ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Susan O'Brien, MD

Predicting Treatment Outcomes in Older Patients With Acute Myelogenous Leukemia

Heidi D. Klepin, MD, MS
Associate Professor
Internal Medicine Section on Hematology and Oncology
Wake Forest Baptist Health Comprehensive Cancer Center
Winston-Salem, North Carolina

H&O Why is there uncertainty regarding treatment options for older adults with acute myelogenous leukemia (AML)?

HK AML provides one of the most dramatic examples of age-related outcome disparity in oncology, owing to the morbidity of the disease and the intensity of treatment. Older adults represent more than half of all new cases of AML and experience significantly inferior outcomes than younger patients, with higher rates of treatment-associated toxicity and lower overall survival. Despite many years of developing elderly-specific trials aimed at testing new therapeutic approaches for older adults with this disease, there has been minimal change in the relatively dismal outcomes seen in this population. However, clinical trials have shown repeatedly that selected older adults can tolerate intensive therapy and experience long-term benefits, including extended survival, when treated in a fashion similar to that used in middle-aged patients. A major challenge is identifying those patients who are likely to benefit from intensive treatment at the time of diagnosis.

H&O What are the current treatment recommendations for older AML patients?

HK There is no standard of care approach to the treatment of most older adults with AML. Treatment recommendations for older adults with this disease range widely, and are often based to a large extent on chronologic age. The primary area of consensus relates to those older adults with significant comorbidities or poor functional status at the time of diagnosis. It is clear that these patients are unlikely to benefit from intensive therapies. There is no consensus regarding optimal treatment strategies for the majority of older adults who do not have a major comorbidity or severe functional impairment at the time of diagnosis.

H&O What efforts have been made to identify older patients who are likely to benefit from treatment? What have studies largely failed to focus on?

HK Research aimed at identifying older adults who are more likely to benefit from treatment has primarily focused on age-related alterations in tumor biology. Few studies have evaluated patient-specific characteristics—such as comorbid conditions, functional status, and cognitive status—all of which may be equally important in determining tolerance to treatment. Until now, chronologic age and tumor biology have largely defined how we study new treatments for AML in the older patient. What we have neglected is how to better stratify vulnerability with respect to patients' characteristics, since chronologic age is not indicative of their physical function or how well they will tolerate treatment.

H&O Please describe the design and setting of your study on older AML patients.

HK We designed a prospective single-institution study focused specifically on older adults (≥60 years old) with AML to test the utility of bedside geriatric assessment in pre-
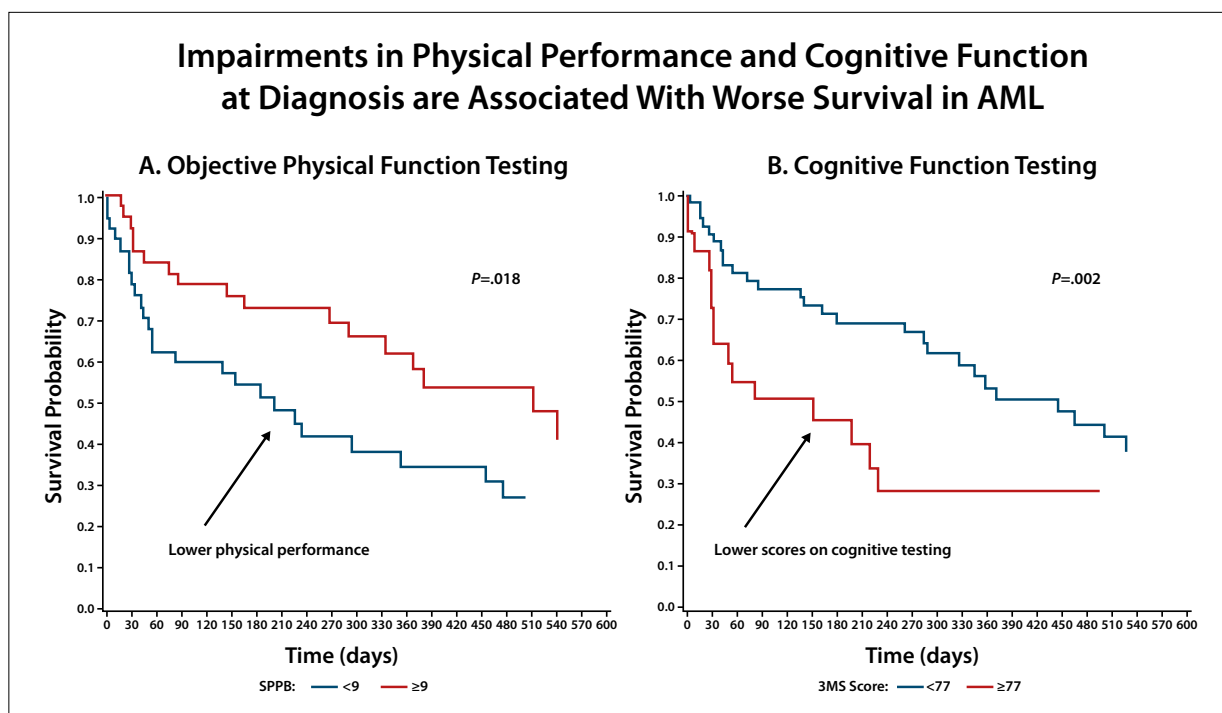
Impairments in Physical Performance and Cognitive Function at Diagnosis are Associated With Worse Survival in AML

