Review Article

Clinical geriatric assessment in older patients with lymphoma: a narrative review

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Background and Objective: Aging is a highly individualized global process involved in cancer pathogenesis, response to therapy and susceptibility to adverse events (AEs), resulting in physiological, medical, and psycho-cognitive changes. The attempt to stratify patients according to their fitness in order to define the best tailored treatment, thus avoiding under- or over-treatment, is an important issue of geriatric hematology. Chronological age and performance status (PS) evaluation do not account for the complexity of older patients; for this reason, comprehensive geriatric assessment (CGA) was recognized as a multidimensional, interdisciplinary diagnostic process focusing on determining an older person's medical, psychosocial, and functional capabilities to develop a coordinated plan to guide treatment decisions and long-term follow-up. Various tools and scores exploring different geriatric domains have been developed and validated. Aim of this review is to define the aging process in its aspects that influence lymphoma management and to summarize the available tools to define patient fitness, remarking the importance of performing a geriatric assessment (GA) in older patients affected by lymphoma.

Methods: We searched English reviews or original articles from January 1, 2007 to February 28, 2022 focused on the topic of GA and we performed a comprehensive revision of the different tools and their application in the field of lymphoma.

Key Content and Findings: This review describes the different and complex biological changes contributing to the aging process, the different tools available to define the fitness of older patients with aggressive lymphoma and the usefulness of GA in identifying risk categories with different overall survival (OS).

Conclusions: Defining fitness of older patients through a CGA is increasingly recognized as an indispensable way to support treatment decisions in older patients with aggressive lymphoma and this approach should in future be applied also in other lymphoma subtypes.

Keywords: Geriatric assessment (GA); lymphoma; older patients

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Introduction

Rationale and background

Sixty percent of patients affected by the most common lymphoma subtypes are older than 65 years, and this proportion will increase in the future due to the demographic changes and aging of the population (1).

At the same time, treatment options even for older patients have dramatically increased over the past years, driving the need of individualizing therapy in order to avoid under- or over-treatment (2,3). Furthermore, with the progressive improvement of socio-economic conditions and

Table 1 Search criteria

Items	Specification
Date of search	Search conducted between January 1, 2007 and February 28, 2022
Databases and other sources searched	PubMed database
Search terms used	Lymphoma, aging, frailty, immunosenescence, geriatric assessment, sarcopenia, elderly, chemotherapy
Timeframe	None specified
Inclusion and exclusion criteria	English-language papers published in peer-reviewed, international journals
Selection process	All authors participated in literature selection, conducted independently

supportive care measures, the overall performance of older patients has become progressively better, making many of them suitable for treatment approaches with curative intent. An important goal of geriatric hematology is to stratify patients according to their fitness and to identify the individual risk and prognosis, in order to define the best tailored treatment for each patient. Traditionally used lymphoma prognostic tools [such as International Prognostic Index (IPI)] do not account for the complexity of older patients and are inadequate to drive the decision-making process in this group of patients (4). Conversely, comprehensive geriatric assessment (CGA), can detect age-related problems not typically identified by a routine history and physical examination that may be predictive of mortality (5). Moreover, a risk-based approach for older patients should be different from that used for younger patients: in the former group, endpoints like the risk of hospitalization, the loss of physical or social functioning and a further deterioration of the quality of life may be as important as overall survival (OS) (4).

The recent interest addressed to geriatric oncology and more recently to geriatric hematology comes from the awareness that older patients were underrepresented in clinical trials. However, most of the recent studies involving this category of patients still lack a geriatric assessment (GA) and frail patients are still excluded.

Objectives

The present review aims to define the aging process in its aspects that influence lymphoma management in older people and to summarize the available tools and assessment scores to define patient fitness, highlighting recent acquisitions and future perspectives. We present the following article in accordance with the Narrative Review reporting checklist (available at https://aol.amegroups.com/article/view/10.21037/aol-22-6/rc).

Methods

A literature search was done addressed to the English reviews or original articles focused on the topic of GA in older people with cancers and in older patients with lymphoma from January 1, 2007 to February 28, 2022 (*Table 1*). Specific searches addressed to particular tools were done without time frame and some useful paper were considered even if published before.

