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Can we incorporate geriatric assessment in the management of acute lymphoblastic leukemia in older adults?

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ABSTRACT

Acute lymphoblastic leukemia (ALL) is an uncommon disease. Approximately 14% of new ALL cases occur in adults aged 60 and over, and the three-year overall survival in this population is poor at 12.8%. Older adults with ALL are heterogeneous in terms of their underlying health status, which can make treatment selection challenging given the disease rarity and limited inclusion of older patients in clinical trials. A comprehensive geriatric assessment (CGA) is a compilation of tools to assess multiple domains such as physical function and cognition, and may assist in guiding treatment selection and supportive care interventions. However, studies on the use of CGA are limited in older adults with ALL. In this review, we discuss the utility of CGA in patients with various hematologic malignancies. Using two patient cases of ALL, we also describe how CGA may be use to guide treatment and supportive care interventions.

1. Introduction

Acute lymphoblastic leukemia (ALL) is an uncommon malignancy with an estimated 5,970 new cases in the United States in 2017 [1]. Approximately 14.2 % of new ALL cases are diagnosed in adults aged 60 and over (60–69: 5.9%; 70–79: 4.8%; ≥80: 3.5%) [2]. Although a recent analysis of the Surveillance, Epidemiology, and End Results (SEER) database suggests improvement in overall survival (OS) in this population, three-year OS remains poor (12.8%) [3]. The poor outcome in older adults is multifactorial secondary to their tumor biology [e.g. higher prevalence of poor-risk cytogenetics and Philadelphia chromosome (Ph) positive which are poor prognostic factors] and lower physiologic reserve that decreases their ability to tolerate intensive treatment and increased their susceptibility of experiencing treatment toxicities and mortality [4,5]. In the Medical Research Council (MRC) United Kingdom ALL XII/Eastern Cooperative Oncology Group (ECOG) E2993 that includes almost 1500 patients with ALL who received intensive treatment, age was a risk factor for lower disease-free survival (DFS) and OS [6]. However the treatment of ALL has evolved in the last decade with an increasing availability of novel agents that appear to be better tolerated and, therefore, are attractive options for the treatment of older patients. With aging, there is increasing heterogeneity in the underlying health status of older adults. Routine performance scales such as Karnofsky and ECOG performance scales do not accurately capture their underlying physiological status thereby masking underlying physical, psychological and cognitive impairment [7]. The differing health status of older adults makes it important to assess their underlying physiologic reserve.

2. Comprehensive geriatric assessment

Comprehensive geriatric assessment (CGA) has been utilized to better understand older adults' underlying health status. A CGA is a compilation of tools to assess multiple domains including physical function, psychological status, cognition, comorbidities, nutrition, social support, geriatric syndromes, and medications. CGA has been validated in both the geriatric and/or geriatric oncology populations for predicting drug discontinuation, adverse events (e.g. hospitalizations and chemotherapy toxicities), and survival [8–13]. CGA can also assist with treatment decision-making as well as to guide supportive interventions [14,15]. However, no published clinical trials have evaluated the use of CGA in older patients with ALL. Therefore, it is unclear whether CGA may be helpful, which domains should be included in a CGA and how this information can be used to guide management in older patients with ALL.

The initial presentations of older patients with ALL and acute myeloid leukemia (AML) are similar. In multiple AML studies, CGA domains have been found to be prognostic. In older patients receiving intensive chemotherapy, Klepin and colleagues found that OS was worse in those who had cognitive impairment, measured using the Modified Mini-Mental State examination [Hazard Ratio (HR) 2.5, 95% Confidence Interval (CI) 1.2–5.5] and had objective impairment in physical function, measured using the Short Physical Performance Battery (SPPB) [HR 2.2, 95% CI 1.1–4.6] [16]. In older patients receiving either induction or palliative chemotherapy, Wedding and colleagues also demonstrated that

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impairment in instrumental activities of daily living (IADL) predicts shorter OS (HR 4.3, 95% CI 1.7–10.5) [17]. In older patients with AML and myelodysplastic syndrome (MDS) receiving best supportive care, hypomethylating agents or induction chemotherapy, Deschler and colleagues demonstrated that impairment in activities of daily living (ADL) (HR 2.1, 95% CI 1.1–3.9) and higher level of fatigue (HR 2.1, 95% CI 1.2–3.7) were predictive of worse OS [18]. Similarly, in older patients with newly diagnosed AML, Sherman and colleagues found that the risks of death were higher in those who reported difficulty doing strenuous activity (HR 2.2, 95% CI 1.2–4.0) and had pain (HR 2.2, 95% CI 1.2–4.0) [19]. In addition, patients with more comorbid conditions as defined by the Hematopoietic Cell Transplant-Co-morbidity Index (HCT-CI) (HR 1.9, 95% CI 1.2–3.1) had higher mortality rates [19]. Of note, no studies have prospectively evaluated the use of CGA in treatment allocation for older patients with AML.

Geriatric assessment has been utilized in the evaluation of older adults undergoing Hematopoietic Stem Cell transplantation (HSCT). In a study with 203 older patients (6% had ALL), lower OS was shown in those with limitations in IADL (HR 2.4, 95% CI: 1.6–3.6), slow gait speed (HR 1.8, 95% CI 1.1–2.8), impaired mental health based on the Mental Component Summary of the Medical Outcomes Short Form-36 health-related quality of life questionnaire (HR 1.7, 95% CI 1.1–2.5) and higher comorbidity score on HCT-CI (HR 1.6, 95% CI 1.7–2.3) [20]. Similar to AML, no studies have prospectively evaluated the use of CGA in transplant determination for older patients.

