Review article


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\textbf{ABSTRACT}

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma in the elderly, and is increasing in incidence. Although significant therapeutic advances have recently been made in the care of older patients with DLBCL, based upon results of randomized clinical trials, many older patients are not eligible for such trials due to comorbidities and functional decline. Pre-treatment evaluation of older patients to ascertain potential tolerance to therapy is especially important in therapeutic decisions for this population. Evaluation by performance status alone is insufficient, especially in the elderly, and consideration of the impact of comorbidities and functional/social decline needs to be included in such assessment. As part of an International Society of Geriatric Oncology (SIOG) task force, the issues of prognosis, comorbidities, geriatric assessment, and supportive care measures in older patients with DLBCL will be reviewed, and recommendations for assessment and allied care made.

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1. Introduction

Non-Hodgkin’s lymphoma (NHL) is common in both genders with an increasing incidence, especially in those >60 years of age [1–3]. Diffuse large B-cell NHL (DLBCL) is a common NHL subtype in the elderly, with poorer prognosis than in younger patients. Therapy in the older and/or frail population is complicated by comorbidities, as well as pre-existent alterations in functional status. Because of these issues as well as the lack of treatment guidelines for the elderly, the International Society of Geriatric Oncology (SIOG), an expert international panel of physicians with academic expertise in geriatric hematology convened to review DLBCL in the elderly, specifically to address prognosis, impact of comorbidities, role of geriatric assessment, and supportive care measures in the care of this patient population. The issues of treatment in this patient population, including initial therapy and approaches to the relapsed and refractory patient, are covered in a separate manuscript.

2. Demographics and Staging of DLBCL in the Elderly

With an overall age-adjusted incidence rate between 6 and 8/100,000 per year in western populations, DLBCL is the most common subtype of NHL. A greater proportion of elderly patients are diagnosed with DLBCL, compared to younger patients [1]. Incidence rates increase dramatically with advanced age, exceeding 30/100,000 per year in patients >65–70 years old [2–4]. In population-based cancer registries, median age at diagnosis is between 70–75 years; approximately two-thirds of DLBCL cases occur in patients ≥65 years of age [3,4]. Incidence rates are higher in males than females, with a 2:1 ratio in the elderly.

Net survival (NS) is the survival that would be observed if cancer was the only possible cause of death, and constitutes an interesting indicator in population studies. Recent NS data from 16 French DLBCL registries between 1989–2004 showed that age at diagnosis was a major prognostic factor [5]. Overall, five-year NS was 47% (95% CI: 45–49), but 43- and 40-fold decreases in five- and ten-year NS respectively, were found in young men (15–45 years old) and men > 75 years of age. Among the oldest patients (i.e. 65–75, versus >75 years), the five-year NS dropped in men from 45% (95% CI: 40–50) to 26% (95% CI: 22–31). Similar observations were found in women, as well as in other European and American series [2,6,7].

The histologic classification of NHL has evolved from the 1982 International Working Formulation (IWF), to the 1994 REAL (Revised European American Lymphoma) schema, and lastly the 2001 World Health Organization (WHO) classification (updated in 2008), which includes morphologic, immunophenotypic, and genetic features, as well as clinical aspects [8–10]. Diagnostic material should be submitted for histologic, immunophenotypic, immunohistochemical, cytogenetic, and molecular analysis. Non-Hodgkin lymphoma staging recommendations have been recently updated [11]. Although the division into limited (I–II) and advanced (III–IV) stage disease remains, the suffixes for A and B symptoms will no longer be used. Staging evaluation in the elderly should include physical examination, complete blood count with differential, lactic dehydrogenase (LDH), hepatitis B/C serologies, CT scans of chest, abdomen, and other
sites as appropriate, and functional imaging with PET scan (more sensitive in extranodal sites). In those elderly patients for whom these scans may not be feasible, CXR and abdominal ultrasound procedures may be considered. Bone marrow biopsy is no longer indicated for staging [11]. Assessment of cerebrospinal fluid cytology should be considered for patients at high risk of central nervous system involvement. Baseline determination of cardiac ejection fraction is necessary prior to anthracycline-based therapy.