Discussion

Aging

Aging is a complex natural process that progressively leads to loss of physiological integrity, with organ disfunction, increased inflammatory status and susceptibility to genetic damages and epigenetic modifications. Time-dependent accumulation of cellular alterations in post-mitotic and adult stem cells, which are responsible for maintaining tissue homeostasis (6), leads to transcriptional changes, telomere shortening, loss of proteostasis, disregulation of nutrient sensing, mitochondrial dysfunction, impaired cell-to-cell communication, and cellular senescence (7-9). These age-related changes affect a variety of tissues (adipose tissue, muscle, skin, mucosa) and organs (brain, liver, gut), with accumulation of senescent cells, increased release of pro-inflammatory components, resulting from cell death or damage, and enhanced activation of the coagulation pathway, all resulting in a pro-inflammatory state (10). A central player in aging-related alterations is the immune system, subject to a process defined "immunosenescence",

i.e., a multifactorial and dynamic adaptation/remodeling of both natural and acquired immunity resulting in decreased immune function (10). These alterations may lead to a low-grade, chronic, self-reactive inflammation called "inflammaging" (11) that plays a trigger role in most chronic diseases in older people, including cancer (12,13). These changes involve thymus and bone marrow and account for the increased frequency and mortality for infections in older people, found even during chemotherapy. In particular, neutrophils present impaired phagocytosis, degranulation and reactive oxygen species (ROS) production, accounting for the increased susceptibility to bacterial invasions and sepsis (10). Moreover, age-related decline in hematopoiesis and thymic involution reduces the pool of naïve T cells and amplifies the pool of oligo-clonal memory T cells, unbalancing the ratio between pro-inflammatory and regulatory T cells, with consequent reduced ability in preserving immune homeostasis and in responding to neoantigens (10,14). Age-related T-cell alterations need further investigation even at the light of the diffusion of adoptive cellular immunotherapy, in which various patient-derived immune cells are modified and re-infused, since their characteristics may be relevant in response to therapy (14). Overall, immunosenescence and inflammaging are involved in both cancer development and treatment-related problems.

Of note, not all old individuals present the same age-related changes: the genetic background and the immunobiography (i.e., the combination of lifelong immunological experience, sex, gender, diet, exercise, microbiome) account for the heterogeneity of the immune phenotype in older people (10).

The described biological events result in physiological, medical, and psycho-cognitive changes that make aging a multidimensional problem. Therefore, aging is a highly individualized process, and chronological age alone should no more guide clinical choices.

In summary, older patients have functional and immunological characteristics that are very different from younger ones and that may be different from one individual to another (10). Defining a patient's biological age is essential in order to best individualize treatment programs and requires a comprehensive assessment approach.

Aging staging

Since aging is a global process, involved in cancer pathogenesis, response to therapy and susceptibility to adverse events (AEs) (7,15), the 2018 European Society for Medical Oncology (ESMO) guidelines recommend to take into account different issues in the treatment decision process for older cancer patients: (I) the specific disease, to define the potential goal of therapy, (II) the available treatment, to define the toxicity risk, and (III) the patient's fitness and preferences, to better tailor treatment choices (2).

Disease-related issues

Based on the different nature of diseases and the available therapies, the goal of treatment may change: as far as aggressive lymphomas are concerned, there is a strict correlation between achievement of complete remission (CR) and OS, while this is not always true for indolent diseases. In diffuse large B cell lymphoma (DLBCL), proper immune-chemotherapy may lead to cure even in older people (16-19); since few of these patients can be later candidate for aggressive second-line therapies, the choice of an induction treatment with curative intent is even more challenging (20). Moreover, the unfavourable biologic and genetic profile observed in older patients with aggressive lymphoma (21) may justify an intensification of induction treatment (22). However, in this setting, aggressive-treatment may result in life-threatening side effects or compromised quality of life, while a reduction in the dose level or intensity may compromise the chance of achieving CR (23). Thus, patient selection is essential in order to avoid under- or over-treatment.

On the other hand, with the availability of oral targeted therapies, many patients with indolent lymphoma judged as "unfit" for chemotherapy may now be treated with the intent to prolong survival. However, also in this setting, critical issues, like adherence to therapy, drug-interactions, hematological and non-hematological side effects, may lead to treatment delay or discontinuation: approximately 50% of patients affected by chronic lymphocytic leukemia treated with ibrutinib in "real-world" undergo a dose modification and/or interruption, with the risk of reducing EFS and OS (24,25).