A. Objective Physical Function Testing

B. Cognitive Function Testing

P=.018

P=.002

Figure. A, Impaired physical performance was associated with worse overall survival among older adult patients treated for AML (N=74). Median survival differed using log-rank testing. B, Lower baseline cognitive function was associated with worse overall survival among older adult patients treated for AML (N=73). Median survival differed using log-rank testing.

dicting treatment outcomes. We hypothesized that improved assessment of specific patient characteristics that vary among individuals of the same age would enhance our ability to predict who would tolerate and benefit from aggressive therapy. The geriatric assessment consisted of several brief questionnaires and physical performance tests, which were designed to measure physical function by self-report and objective evaluation, cognition, mood (depression and distress), and comorbidity. We were particularly interested in the utility of objective physical function testing, which minimizes biases associated with self-report and allows for standardization of measurements. The physical performance measures used included the short physical performance battery (a brief 4-meter walk, repeated chair stands, and balance testing) and grip strength. The entire assessment was administered in approximately 30 to 40 minutes by a nurse prior to initiation of intensive chemotherapy.

H&O What were the main goals and key findings in this study?

HK The primary outcome of the study was overall survival. After adjusting for clinical and biological factors known to be associated with survival in older AML patients, we found that impairment in both objectively-

measured physical performance (Figure A) and cognition (Figure B) were independently associated with worse survival among these patients. It is important to note that all patients enrolled in this study were already highly selected and deemed fit for intensive therapy by standard oncology assessment strategies. In this setting, assessments of cognition and physical performance were able to detect vulnerability which, although clinically significant, might otherwise be undetected.

H&O How have you built upon this observational study?

HK A key next step is validation of our findings in a multisite setting. Studies to validate the utility of geriatric assessment measures in the setting of therapy for AML are ongoing in the cooperative group setting. If validated, simple assessment measures of physical function and/or cognition may be used to help further individualize treatment decision-making for older adults in clinical practice. Identifying characteristics that can predict vulnerability to excessive toxicity may inform designs of future clinical trials by facilitating the development of treatment strategies specifically for vulnerable or frail older adults. Finally, this research may inform interventions to address vulnerability.

Building upon our observational study, which showed the prognostic significance of lower physical performance at diagnosis, we have developed a physical activity intervention to minimize functional decline associated with intensive therapy. This single-institution pilot study is ongoing. The goal of this work is to facilitate development of active supportive care strategies to prevent functional decline during treatment, which will maximize treatment benefits and quality of life.

H&O What are the biggest remaining challenges?

HK One area that presents major challenges is in identifying patients most likely to benefit from treatment and developing treatment plans that account for age-related changes in tumor biology and physiologic reserve. Clinical trials that account for heterogeneity in both tumor biology and patient characteristics are needed in order to fully understand how to effectively individualize therapy. Another challenge occurs after remission because older adults do not stay in remission to the same degree that younger patients do. Research should focus not only on determining which induction therapies are optimal for older patients, but also on keeping older AML patients in remission longer, ideally until their disease is cured.

H&O What does the future hold?

HK I think that we will continue to see more targeted therapies emerge, which will lead to more subgroup selection in clinical trials. Targeted therapies will undoubtedly play a large role in AML therapy for patients of all ages. However, advances in such treatments will likely develop faster in the older patient population, as these agents typically offer less treatment-related toxicity. Utilizing both molecular testing and geriatric assessment strategies to define subsets of patients to target with novel treatment paradigms will likely be a focus of future clinical trials. To accomplish this, identification of the most efficient screening tools will be necessary in order to translate geriatric assessment into clinical practice and individualize treatment decision-making. Ideally, patients should be encouraged to participate in treatment decision-making and made fully aware of the risks and benefits of all available treatment options. This understanding should include not only chances of cure and treatment-related mortality, but also the likely trajectory of quality of life and independence. As our healthcare system continues to evolve, these types of outcomes are going to be critical in defining what an optimal treatment strategy really is for any given patient.

Suggested Readings

Klepin HD, Geiger AM, Tooze JA, et al. Geriatric assessment predicts survival for older adults receiving induction chemotherapy for acute myelogenous leukemia. *Blood*. 2013,23;121(21):4287-4294.

Sherman AE, Motyckova G, Fega KR, et al. Geriatric assessment in older patients with acute myeloid leukemia: a retrospective study of associated treatment and outcomes. *Leuk Res*. 2013;37(9):998-1003.

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