3. Prognostic Factors for Outcome

DLBCL is a heterogeneous disease in terms of clinical features, prognosis and therapeutic response, related to many molecular pathways and pathogenic mechanisms involved in oncogenic transformation. Predicting prognosis of patients with DLBCL has been a “moving target” as new therapies emerge and alter treatment paradigms. Although earlier studies stratified patients into different clinical risk groups, recent research has been directed towards identifying biomarkers, most of which are for patients of all ages, to refine prognostication (Table 1). Although very few trials have specifically addressed prognosis of elderly patients with DLBCL, adverse disease subtypes including immunoblastic morphology, activated B-cell (ABC) subtype, as well as Epstein Barr virus-positive DLBCL are overrepresented in elderly individuals [12,13]. In addition, immunosenescence, with deterioration in innate and adaptive immunity, is observed [14]. Selective depletion of lymphoid-competent hematopoietic stem cells may explain decreased lymphopoiesis with age [15,16]. Although such senescence is now identified in the elderly with cancer, data specific to DLBCL are lacking [17].

3.1. Clinical Prognostic Models

The International Prognostic Model (IPI) was derived and validated from a dataset of >2000 patients treated with anthracycline-based chemotherapy in the pre-rituximab era [18]. Five adverse prognostic factors were identified: age > 60 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≥ 2, stage III/IV disease, > one extranodal disease site, and elevated LDH. Individual patients were stratified into four prognostic risk groups (low, low intermediate, high intermediate, high) with five-year survival rates of 73%, 51%, 43% and 26% respectively. Subsequently, the age-adjusted IPI was utilized for elderly patients. In an effort to assess its utility in R-CHOP-patients, British Columbia investigators analyzed registry data of 365 patients (median age 61 years) [19]. With the traditional IPI scoring system only two distinct prognostic groups were identified. However, when IPI scores were redistributed into a revised-IPI (R-IPI) scoring system, three groups with distinct prognoses were identified (very good risk, good risk, poor risk, with four-year survivals of 94%, 79% and 55%, respectively). In subsequent outcome analysis of 1062 patients receiving rituximab-based chemoimmunotherapy in three prospective trials, Ziepert et al., concluded that the IPI score retained its significance for event-free (EFS), progression-free (PFS), and overall survival (OS), although rituximab did significantly improve outcome within each IPI subgroup [20]. Another prognostic model, the Elderly-International Prognostic Model (E-IPI), utilizing an age cut-off of 70 (as opposed to 60) years, has been recently proposed, but needs validation in other datasets of prospectively treated patients > 60 years of age [21].

3.2. Prognostic Biomarkers and Gene Expression Studies

Individual biomarkers have provided insight into molecular pathways driving lymphomagenesis, and a platform for rational design of targeted therapy. However, limitations of prognostic use of biomarkers include: the complexity of mechanisms involved in transformation to a malignant phenotype, the retrospective nature of most biomarker studies, lack of standardization of methodology used to evaluate the biomarker, differences in “cut-off” thresholds used to define “positivity”, and lack of revalidation in patient cohorts treated prospectively with rituximab-based chemoimmunotherapy. In a recent review, markers studied in the rituximab era were specifically addressed [22]. Markers studied most extensively relate to genes and their protein products involved in apoptosis (BCL2, survivin and Fas), cell-cycle regulation (p53), markers of cellular proliferation (Ki-67), markers related to B-cell differentiation (BCL6, FOXP1), and markers germane to angiogenesis (HIF-1α and VEGFR2) [23-33]. There is considerable interest in the adverse prognostic outcome associated with MYC gene rearrangements and myc protein overexpression, as well as inferior outcome associated with the so-called “double-hit lymphomas” involving translocations of both MYC and BCL2 [34-39].

Gene expression studies utilize molecular profiling to simultaneously study the expression of multiple genes at an mRNA level. Initial pivotal studies identified two major subtypes of DLBCL: germinal center B-cell (GCB) and activated B-cell [40-42]. Compared to ABC subtype, patients with GCB subtype had a significantly better prognosis (five-year survival of 76% versus 16%) with anthracycline-based chemotherapy. The ABC subtype accounts for 60–70% of DLBCL in patients > 80 years of age [43-45]. Another seminal gene expression study, in which three molecular signatures were identified (germinal center B-cell

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Table 1 - Prognostic factors for outcome in older patients with DLBCL