Lymphoma-related prognosis is an important issue to consider in the decision-making for old patients: since life expectancy may widely vary according to their health status, establishing prognosis based on treatment of the lymphoma and prognosis based on the competing risks of mortality is important for identifying patients who would benefit most from the optimal treatment strategies (3,7). The 2018 guidelines from the American Society of Clinical Oncology (ASCO) recommend the use of a validated tool to estimate

the "non-cancer" life expectancy, in order to individuate the goal of therapy based on the possibility that the patient will live enough to experience survival benefits from the cancer treatment (3).

Treatment-related issues

The decline in the functional reserve of different organ systems affects pharmacokinetics and pharmacodynamics of antineoplastic drugs, with enhanced drug toxicity.

Even if pharmacokinetic data are lacking in very old patients, some trials (26,27) demonstrated that reduced doses of antracycline in older patients led to similar outcomes, suggesting an increased half-life of drugs or drug metabolites; a decreased rituximab clearance has been observed in older female patients, even if there is not enough evidence to modify dosage (28). Aging is often associated with a decline in total body water, alterations in fat/muscle mass and decrease in albumin and hemoglobin concentration, leading to a reduction of the volume of drug distribution (29). Most antineoplastic drugs are administered according to body surface area (BSA), which account for height and weight, but not for body composition (adipose tissue and muscle mass). There is some evidence that pharmacokinetics and drug toxicity are more associated with lean body mass than with BSA (30,31). In particular, a recent study observed that grade 3–4 toxicity during or after rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) for DLBCL was associated with poorer body composition (reflecting a loss of muscle) measured by computed tomography (CT) scan (32). Further studies will be necessary to confirm these results and to develop novel dosing strategies, but probably the different fat/muscle distribution in older patients may only partially explain the more elevated toxicity rate. Renal and hepatic functions are often decreased in older people; the decline in glomerular filtration rate leads to reduced excretion of active drugs or metabolites (29) and the hepatic metabolism of drugs may be influenced by the decline in intracellular activity of P450 cytochrome enzymes and by interactions due to polypharmacy. In summary, drug absorption, distribution, metabolism and elimination are altered in older individuals, contributing to increased treatment toxicity and to the need of treatment modulation.

Pharmacodynamic changes may cause a reduced efficacy of the cytotoxic chemotherapy, due to increased prevalence of multidrug resistance and resistance to apoptosis (15). At the same time, in older individuals tissue susceptibility to the drug damage is enhanced by the decreased stem cell reserve that compromise the tissue recovery, by the cellular delay in DNA repair and by the pre-existing reduction in functional tissues so that a further damage may lead to organ failure (15). Older patients have higher rates of therapy-related cytopenia due to reduced bone marrow reserve and reduced neutrophils microbicidal activity, which account for increased susceptibility to invasive bacterial diseases (10). However, older patients maintain an adequate response to granulocyte-colony stimulator factors (G-CSF), so that G-CSF prophylaxis reduces mortality in older patients treated with chemotherapy (33) and its use is therefore recommended by international guidelines (34). At the same way, to counteract a major incidence of tumor lysis syndrome in this group of patients, the use of a pre-phase treatment becomes of paramount importance. Antracyclines are at the basis of many chemotherapy regimens, but their utilization is limited by cumulative dose-related cardiotoxicity, with progressive myocardial damage resulting in congestive heart failure (CHF). The incidence of cardiotoxicity is higher in patients older than 65 years, with a median time between end of therapy and development of clinical cardiotoxicity of 3.5 months; a careful assessment of cardiovascular profiling at baseline and close surveillance with cardiac biomarkers/imaging within 3–4 months from the beginning of chemotherapy are particularly important in older people (2,35). Modulation of chemotherapy dosage has been proposed by different authors with the same purpose, obtaining interesting results in aggressive lymphoma (36,37). Nevertheless, the rate of toxic death rate in older patients is exacerbated (7).