Collectively, the existing studies in the AML/MDS and transplant settings suggest that a CGA may be helpful, and should at least include an assessment of patients' comorbidities, physical function, and cognition. These assessments may be adapted for older patients with ALL who have similar disease presentations and courses. If time permits, other domains such as nutritional status, social support, medications, mental status, symptom burden, and geriatric syndromes should be evaluated as well. Table 1 shows the various geriatric assessment domains and examples of tools that can be used to assess each domain. Readers are encouraged to refer to other more comprehensive papers on CGA and commonly used tools for each of these domains [9,21–23]. The mean time to completion of a geriatric assessment ranges from 15 to 44 min and the variable time is due to inclusion of different domains and assessment tools [8,9,24–26]. Nevertheless, a large proportion of these assessments are patient-reported and the objective assessment typically requires <10 min to complete. For most patients with ALL who are usually seen and evaluated in the hospital, this would be feasible to implement.

A number of studies and guidelines have adapted a geriatric assessment to assist with risk categorization, although they are mostly focused on solid tumors and lymphoma [27–30]. Most of these risk stratifications categorize patients into three groups: fit, vulnerable/intermediate, and unfit. However, the evidence is still lacking on how to risk stratify older patients with ALL. CGA can also guide supportive care interventions such as exercise, cognitive rehabilitation, optimization of nutritional status, and concomitant medications prior to or during treatment. Using two patient cases of ALL, we describe how we incorporated CGA in guiding treatment and supportive care interventions.

Table 1
Geriatric assessment domains and example of tools to assess each domain

Domain	Tool
Comorbidities	Charlson Comorbidity Index [70] Hematopoietic Cell Transplant-Comorbidity Index [19,20] Cumulative Illness Rating Scale [71] Cumulative Illness Rating Scale-Geriatric [30,72] Visual and/or hearing deficits
Physical function	Activities of daily living [18,73] Instrumental activities of daily living [74] Short physical performance battery [16] Timed up and go [75]
Cognition	Mini mental state examination [76,77] Modified mini mental state examination [16] Montreal cognitive assessment [78,79] Clock-drawing test [80] Blessed orientation-memory-concentration test [79] Mini-Cog [81]
Symptoms burden (including quality of life, pain, or fatigue)	EORTC QLQ-C30 [18] SF-36 [20]
Psychological status	Geriatric Depression Scale [82,83] Distress thermometer [84]
Polypharmacy	Number of medications Beers criteria [85] STOPP and START criteria [86]
Nutrition	Body mass index (weight and height) Mini nutritional assessment [87,88]
Geriatric syndromes [72]	Dementia Delirium Falls Incontinence (fecal and/or urinary) Osteoporosis or spontaneous fractures Neglect or abuse Failure to thrive

Abbreviations: EORTC QLQ-C30, European Organisation for Research on Cancer Treatment Quality of Life Questionnaire; SF-36, Medical Outcomes Short Form-36 health-related quality of life questionnaire; START, Screening Tool to Alert Doctors to Right Treatment; STOPP, Screening Tool of Older Person's Prescriptions

3. Patient 1

A 72-year-old man with a history of hypertension, hypothyroidism, and osteoarthritis presented with fatigue, weakness, chills and night sweats. The complete blood count with differential revealed a white blood cell count of 1600 per microliter (μL), hemoglobin of 7.5 g per deciliter (dl) and platelet count of 100,000/μL. A bone marrow aspirate and biopsy confirmed B-cell acute lymphoblastic leukemia. Chromosomal analysis revealed a normal male karyotype. Molecular genetic evaluation for the break point cluster region (BCR)/abl kinase one (ABL1) transcript was negative. The diagnosis was Ph negative (Ph−) B-cell acute lymphoblastic leukemia.

In the last two decades, it has been demonstrated that younger patients with ALL have better outcomes when treated on pediatric-inspired ALL protocols compared to adult ALL protocols [31,32]. Pediatric protocols include higher dose of non-myelosuppressive therapies, including L-asparaginase. The induction, post-remission therapy, central nervous system (CNS) prophylaxis, and maintenance therapy also vary [32]. However, a pediatric-based protocol is generally not used in adults aged ≥40 years given higher rates of adverse events and toxicities including hypersensitivity reactions, hepatotoxicity, thrombosis, infections, and treatment-related deaths [33–35]. The optimal induction regimen for older patients with Ph− ALL is an active area of investigation. Multiple clinical trials have been conducted in the past decades but intensive therapy has not shown to significantly improve outcomes [36]. The largest trial in older adults was done by the German Multicenter Study Group for Adult ALL (GMALL) [37]. Two hundred and sixty eight patients (median age 67 years, range 55–85) were included. The regimen consists of induction with multiple chemotherapy agents including idarubicin, dexamethasone, vincristine, cyclophosphamide, and cytarabine followed by consolidation and maintenance therapy (Berlin-Frankfurt Munster) [37]. Rituximab was given to those patients who expressed CD20 antigen on their lymphoblasts. Complete response (CR) rate during induction was 76%, early death was 13%, and death during CR was 6%. Five-year OS was 23%. Table 2 outlines three prospective trials showing the regimen, age range, and outcomes [33,35,37,38].

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