<table>
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<tr>
<th>Clinical factors (age-adjusted International Prognostic Index)</th>
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<td>&gt;1 extranodal disease site</td>
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<td>Germinl center B-cell, activated B-cell subtypes</td>
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<tr>
<td>Apoptosis (BCL2, survivin, Fas)</td>
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<td>Cell-cycle regulation (p53)</td>
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<td>Cellular proliferation (Ki-67)</td>
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<td>B-cell differentiation (BCL6, FOXP1)</td>
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<td>Angiogenesis (HIF-1α, VEGFR2)</td>
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[GCB], stromal-1, stromal-2 signatures) illustrated the importance of tumor microenvironment [43]. The stromal-1 signature, characterized by genes associated with connective tissue growth factor and cells of monocyte/macrophage lineage, correlated with significantly superior prognosis compared to the stromal-2 signature, which was associated with genes involved in angiogenic pathways.

3.3. Immunohistochemical Algorithms

Major limitations of gene expression studies are that they are expensive, time-consuming, require fresh vital or fresh frozen tissue, and are not readily available outside a research setting. For application in community settings, investigators have used immunohistochemical (IHC) studies on paraffin-embedded tissue as surrogates for gene expression, to provide a semiquantitative assessment of protein expression thought to be biologically relevant in lymphoma pathogenesis [46–48]. Although these IHC-based tests are more readily available and easier to perform, there are conflicting results of their diagnostic utility, and there is currently no consensus about the best IHC model predictive of prognosis in rituximab-treated patients.

In summary, the standard of care for prognostication remains clinical prognostic models as the age-adjusted IPI. Collaborative research endeavors will allow incorporation of biomarker-based prognostic models to better stratify patients in the context of prospective clinical trials, identify novel therapeutic targets, assure uniform outcome reporting, and help clinicians individualize therapy for patients based on an improved understanding of the molecular pathways involved in lymphomagenesis.

4. Concept of Age-Adjusted Life Expectancy and Individualized Treatment

To individualize treatment decisions in elderly patients with DLBCL, decision-making should be based upon risk scoring and integration of age-related life expectancy, as well as geriatric assessment, that can aid in classifying patients as fit or frail [49]. The survival rate of a given patient with DLBCL should be compared with an age- and sex-matched population, which is available in public age statistics in many western countries (including CDC/NCHS, National Vital Statistics System [http://www.cdc.gov/nchs/nvss.htm], Statistic Austria [www.statistik.at]) [50,51]. Even in the elderly, DLBCL shortens life expectancy dramatically [2,5–7]. This highlights the need for appropriate, and whenever possible curative, treatment of DLBCL. An even more precise prognostication of life expectancy in elderly individuals is based upon integration of self-reported health, with divisions into upper, middle and lower quartiles of life expectancy [52]. With the integration of comorbidities and functional capacities, a scoring system was developed to predict four-year mortality in elderly patients [53,54]. These scores are useful in daily practice to predict life expectancy and develop an individualized therapeutic approach. A multidimensional approach to geriatric assessment, which integrates functional capacities, comorbidities, cognitive function, social support, emotional status/ depression, nutritional status, and polypharmacy, can aid in assessing biological–physiologic age, which is more important than chronological age in developing individualized therapy approaches, as well as predicting tolerance to therapies.

5. Comorbidity and Geriatric Assessment

Comorbid conditions in the elderly are common, present in 60–70% of NHL patients >60 years and associated with poorer outcome (Table 2) [55]. Consequences of comorbidity include increased treatment-related mortality and toxicity, leading to dose reductions with resultant lower dose intensity and higher rate of treatment failure [56]. Likewise polypharmacy, with the issues of multiple medications, potential drug interactions, and patient compliance, is common in elderly patients with comorbidities. Additionally, comorbidity frequently precludes clinical trial participation, limiting validity of reported studies in older NHL patients. Oncology-specific measures of comorbidity are needed to guide decision-making.

The comorbidity index of the National Institute of Aging/National Cancer Institute was applied in a Netherlands population study of 381 patients with aggressive lymphoma, revealing high impact comorbidity doubled risk of death, independent of the IPI [55,57]. The Cumulative Illness Rating Scale (CIRS) has been employed in the EORTC cooperative group setting to assess comorbidity in the context of prospective trials targeting frail DLCL patients [58]. This measure identified severe comorbidities in 37–47% of patients and was part of the functional definition of frailty.