Screening tests to predict toxicity have been developed in oncology and are recommended by 2018 ASCO guideline (3). The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score predicts chemotherapy-related grade 3 hematologic and grade 3–4 non-hematologic toxicity; it has been validated for patients aged ≥70 years and its administration takes 20–30 minutes (38). The original cohort included 78 out of 518 patients with non-Hodgkin lymphoma (NHL) treated with CHOP regimen, but the score has not been validated in other hematological settings (rituximab-containing therapy, other regimens). The Cancer Aging and Research Group toxicity tool (CARG-TT) is a shorter tool (less than 5 minutes to complete) that calculates the risk of any grade 3 to 5 toxicity, validated for patients aged ≥65 years (39,40). Lymphoma patients were not included in the first paper; subsequent studies conducted in the hematological setting obtained contrasting results (41,42). Therefore, new studies are needed to

establish the usefulness of toxicity predictive tools in the hematological field. A study from Miura *et al.* moves in this direction, with the development of a score defined as the Age, Comorbidities, and Albumin (ACA) index, considering age >75 years, serum albumin level <3.7 g/dL, and Charlson Comorbidity Index (CCI) score ≥3. This score stratifies prognosis, tolerability to cytotoxic drugs, and adherence to treatment of older patients with DLBCL treated with R-CHOP (43,44).

Patient-related issues

Since aging is an individualized condition, "staging the aging" (45) is essential to establish patient fitness to guide therapeutic choices. Although there are no standard definitions for this term, in geriatric oncology "fitness" describes the condition in which a patient may be usefully treated similarly to a younger one without increased risk of AEs, since the hematological malignancy alone is the crucial factor that could alter his life expectancy (2). On the other hand, "frailty" describes a condition in which most functional reserves are exhausted (9,46) with reduced tolerance to stressors and greater risk of adverse health outcomes and disability (47); therefore, frail patients would probably not benefit from any active treatment but only from best supportive care (2). Patients who do not meet criteria for "fitness" or "frailty" are usually defined as "unfit", "vulnerable" or "pre-frail" and are at high risk of treatment-related and unrelated AEs if treated with standard therapy (2). In this last group, the choice of a tailor-made treatment is of particular importance.

The assessment of these categories has traditionally been based on the evaluation of different domains described by an expert panel of geriatric oncologists: functional status, comorbidity, cognition, mental health status, nutrition, social status and support, fatigue, polypharmacy and presence of geriatric syndromes (48). Various tools are available to investigate these domains, differently associated to build a CGA. The superiority of one tool over another has not been proven and choice of instrument might rely on local preference, aim of the tool, or resources (48). Since different diseases are characterized by different prognosis and treatment-related toxicity, the criteria for defining patient's fitness may also vary (2,49). For example, the proportion of older patients who may be considered fit for standard treatment is likely higher in indolent than in aggressive lymphomas. In the same way, fitness for a transplant suitability may require more stringent parameters. Therefore, in order to better manage hematological older patients, specific scores have been developed and are under evaluation in clinical practice (19,50-52).

Since geriatric impairments are associated with treatment-related toxicity, treatment non-completion and mortality (5,53), current guidelines agree in suggesting some form of GA in older patients with hematological malignancies (2,3,54,55). In particular, ESMO Consensus Conference on malignant lymphoma (2) recommends GA in patients aged 70 and older receiving chemotherapy for aggressive and indolent lymphomas. Garric analyzed the impact of CGA on decision making in older patients with hematological malignancies. The change in treatment plans that he observed in 21.7% of patients (56) confirms the 28% reported by Hamaker describing the effect of a geriatric evaluation on treatment decisions and outcome for older patients with hematologic and solid neoplasms (57).

Other than informing patients' prognosis and fitness to standard treatment, evidences are accumulating that GA can be useful in designing therapeutic algorithms: some studies evaluated modified regimens or therapy dosages based on GA with promising results (36,37,58-60). Further studies are needed to identify the best GA-based algorithm for treating patients and their effect even on outcomes other than survival. Actually, there is a lack of studies investigating the association between geriatric impairments and endpoints considered important by older patients, such as quality of life and function after treatment (61). Incorporating patient-reported outcome measures (PROMs) would be important to better guide treatment decisions (46).

