

been known. In this study, Ji et al demonstrate that up-front steroid therapy improves time to resolution of KMP, as well as durability of platelet response. Overall lesion response was also improved in the group receiving up-front steroids with sirolimus. This effect was seen as far out as 12 months following the initiation of therapy. Importantly, this benefit was seen without an increase in infectious complications, which is 1 of the arguments against steroid use in infants and young children.

Ji et al speculate that the combined neoplastic and inflammatory nature of KHE is best treated with pharmacotherapy that targets both key pathologic features of this vascular tumor. Indeed, there are data from the literature on infantile hemangiomas that corticosteroids suppress VEGF signaling and may suppress other proangiogenic factors.<sup>9</sup> Corticosteroids have also been found to have inhibitory effect on angiopoietin-2 expression in endothelial cells and in other tumor types.<sup>10</sup> It is possible that early blunting of lymphangiogenesis within the tumor prevents rapid tumor expansion and the cycle of inflammation, activation of coagulation, and tumor growth, thus improving near-term and longer-term outcomes.

Inflammation, disrupted vasculogenesis, and severe consumptive coagulopathy are all key to the dangerous pathophysiology and aggressive presentation of KHE. Prospective treatment and risk-stratification studies, such as performed by Ji et al, are needed to better understand this rare tumor and improve patient outcomes, but the lessons learned from such endeavors are not unique to KHE. Identification of the complex mechanisms regulating angiogenesis, lymphangiogenesis, and disrupted coagulation and inflammation at the endothelial cell level are key to improving our understanding of many disease processes and malignancies. As novel therapeutic agents are identified that target these pathways, treatment options for patient with rare tumors like KHE will expand.

*Conflict-of-interest disclosure:* The authors declare no competing financial interest. ■

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- DOI 10.1182/blood.2022015412  
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## CLINICAL TRIALS AND OBSERVATIONS

Comment on Min et al, page 1646

# Toward consensus on geriatric assessment in AML

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**In this issue of *Blood*, Min et al<sup>1</sup> report on the use of geriatric assessment tools to predict toxicity and survival among older adults receiving intensive induction therapy for acute myelogenous leukemia (AML).**

Despite the expanding treatment options for AML, outcomes for older adults remain poor.<sup>2</sup> As a group, older adults derive less benefit and experience more toxicity from therapy. As individuals, however, older adults vary greatly in their resilience to the stresses of treatment. Chronologic age alone is insufficient to characterize “fitness” for potentially curative intensive treatment. Reliable criteria that enhance prediction of treatment tolerance and benefit are needed to inform treatment decisions and guide “precision medicine” trial design.

Geriatric assessment is a promising strategy to help define “fitness” and predict resilience.<sup>3</sup> It consistently identifies unrecognized vulnerabilities among older adults with hematologic malignancies and can be performed at the time of AML diagnosis.<sup>4-6</sup> Which specific domains or measures are most important in the

context of AML therapy has remained an open question. Answering this question would help with clinical trial design at a global level and at an individual level would help select treatments that optimize benefits and risks for an older adult patient. To date, there is evidence that specific geriatric measures evaluating objective physical functioning (short physical performance battery [SPPB]), cognition, and mood are predictive of survival among older adults receiving intensive AML therapy.<sup>5,7</sup> These observations, however, have not yet been independently validated.<sup>8</sup>

Min et al sought to validate prior observations and provide a standardized set of geriatric assessment measures for use in clinical trials and practice. The authors also extended prior work by evaluating these measures for the prediction of toxicity. Their results validate the importance

of measuring physical function, cognitive function, and mood in predicting vulnerability to intensive therapy for AML.

This single-institution study enrolled adults 60 to 75 years of age with good performance status who were to receive intensive induction therapy. Geriatric assessment was performed prior to initiation of treatment.<sup>5</sup> The assessment included an extensive physical function evaluation (both self-report and objectively measured), as well as validated measures of cognition, emotional health, nutritional status, and social support. After adjusting for age, performance status, and comorbidity, 2 geriatric measures were associated with nonfatal toxicities. Specifically, lower performance on the SPPB (4-meter walk, repeat chair stands, and balance testing) and impaired cognition measured using the Mini-Mental State Exam were associated with higher odds of grade 3 to 4 infection (both) and renal failure (SPPB only). Prolonged hospitalization was associated with cognitive impairment, possibly related to a higher incidence of delirium.

When evaluating factors associated with higher all-cause mortality, the SPPB again was independently predictive as was a positive depression screen using the Geriatric Depression Scale. Given the consistent predictive utility of the SPPB, which is a composite measure, the authors investigated each of the components and found that gait speed and the sit-to-stand (timed repeat chair stands) were similarly predictive of survival. Exploratory analyses indicated that adding the SPPB (or a component measure such as gait speed) and the depression score to existing prediction models such as the Wheatley index could improve its predictive power. Although exploratory, these findings suggest a significant added value.

This study is important for several reasons. First, the results highlight 3 geriatric assessment domains (physical, cognitive, and emotional) that are relevant for

prediction of outcomes in the setting of intensive therapy for AML. Although the evidence base remains small, results consistently indicate that, at a minimum, measures assessing these domains should be included in clinical trials to better stratify for risk. Second, the results confirm the value of assessing objectively measured physical function before intensive therapy. The SPPB was the only measure predictive of both toxicity and survival in this study and was previously shown to predict survival at induction and after remission.<sup>5,7</sup> The SPPB is a more sensitive measure of function than self-reporting. Good performance on the SPPB more reliably identifies older adults who are “fit” for intensive therapy. The authors also found that either gait speed or the sit-to-stand test provides similar evidence as the full SPPB. Gait speed is a consistent predictor of disability risk, hospitalization, and mortality in older adult populations,<sup>9</sup> earning it the nickname of “5th vital sign” in geriatrics. We now have evidence to support its use in AML. A third important observation is that the geriatric measures performed similarly in a Korean and US population supporting the global utility of these tools. The measures evaluated here, however, may not be sufficient to predict variability of outcomes for older adults receiving less-intensive therapies. The patients included in this trial all had a good performance status (ie, were highly selected). Finally, it is important to recognize that these findings can support testing interventions to modify vulnerability. Fitness can be dynamic, and interventions designed to optimize fitness by targeting physical performance and mood should be pursued simultaneous with design of novel therapeutic strategies.

In summary, the work by Min and colleagues moved the field forward by identifying reproducible tools to characterize fitness for intensive therapy that can be incorporated into clinical trials and used at the bedside to guide treatment decision making.

*Conflict-of-interest disclosure:* The author declares no competing financial interests. ■

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DOI 10.1182/blood.2021015200

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