As comorbidity is an important consideration in treatment planning and prognosis, studies have examined its impact. In a retrospective review of 140 patients with DLBCL >70 years of age, treatment outcomes were related to standard IPI risk stratification [59]. Cardiovascular complications, peripheral neuropathy and diabetic complications exacerbated by prednisone were the most common comorbidities. Lymphoma was the cause of death in 76% of patients. The Eindhoven Cancer Registry was examined to determine severity of comorbidity among older patients (median age, 64 years) in the Netherlands [55]. Comorbidity was defined as all diseases present at cancer diagnosis, with severity classified according to the National Cancer Institute index. For aggressive NHL patients, comorbidities were present in 48% of patients <60 years old and 78% of older patients. The chance of receiving chemotherapy was only influenced by age, with the likelihood for those >60 years only one third that of younger patients (p = 0.05). Severity of comorbidity had no independent effect on receipt of

| Table 2 – Impact of comorbidities on treatment agents for older patients with DLBCL |
|---------------------------------|-----------------|
| Cardiovascular (anthracyclines) | Renal dysfunction (platinum derivatives) |
| Pre-existent peripheral neuropathy (platinum derivatives, taxanes, vinca alkaloids, lenalidomide) | Diabetes (prednisone) |
| Pre-existent marrow compromise (prior chemotherapy, radiation) | (any myelosuppressive agents) |
| Dementia (all therapy) |

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Chemotherapy. However, among patients with aggressive NHL and cardiovascular comorbidity, the likelihood of receiving chemotherapy was only 40% compared to those without comorbidity (p = 0.04). The chance of receiving CHOP-like chemotherapy was 40% for those >60 years compared with younger patients, after adjustment for gender, stage and severity of comorbidity. Dose reductions were not more common in older patients and did not occur more frequently among patients with high impact comorbidity. Hematologic toxicity was the most common reason for dose reduction. There was no difference in spectrum and incidence of toxicity comparing older and younger patients. Severity of comorbidity had no significant impact toxicity occurrence, except for patients with cardiovascular comorbidity. In aggressive NHL, three-year crude survival was 62% for patients aged 40–60, and 41% for those >60, years. Survival decreased significantly with increasing IPI risk score, and was significantly lower for patients with high impact comorbidity.

Cardiovascular comorbidity is most significant for older patients. Certain agents, especially the anthracyclines, have potential cardiotoxicities, including QT prolongation, myocardial ischemia, and congestive heart failure (CHF) [60]. Any doxorubicin use was associated with a 29% risk of CHF in a Surveillance, Epidemiology, and End Results (SEER) Medicare database. CHF risk increased with number of doxorubicin claims, increasing age, prior heart disease, comorbidities, diabetes, and hypertension. Patients with prior heart disease were less likely to receive doxorubicin. Hypertension was synergistic with doxorubicin for CHF risk. Patients with hypertension and diabetes had 58% and 27% higher risks of developing CHF. Advanced age was a strong predictor both of withholding doxorubicin and subsequent CHF. Those >80 years had more than double the CHF risk as patients 65–70 years old. Older patients who received <six treatments had no increase of CHF, but had benefit. As such, screening workup of patients to receive potentially cardiotoxic agents should include historical assessment of risk factors as hypertension, atherosclerotic cardiovascular disease, diabetes, CHF, and prior exposure to cardiotoxic drugs or thoracic radiation, and baseline electrocardiogram and either echocardiogram or MUGA scan [61]. Cumulative upper doses of anthracyclines should not be exceeded (i.e., 400–450 mg/m² for doxorubicin; 140 mg/m² for mitoxantrone), and serial monitoring of cardiac function by exam/echocardiogram/MUGA scan should be done. Relevance of biomarkers as troponin or brain natriuretic peptide for prediction and follow-up of cardiotoxicity has not yet been delineated. Use of less cardiotoxic therapy, particularly liposomal anthracyclines, should be considered [62]. Potential cardiotoxicity of novel targeted agents also should be considered.