In addition, GA might be a useful tool to identify problems liable to specific non-oncological actions aimed to enhance quality of life and treatment tolerance. In the oncologic setting, some evidence is emerging that the implementation of GA-guided cares may improve patients' outcome (62-64). In the hematological context data are lacking, even if a cooperation between hematologists and geriatricians is increasingly looked at as the best way to enhance subsequent treatment options and outcomes (46,65). An example of this collaboration in the hematological setting has been recently described by Wall: when referred to geriatric evaluation, specific interventions were recommended in a large portion of patients; in particular, pharmacy modifications were indicated in 54% of patients, nutrition supplementation in 44%, and rehabilitative therapy in 37% (66). Evidence is required to evaluate if these actions would enhance patients' hematological outcome.

Furthermore, GA has been essentially evaluated at

baseline as a mean to define patients' prognosis and fitness to treatment. Recent observations suggest that GA might likely be extended in a longitudinal way, to inform supportive care interventions even during therapy and survivorship care, in order to enhance quality of life, treatment tolerance and recovery (65). Indeed, chemotherapy has significant impacts on aging biology, which may result in functional and cognitive decline. Therefore, a follow-up GA was recommended especially if a subsequent therapeutic modality is planned, such as consolidative autologous transplantation or maintenance.

Geriatric tools

Many tools are available to evaluate functional status, comorbidities, physical performance, psycho-cognitive functions and socio-economic environment.

(I) Functional status

Impaired abilities are one of the main factors to assess, since they appeared to predict hospitalization (67) and mortality (53).

(i) Eastern Cooperative Oncology Group (ECOG)/ Karnofsky performance status (PS) score

ECOG PS (68) is the most traditionally used tool to assess functional status and to predict tolerance to treatment, but PS alone is inadequate and should not be used as the only measure of an older patient's function (69,70). A recent review from Scheepers revealed a median proportion of patients with at least one geriatric impairment of 51%, compared with a median proportion of patients with ECOG PS ≥2 of 29% (5). Especially in very old patients, the current PS does not discriminate disease-related issues from pre-existing conditions: the symptoms related to the onset of a malignant hemopathy may temporarily worsen a patient's PS, with a rapid improvement after a short course of pre-phase therapy. Therefore, PS mainly refers to current disease status while the GA must be referred to the pre-existing patient's condition (6,60).

(ii) Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL)

ADL score evaluates the patient need of help in basic daily activities (bathing, dressing, toileting, transferring, continence, feeding), while IADL score evaluates the patient dependence in activities necessary for living alone in the community (ability to use telephone, shopping, food preparation, housekeeping, laundry, mode of transportation, responsibility for own medications). In the recent review from Scheepers, impairments in ADL are recognized in 18% (range, 4–67%) and in IADL in 37% (range, 3–85%) of older patients (5). The association between these scores and survival is well defined: in multivariate analyses, they are associated with mortality in both indolent and aggressive NHL (5,71). Remarkably, an association of ADL and IADL with prognosis has been found even in Hodgkin lymphoma (HL) patients, a context in which there is a paucity of data compared to NHL. A retrospective study on older patients affected by HL showed that International Prognostic Score (IPS) was not prognostic in this subset of patients, unlike age >70 years and loss of ADL (72); in a more recent prospective study, loss in any IADL was associated with an inferior PFS in multivariable analysis (73).

(II) Comorbidity scores and polypharmacy evaluation

The presence of comorbidities is associated with decreased life expectancy in general population and cancer patients (74). About 2/3 NHL patients older than 60 years have at least one comorbidity, and the presence of two or more is associated with a reduced 5-year OS compared with their absence (75). The type of comorbidity is also important: heart disease, diabetes, chronic obstructive pulmonary disease and renal failure are high impact comorbidities; when present, the risk of death in NHL is twice as high compared with patients without comorbidity independently from IPI score (76).

Different comorbidity indexes have been applied to assess the risk of death and therapeutic complications due to pathological conditions other than cancer (77), including CCI (78) and Cumulative Illness Rating Scale-Geriatrics (CIRS-G) (79). Both scores have been incorporated into various GAs after correction for hematological comorbidities.

Even the polypharmacy, defined as the assumption of three drugs or more, has been associated with prognosis, maybe for the correlation with the presence of comorbidities (5).

