcitabine/oxaliplatin (R-Gem-Ox) [III, B] [131]. Other agents, such as bendamustine [132] and pixantrone [133], have been associated with some efficacy in these patients. Ideally, and if suitable, patients should be considered for clinical trials testing novel small molecules, novel immunotherapy approaches or maintenance strategies, as recently reported for lenalidomide [134]. For those patients with primary refractory disease, the outlook is very poor; however, consideration for clinical trials is an option for suitable patients.

Panel recommendations for treatment in routine clinical practice.

First-line treatment:

Recommendation 7.4: A CGA is recommended to guide treatment choice.

Level of evidence: III
Strength of recommendation: A
Consensus: 100% yes (23 voters)

Recommendation 7.5: The aim of treatment in fully fit patients who are <80 years old should be curative, with a full-dose anthracycline-based regimen preferred. R-CHOP is the recommended first-line treatment choice.

Level of evidence: I
Strength of recommendation: A
Consensus: 100% yes (23 voters)

Recommendation 7.6: For fully fit patients who are >80 years old without comorbidities, dose-attenuated R-CHOP may be appropriate.

Level of evidence: III
Strength of recommendation: B
Consensus: 100% yes (23 voters)

Treatment of relapsed patients:

Recommendation 7.7: For relapsed fit (no organ dysfunction, PS 0–1, no comorbidities), transplant-eligible patients, appropriate salvage treatment with R-DHAP, R-ESHAP, R-ICE or R-GDP is indicated. In the event of an adequate response, ASCT is recommended.

Level of evidence: II
Strength of recommendation: A
Consensus: 100% yes (23 voters)

Recommendation 7.8: For transplant-ineligible patients, dose attenuated R-DHAP, R-ESHAP, R-ICE, or less intense regimens such as R-Gem-Ox, are appropriate.

Level of evidence: III
Strength of recommendation: B
Consensus: 100% yes (23 voters)

Recommendation 7.9: For transplant-ineligible patients, single-agent chemotherapies such as bendamustine or pixantrone may be considered.

Level of evidence: I (pixantrone), II (bendamustine)
Strength of recommendation: C
Consensus: 100% yes (23 voters)

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Appendix

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