In another single institution analysis of patients ≥ 80 years of age, 87% had at least one comorbid illness, with a prior history of cardiovascular disease being most common [63]. Stratification of patients according to the Charlson index was 0 (13.7%), 1 (36.6%), 3–4 (33.7%), and >4 (15.1%). Anthracycline-based chemotherapy was administered in 32.2% of patients with aggressive lymphoma. Lymphoma was the predominant cause of death (57.5%) with comorbidity accounting for 13.7%.

In another evaluation of older NHL patients from Singapore, there were no significant differences in baseline demographics and lymphoma characteristics among patients aged 60–74 and those >75 years, except for PS [64]. In multivariate analysis, lymphoma characteristics as histology, PS, and stage were useful in predicting survival for patients <75 years of age. Among patients aged ≥75, the only independent prognostic factor for survival was PS. The data may be interpreted that PS, comorbidity, and functional status need to be independently assessed [65].

5.1. Comorbidity and Functional Status

Comorbidity is important in overall patient survival and may influence benefits and toxicity of cancer therapy. The association between comorbidity and survival was evaluated by Charlson who determined that number and severity of comorbid illnesses can predict survival in general medical patients admitted to an inpatient unit [66]. Although disease stage is a crucial determinant of survival, comorbidity increases complexity of management and impacts survival [58].Satariano and Ragland assessed the effect of comorbidity and disease stage on three-year survival in women with breast cancer, and found comorbidity to be a strong predictor of survival, independent of disease stage [67]. The association between functional status and comorbidity was evaluated in another study of older patients with cancer, which demonstrated that these factors are independent, thus each needs separate assessment [65]. Traditional oncology measures as Karnofsky score (KPS) and PS may not address issues that would be uncovered with use of geriatric-specific assessment, as polypharmacy, availability of social support, ability to use the telephone, and depression. The degree of dependency and geriatric functional scores can predict survival in older patients. Future oncology clinical trials would benefit from incorporation of easy-to-administer functional scales, to aid in predicting toxicity and outcome [68]. Currently available functional scales include self-reported measures as ability to complete activities of daily living (ADL) and instrumental (I)-ADL, as well as performance-based tests as get up and go and gait speed.

5.2. Dementia as Comorbidity

Treatment of patients with dementia is a significant issue in oncology [69]. In a tertiary cancer center, 18% of patients screened positive on the Mini Mental Status Examination, and is likely an underestimate of overall incidence [70,71]. Cognitively-impaired patients have markedly reduced survival compared to nonimpaired patients [72]. Although consideration should be given for potential life-extending therapy, this should be balanced against potential toxicities. In a SEER colon cancer database review, patients with dementia are more significantly less likely to have undergone histologic diagnosis, be offered surgical resection, or adjuvant chemotherapy. Immediate caregiver support is imperative if therapy is to be offered. The risk of toxicities that can cause delirium, as diarrhea, dehydration, or febrile episodes, is higher in impaired patients. Chemotherapy with which these toxicities are common should be avoided or at least used with extreme care, paying careful attention to dosing and adjunctive supportive measures (i.e., growth factors, hydration, etc.). Delirium may also complicate surgery. Elective surgery is...
markedly preferred to emergency surgery, with improved outcome including markedly decreased mortality [73].

5.3. Endorgan Dysfunction as Comorbidity

Patients with endorgan dysfunction are usually excluded from clinical trials, particularly for new drugs. Assessment of endorgan dysfunction is critical to guide physicians in cancer therapy dosing [74–79].

Renal dysfunction is common in the elderly, and impacts choice of potential therapeutic agents [80]. Recommendations for chemotherapy dosing of older patients with renal insufficiency have recently been summarized in International Society of Geriatric Oncology (SIOG) task force publications [81,82]. When studying a new drug that is not renally excreted, serum creatinine and/or creatinine clearance requirements may need to be relaxed. Additional research is needed to determine which of the available creatinine clearance formulae (modification of diet in renal disease (MDRD), Cockcroft-Gault) is most accurate in older patients [83,84]. Depending on methodology utilized, creatinine clearance can vary and therefore influence clinical trial eligibility and affect perceptions of safety. Additionally, evaluation of renal function in extreme obesity or cachexia is often not valid. Most drugs used in DLBCL treatment as cyclophosphamide, vincristine, doxorubicin (i.e., CHOP), bendamustine, or liposomal doxorubicin are characterized by limited renal elimination, thus dose adjustments are not needed and use of these agents is feasible in most elderly patients. The nephrotoxicity of platinum derivatives limits their usage. Appropriate hydration is warranted and co-administration of nephrototoxic drugs should be avoided.