(III) Physical performance

(i) Nutrition

Malnutrition is quite common in older people, due to different causes such as decreased threshold for bitter taste, increased threshold for sweet taste, decreased gastric secretion, depression, forgetfulness, limited mobility, decreased ability to feed oneself and it is associated with increased chemotherapy toxicity (31). The risk of malnutrition is present in about half of older hematologic patients (5,53) and may be evaluated by objective parameters [body mass index (BMI)], specific tools [Mini Nutritional Assessment (MNA)], or laboratory parameters (serum albumin level).

MNA (80) is a short nutritional screening tool combining

anthropometric measures with risk factors for malnutrition; it takes 10–15 minutes to complete. In a prospective study by Aaldriks, altered MNA score was associated with treatment withdrawal and mortality in older patients treated with R-CHOP for NHL (81).

Low serum albumin is a laboratory finding associated with malnutrition, even if it can also reflect disease activity and inflammatory state; different studies revealed a presence of hypoalbuminemia in about 1/3 of older patients with different NHL subtypes and recognized an association with prognosis (27,82-85).

(ii) Sarcopenia

Sarcopenia is a disorder characterized by progressive and generalized loss of skeletal muscle mass and function, associated with increased adverse outcomes including falls, functional decline, frailty, and mortality (86). Sarcopenia may occur during normal aging and is highly prevalent in older individuals (87), showing a significant overlap with frailty. Age-related sarcopenia results from inflammaging and altered balance in protein synthesis and degradation typical of older age; pro-inflammatory cytokines, malnutrition, and reduced physical activity contribute to affect muscle mass (88,89).

The European Working Group on Sarcopenia in Older People (EWGSOP) published in 2018 the revised guidelines, recommending the determination of both muscle function (through grip strength or chair stand test) and muscle mass [through dual-energy X-ray absorptiometry (DXA), magnetic resonance imaging (MRI), or CT] for the diagnosis (86). In particular, low muscle strength is the primary parameter for sarcopenia, while detection of low muscle quantity and quality confirms the diagnosis and poor physical performance is indicative of severe sarcopenia (86).

In solid neoplasms, sarcopenia has been associated with an increased risk of death, reduced tolerance to chemotherapy and decreased quality of life (90-93). Evidences are accumulating even in the hematological setting, especially in DLBCL (88) and HL (94), in particular for male patients (94,95). A recent meta-analysis from Xu *et al.*, conducted for evaluating the predictive value of sarcopenia, associates sarcopenia with poor OS and PFS, lower rates of CR and of treatment completion in patients with DLBCL treated with R-CHOP (88). The weakness of the majority of these studies is that the diagnosis is often based only on imaging and not on strength measures, and that different definitions and cut off are applied; furthermore, sarcopenia is often not well differentiated by "cachexia", a different clinical condition according to the more recent definition (86). New studies taking into account the recent definition of sarcopenia are ongoing to better evaluate its role as a prognostic risk factor in patients with different types of lymphoma (NCT03552003).

(iii) Strength objective measures

Different tests have been developed to objectively determine strength in older patients. Among these, gait speed and grip strength have been evaluated by Liu *et al.* in patients aged 75 years and more with hematological malignancies (67). Gait speed was obtained through the 4-m gait speed test, taking less than one minute; grip strength was measured using a hydraulic hand dynamometer. Each 0.1-m/s decrease in gait speed was associated with increased mortality and unplanned hospitalizations, with the strongest association in the subgroup of patients with NHL, even in patients with ECOG PS 0–1. Grip strength also correlated with survival but its interpretation is more challenge, so the authors suggest its utilization in patients in which a gait speed cannot be obtained (67). Gait speed is shorter and less tiring than other tests such as the Short Physical Performance Battery (SPPB) and safer than Get Up and Go (GUG) test.

This test has an independent value in predicting mortality because walking is a complex function, integrating different physiologic systems: the central nervous system, the peripheral nervous system, the perceptual system, muscles, bones/joints, and energy production/delivery (45). Therefore, dysfunctions of all these systems may converge to impact gait speed, which may be considered as a measure of patient's functional status.

(IV) Psycho-cognitive function

A cognitive impairment is present in 17% (range, 0–44%) of older hematologic patients and was associated with mortality (5) and with treatment-related mortality (96). In particular, in a recent prospective study, impaired working memory was associated with worse median survival in multivariate analysis when adjusting for age and comorbidities, either in indolent and aggressive hematological cancers (97).