Chemotherapy-induced peripheral neuropathy (CIPN) is a potential side effect of several drugs utilized for DLBCL therapy, as platinum derivatives, taxanes, vinca alkaloids, and lenalidomide. General recommendations are to monitor for neuropathy and hearing loss, and consider alternative regimens with non-neurotoxic drugs. There are no age-specific guidelines for dose reduction of these agents in the elderly/frail. Development of CIPN is influenced by factors as cumulative dose, co-administration of neurotoxic drugs, and presence of predisposing factors as diabetes or alcohol abuse. No agents have proven effectiveness in prevention of CIPN [85].

5.4. Comprehensive Geriatric Assessment and Frailty Measures (Table 3)

The comprehensive geriatric assessment (CGA) is a fundamental tool in care of geriatric patients, but integration and application of this tool in oncologic practice are in evolution. The goals of CGA are to guide selection of interventions to restore or prevent health decline, recommend an optimal care environment, and monitor clinical change over time. Components of the CGA include functional assessment, comorbid medical conditions, nutritional status, cognitive function, psychological state, social support, and medication review. Unfortunately, complete CGA is time-consuming and often impractical in a modern oncology practice given logistic and resource constraints. Hence, there is a pressing need for an easily, rapidly applied, effective, and validated tool in the oncologic setting. Current methods, as assessing KPS/PS, ADL, and IADL, are limited in scope and ability to assess multiple domains. Screening tools, as the vulnerable elders survey (VES-13), to identify those at-risk individuals in need of more formal CGA, require prospective oncologic validation [86].

A SIOG task force concluded that although CGA should be utilized for elderly oncology patients, with or without screening, currently a specific CGA tool cannot be recommended given available data [87]. Multidisciplinary senior adult oncology programs, as the model program at the Moffitt Cancer Center (Tampa, FL), have integrated CGA into a team approach and serve as paradigms for the creation of similar oncogeriatric programs. Ongoing efforts are resulting in more approachable mechanisms for general use in the elderly. Hurria et al. have developed a CGA that is self-administered and feasible in the outpatient setting, with assessment across multiple domains [88]. This CGA is currently being validated in both a larger prospective study and the oncology cooperative group setting [86].

An abbreviated assessment has been used in small NHL series. Winkelmann et al. evaluated 143 patients, median age 63 years (29% ≥ 70 years), and found that comorbidity and dependence in IADL were associated with overall survival [89]. However, their results did not account for lymphoma subtype or therapy. Tucci et al. evaluated patients, aged ≥65 years, with CGA prior to therapy [90]. As CGA results were blinded, treatment decisions for aggressive or palliative therapy were made solely by clinical judgment. As CGA was able to differentiate fit versus unfit patients better than clinical judgment, they concluded that CGA is an efficient method to identify which patients should receive anthracycline-containing chemotherapy. However, these algorithms need validation in large prospective, randomized trials before CGA is used to determine whether or not curative therapy should be administered.

Figuring prominently in the IPI, PS has typically been assessed with KPS or ECOG PS tools for initial risk assessment. Unfortunately, these assessments are subjective and not good predictors in the elderly [63]. In an attempt to utilize components of the CGA to better assess PS, Siegel et al. selected three functional tests validated in older populations: “timed up and go”, hand grip, and “Tinetti gait and balance test” [91]. These tests, readily applicable in clinic, may improve functional status discrimination. Efforts as these are refining assessment skills, with the ultimate goal of improving quality of life and therapeutic outcomes by honing decision-making processes [86].
Although there is no one precise definition of frailty, it is important to recognize as such patients are primarily candidates for supportive care. Suggested inclusion criteria include age > 85 years, dependence in ADL, exhaustion, slow gait speed, decreased hand grip, unintentional weight loss, and decreased physical activity. These patients may have increased incidence and severity of therapy-related toxicities and shortened survival. Further research is needed to precisely define frailty, so not to exclude patients from active treatment who still have remaining functional reserve [92–96].

6. Supportive Care Issues in the Elderly

6.1. Introduction

The risk for chemotherapy-related toxicities in older adults has been examined [88,97]. In one series, 500 patients (mean age 73 years) who received solid tumor chemotherapy completed a pre-treatment assessment including sociodemographics, tumor/treatment variables, laboratory tests, and CGA variables [88]. Grade 3–5 toxicities occurred in 53%. Using pre-treatment variables, a three-tiered risk scoring system was developed for toxicity occurrence. A chemotherapy risk assessment scale for high-age patients (CRASH) score was prospectively developed in another study of 518 patients $\geq 70$ years who were to receive chemotherapy [97]. Such multidimensional risk factor assessments as these are of utility in pre-chemotherapy evaluation of older patients, to guide dose adjustment and supportive care measures.

Older patients are likewise at increased risk of hematologic toxicities with DLBCL therapy. Increased age-related comorbidity predisposes to a greater incidence of febrile neutropenia with resultant increased morbidity, mortality, dependence, length of stay, and cost [98,99]. Risk is greatest during early chemotherapy cycles, warranting consideration of supportive care measures (Figs. 1, 2) [100,101].

6.2. Age as a Risk Factor for Neutropenic Fever

Hospitalization for chemotherapy-induced febrile neutropenia is associated with substantial cost and may negatively impact clinical outcome due to associated dose attenuation [100,102]. In one study, 17% of patients experienced at least one hospitalization for febrile neutropenia, and more than half of all initial febrile neutropenia hospitalizations occurred in cycles 1 or 2. Increased risk of febrile neutropenia hospitalization, based on Cox proportional hazards models, was significantly associated with the following baseline characteristics: age $\geq 65$ years (hazard ratio (HR) 1.79; 95% confidence interval (CI) 1.35–2.37), serum albumin $\leq 3.5$ g/dL (HR 1.34; 95% CI 1.01–1.78), planned average relative dose intensity $\geq 80$% (HR 2.70; 95% CI 1.47–4.98), baseline absolute neutrophil count $< 1500/mm^3$ (HR 1.98; 95% CI 1.28–3.06), and presence of hepatic disease (HR 2.18; 95% CI 1.11–4.28). Lack of early myeloid growth factor usage in cycles 1 and 2 was also associated with a trend for increased risk of febrile neutropenia hospitalization. A composite risk score based on these factors effectively distinguished patients at greater risk of hospitalization for febrile neutropenia (p < 0.001), the majority observed during the first cycle of chemotherapy. This risk model, including age $> 65$ years, abnormal liver function tests, renal insufficiency, and receipt of prior chemotherapy, can be used to predict febrile neutropenia.

An Oncology Practice Pattern Study reviewed medical records of intermediate-grade NHL patients who received initial CHOP chemotherapy and identified risk factors associated with time to first febrile neutropenic event [103]. Risk of febrile neutropenia was significantly associated with age $\geq 65$ years (p = 0.001), cardiovascular disease (p = 0.020), renal disease (p = 0.006), baseline hemoglobin $< 12$ g/dL (p = 0.018), $> 80$%
planned average relative dose intensity (ARDI) \( (p = 0.018) \), and no prophylactic myeloid growth factor use \( (p = 0.046) \). First febrile neutropenic events occurred by day 14 of cycle 1 in half of patients experiencing febrile neutropenia. In multivariate analysis, risk of febrile neutropenia was significantly associated with age \( \geq 65 \) years \( (HR 1.65, 95\% CI 1.18–2.32) \), renal disease \( (HR 1.91, 95\% CI 1.10–3.30) \), cardiovascular disease \( (HR 1.54, 95\% CI 1.02–2.33) \), baseline hemoglobin \(< 12 \text{ g/dL} \) \( (HR 1.44, 95\% CI 1.04–2.00) \), \( > 80\% \) planned CHOP ARDI \( (HR 2.41, 95\% CI 1.30–4.47) \), and no myeloid growth factor prophylaxis \( (HR 2.13, 95\% CI 1.20–3.76) \). This model can identify patients at greatest risk of febrile neutropenia, and therefore candidates for elective prophylactic myeloid growth factor usage.