Mini Mentale State Examination (MMSE) (98) is considered the standard test to evaluate current cognitive function, with a sensitivity of 88% and a specificity of 93% if administered by a professional, taking approximately 15 minutes. Shorter tests with similar sensitivity and specificity are the mini-Cog (99) and the Blessed Orientation-Memory Concentration (BOMC) test (100), both suggested by 2018 ASCO guideline to screening cancer patients for cognition deficits (3).

Symptoms of depression were reported in 25% (range,

10–94%) of older patients by Scheepers (5) and clinically significant depression has been associated with mortality, unexpected hospitalizations, and treatment-intolerance in patients with solid neoplasms, so that 2018 ASCO guideline recommend the evaluation of the Geriatric Depression Scale (GDS) as part of GA (3).

(V) Socio-economic environment

From a psychosocial perspective, the family relationships, the integration in the social context, and the cultural level of a patient may influence the possibility of cure, together with the geographic difficulty in reaching the specialized center. The presence of a caregiver is essential for timely management of AEs and for physical assistance to the patients during therapies (15). Moreover, as reported by Cohen, individuals with lower education and living alone were more likely to fall in the prefrail and frail groups (101), probably due to the association with geriatric conditions such as malnutrition.

GA scores

In order to evaluate at best the global condition of older patients, a multidimensional approach including different of the reported tools has been studied in hematology. A CGA is proved to be an efficient method to stratify older lymphoma patients in order to evaluate their suitability for treatment (19,69,102). Since a complete CGA is time-consuming, requiring more than 1 hour to be concluded thus limiting its use in the daily clinical practice, different abbreviated forms of GA have been validated in NHL. Moreover, the applicability of these abbreviated scores has been demonstrated as feasible either in clinical trials and in real-life oncological settings (19,103).

(I) Simplified CGA (sCGA) and Elderly Prognostic Index (EPI)

A sCGA that includes age (≥80 *vs.* <80 years), comorbidities (according to CIRS-G score, without assessing hematological comorbidities), ADL and IADL has been validated in a cohort of 173 patients >69 years old affected by DLBCL in a study from the Fondazione Italiana Linfomi (FIL) (18). According to this sCGA, three geriatric risk categories (fit, unfit, and frail) are defined. Patients are considered "fit" if they satisfy all of the following conditions: age <80 years, ADL score 6, IADL score 8, CIRS-G: no grade 3–4 comorbidities and fewer than five grade 2 comorbidities. They are considered "unfit" if they have: age >79, ADL 6, IADL 8, CIRS-G: no grade 3–4 comorbidities and fewer than five grade 2 comorbidities; or age <80, ADL 5 and/or IADL 6–7 and/or CIRS-G: no grade 3–4 comorbidities and 5–8 grade 2 comorbidities. All other patients are considered "frail". Patients in the study were treated according to physician's decision and not based on sCGA. A significant difference in OS was observed between fit and unfit/frail patients not explained by differences in treatment intensity; moreover, patients in the unfit and frail group did not show differences in OS according to have received curative or palliative treatment.

The recent study by the FIL (19) validated these results on a broader cohort of 1,207 patients. This larger prospective study allowed to further discriminate the unfit and frail categories through adding an age stratification, thus obtaining a new simplified version of GA (sGA) with three groups: group A, composed by fit and unfit patients younger than 80 years; group B, composed by unfit patients aged ≥80 years and frail patients aged <80 years; and group C, composed by frail patients aged ≥80 years. These three groups have a significantly different 3-year OS of 75%, 58%, and 43%, respectively. This score identifies a group of fit patients younger than 80 years who benefit from a full-dose therapy, a group of unfit patients still eligible for a curative approach with the possibility to use reduced doses in a tailored treatment approach, and a group of frail patients with dismal survival rates whose purpose of treatment still represents an unmet clinical need. Moreover, integrating sGA groups, IPI and hemoglobin level in a 7-point score, a prognostic index (EPI) was built, thus integrating functional and clinic-biological features. EPI identifies three risk groups (low, intermediate and high risk) accounting for 23%, 48%, and 29% of patients, respectively, with an estimated 3-year OS of 87%, 69%, and 42%, respectively. Performing sGA and EPI evaluation requires a few minutes and it has been shown to be feasible in a multicenter setting.