A prospective, randomized trial of patients \( > 65 \) years was performed evaluating the efficacy of primary prophylaxis in patients with solid tumors or lymphoma [104]. Proactive pegfilgrastim use resulted in significantly lower incidence of febrile neutropenia for solid tumor and NHL patients compared with reactive use. It also led to fewer hospitalizations resulting from neutropenia/febrile neutropenia by approximately 50%. Antibiotic use was lower for solid tumor patients receiving proactive pegfilgrastim, and equivalent in the two NHL groups.

6.3. International European Organization for Research and Treatment of Cancer (EORTC) Guidelines

EORTC recommends that patient-related adverse risk factors as older age \( (\geq 65 \) years) be evaluated in overall assessment of febrile neutropenia risk prior to administering each chemotherapy cycle [105]. When using a chemotherapy regimen associated with \( \geq 20\% \) risk of febrile neutropenia, prophylactic myeloid growth factor usage is recommended. With a chemotherapy regimen associated with \( 10–20\% \) febrile neutropenia risk, particular attention should be given to patient-related factors that may increase overall febrile neutropenia risk. In settings for which dose-dense/intense chemotherapy strategies have survival benefits, prophylactic myeloid growth factor support is recommended. Similarly, if reductions in chemotherapy dose intensity are associated with poorer prognosis, primary myeloid growth factor prophylaxis may be used to maintain dose.

6.4. American Society of Clinical Oncology (ASCO) Guidelines

Reduction in febrile neutropenia is an important clinical outcome that justifies myeloid growth factor use when the febrile neutropenia risk is \( \geq 20\% \) and no other equally effective regimen not requiring myeloid growth factor support is available [106]. Primary prophylaxis is recommended for febrile neutropenia prevention in high-risk patients based on age, medical history, disease characteristics, and chemotherapy-related myelotoxicity. Myeloid growth factor use allows modest to moderate increases in dose-density/intensity of chemotherapy regimens. Prophylactic myeloid growth factor support for patients with DLBCL aged \( \geq 65 \) years treated with curative regimens as rituximab-CHOP should be given to reduce incidence of febrile neutropenia and infections.

6.5. Red Blood Cell (RBC) Stimulating Drugs

There are no specific recommendations for the use of RBC-stimulating agents in older patients. ASCO and American Society of Hematology guidelines recommend that for patients receiving myelosuppressive chemotherapy with hemoglobin \(< 10 \text{ g/dL} \), clinicians should discuss potential harms (i.e., thromboembolism, shorter survival) and benefits (i.e., decreased transfusions) of erythropoietin stimulating agents (ESAs) and compare these with potential harms (i.e., serious infections, immune-mediated adverse reactions) and benefits (i.e., rapid hemoglobin improvement) of RBC transfusions [107,108]. Individual preferences for assumed risk should contribute to shared decisions on managing chemotherapy-induced anemia. ESAs should be administered at the lowest possible dose, and increase hemoglobin to the

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Fig. 2 – Time to occurrence of febrile neutropenia with CHOP-like chemotherapy by risk group. Kaplan–Meier plot displays the cumulative proportion of patients who experienced 1 or more episodes of febrile neutropenia over time in days after chemotherapy initiation for both high-risk and low-risk patients (from Ref. [100]).
lowest level possible to avoid transfusions. These agents should be discontinued after 6–8 weeks in nonresponders. ESAs should be avoided in patients with cancer not receiving concurrent chemotherapy, except for those with lower risk of myelodysplastic syndromes, and should be used with caution with chemotherapeutic agents associated with increased risk of thromboembolic complications.

7. Conclusions

Despite treatment advances for older patients with DLBCL based upon prospective randomized trials, many patients are not eligible for such trials based upon underlying comorbidities and functional deficits related to aging. Measures for more formal evaluation of these patients are being developed, and include many more facets than PS alone. Although offering potentially curative therapies to older patients should be done when possible, pre-treatment evaluation should include some formalized assessment and consideration not only of comorbidities, but also of functional, social, and psychological constraints, such that safety and tolerability of a given regimen can be determined. Supportive care measures are of particular importance in the elderly. Routine assessment of these factors in older patients with DLBCL will aid in identifying those patients for whom curative therapies are feasible, as well as determining which patients may benefit most from non-curative supportive regimens, in an effort to provide meaningful quality and quantity of life.

Disclosures and Conflict of Interest Statements

The authors have no conflicts of interest to disclose.

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