(II) Grupo Español de Linfomas y Trasplante Autólogo de Médula Ósea (GELTAMO) prognostic model

The Spanish GELTAMO group created a simple prognostic model based on multivariate analysis of 108 patients more than 80 years old and treated with R-CHOP-like regimens for DLBCL or grade B follicular lymphoma. The score includes age >85 years, R-IPI score 3–5, and CIRS >5. It identifies two risk groups: patients with 0–1 adverse prognostic factors with a median OS of 45 months, and patients with 2–3 adverse prognostic factors with a median OS of 12 months (102).

(III) Geriatric-8 (G8)

The G8 is a fast eight-item questionnaire resulting in a 17-point score, investigating food intake, weight loss, BMI, mobility, neuropsychological problems, polypharmacy, self-

perception of health, and age (104). It has been validated in different cohorts of patients with DLBCL (105-107) as a prognostic index and a useful screening tool for identifying patients who would benefit from a more complete comprehensive assessment, with a score ≤14 indicating the need for a CGA: it has a sensitivity of 85% and a specificity of 64% in detecting frailty (108), thus leading to a high false positive rate. Interestingly, the study by Lee *et al.* (107) identified a lower cut-off value of ≤9.5 as more specific and maintaining a relatively high sensitivity. Furthermore, in this retrospective study, the total average dose intensity (tARDI), defined as the average delivered dose intensity divided by the planned dose intensity through all cycles, was recorded. In the group of patients with G8 score ≤9.5, the mortality risk was higher independently from the tARDI; conversely, in the group of patients with G8 score ≥9.5 the correlation between the tARDI and mortality risk was linear, with a tARDI >80% associated with decreased mortality, thus suggesting that the upper limit of tARDI for standard regimens to improve OS might be appropriate at ≥80% for patients with high G8 scores. The authors suggest the use of this tool in order to stratify patients with DLBCL in terms of a dose adjustment for standard regimens rather than to identify frailty patients who cannot benefit from standard treatment with curative intent, since standard therapy improved OS in all G8 categories.

(IV) Vulnerable Elders Survey (VES-13)

VES-13 is a fast self-reported tool, consisting in 13 items that include age, self-related health, common functional tasks, and ability to complete physical activities (109).

VES-13 score ranges from a minimum of 0 (low risk for decline) to a maximum of 10 (greatest risk for decline), and a score ≥3 defines the patient as vulnerable. Fama *et al.* applied VES-13 in large cohort of 2004 NHL patients, finding that vulnerable status independently predicted 1-year mortality in patients ≥65 years, even in the subset of DLBCL patients treated with immunochemotherapy (110).

Summary and conclusions

Aging is a multidimensional and individualized condition frequently leading to vulnerability.

Lymphomas frequently affect older people, so that stratifying their fitness is essential in order to tailor therapy, thus avoiding under- or over-treatment. GA is superior to clinical judgment and to PS evaluation and is recommended before taking treatment decisions in older patients.

Vulnerabilities detected by GA are associated with treatment-related toxicity and mortality. Many geriatric scores have been validated in the hematological setting, with consistent results regardless of the specific tool used. Thus, a standardized GA has not been recognized worldwide, but different abbreviated and time-sparing GAs are available for clinical use.

Usefulness of GA is evident in the setting of aggressive lymphomas, where the treatment with curative intent has a strong impact on survival. However, the opportunity of performing a GA in older patients is emerging also in other lymphoma subtypes, such as HL (111,112) and even in indolent lymphomas (113). In this last setting, studies are needed to validate GA even by using endpoints different from survival, like quality of life, and exploring new target therapies that, despite being noncytotoxic, show peculiar and sometimes significant toxicities and whose specific effects on older patients are still largely unknown. Another field of interest for future investigations is that of cellular immunotherapies: some evidence is emerging about GA role even in selection of patients for CAR-T cell treatment (114).

A next step, after the early recognition of the frailty status, will be the promotion of multifactorial rehabilitation programs, to improve muscle mass and strength, physical and cognitive performance with the purpose to prevent or delay disabilities in people aged 70 years or more.

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