epigenetic modifiers can induce modifications of chromatin structures and simultaneously influence the expression of multiple genes.[8] Indeed, treatment with KDM5 inhibitors reactivated the expression of multiple genes, beyond those that were silenced by *KMT2D* loss. In addition, several epigenetic modifiers have noncatalytic functions.[9] Thus, inhibition of KDM5 proteins, on the one hand, can rescue the oncogenic phenotype acquired by KMT2D-mutated lymphoma cells, but, on the other hand, it induces additional epigenetic and transcriptional changes.

It is clear that inhibition of KDM5 results in accumulation of H3K4me3 and reactivation of gene expression, but how this culminates in an antiproliferative phenotype is more complex. For example, Heward et al observed downregulation of BCL2 upon treatment with KDM5 inhibitors, which is an indirect consequence of KDM5 inhibition. The dynamic and functional interactions between multiple epigenetic regulators makes it difficult to anticipate how the modification of one element will influence the activity of the others. Moreover, different targets could be reactivated in different tumors, as their expression will be influenced by the presence or absence of other genomic alterations, the stage of the tumor, and the composition of the tumor microenvironment. Thus, heterogenous epigenetic and transcriptional changes may limit the identification of direct targets that could serve as biomarkers of response to KDM5 inhibitors.

Overall, treatment with epigenetic inhibitors offers the possibility of broadly modulating cancer cell transcriptional activity and, although their therapeutic benefit as single agents may present some limitations, their ability to promote the expression of previously silenced genes can favor the presentation of new antigens; thus, their application in combination with immunotherapies could be promising.[10]

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MYELOID NEOPLASIA

Fitness for intensive chemotherapy: a continuing conundrum

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In this issue of *Blood*, Sorror et al[1] address an important issue: Does reducing the intensity of induction therapy in acute myeloid leukemia (AML) improve outcomes in the elderly. A multicenter retrospective and prospective non-randomized cohort study was conducted to examine outcomes with intensive or nonintensive chemotherapy (NIC) among patients stratified by a multimodal AML composite risk score (with higher scores given to older age, increased comorbidity burden, and adverse cytogenetic risk). In addition, the authors examined the impact of chemotherapy intensity on quality of life, patient, and physician perceptions of outcome.

The median age of AML at diagnosis is 68 years; therefore, most patients are considered "elderly" and face the complex decision of whether to choose intensive or NIC for their initial treatment. From a population registry perspective, the proportion receiving intensive chemotherapy (IC) declines with age: 60 to 69 (83%), 70 to 74 (67%), 75 to 79 (39%), and 80 to 84 years (12%) (Swedish Registry 2014-2019; Gunnar Juliusson, Lund University Cancer Centre, written communication, 23 February 2021).[2] Among older adults with AML, complete remission after IC declines with age: 60 to 69 (78%), 70 to 74 (68%), 75 to 79 (62%), and 80 to 84 years (48%), but early death increases: 60 to 69 (6%), 70 to 74 (9%), 75 to 79 (13%), and 80 to 84 years (13%). Two-year survival also declines with age: 60 to 69 (~40%), 70 to 74 (~30%), and 75 to 84 years (~20%). As a result, there is reduced enthusiasm to administer IC to older patients, with the assumption that lower intensity options may spare the patient a prolonged stint in hospital, while maintaining quality of life (QOL) and lowering the risk of early death. In the United States, Surveillance, Epidemiology, and End Results data from 2000 through 2009 indicate that 60% of patients with AML older than 65 years receive no chemotherapy and have a median survival of only 1.5 months.[3]
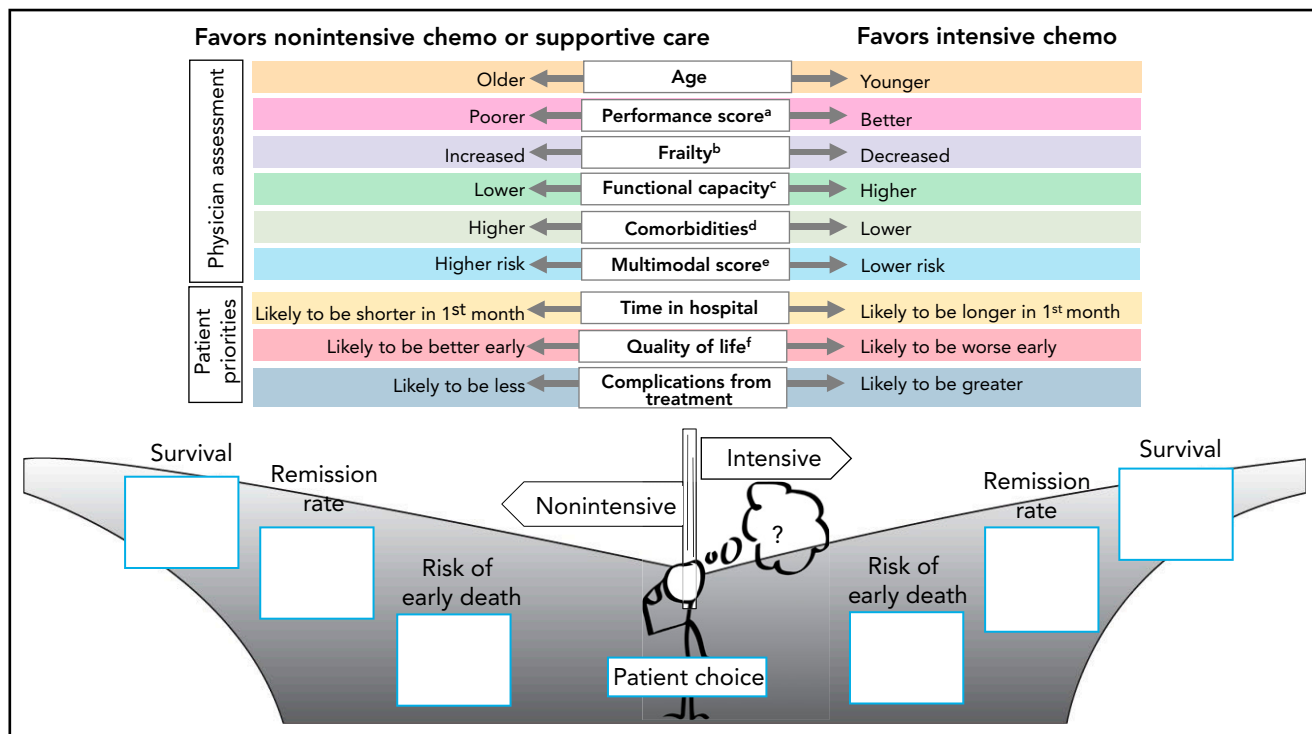
Figure. Factors to consider when evaluating appropriateness of intensive vs non-intensive chemotherapy among older patients with AML. Factors known to increase the risk of early death and reduce survival after IC include increasing age (eg, ≥75 years), poorer performance status ([a]Eastern Cooperative Oncology Group or Karnofsky Performance Scale), increasing frailty ([b]as assessed by the 6-minute walk test, grip strength, or timed chair stand), reduced functional capacity (as assessed by activities of daily living and instrumental activities of daily living), increased comorbidity burden ([d]as assessed by the hematopoietic cell transplant comorbidity index or Ferrara criteria), and higher multimodal AML score ([e]such as with the AML-composite model). The physician should also assess the importance to the patient of time spent in hospital, the current impact of AML on his or her quality of life ([f]as assessed by Functional Assessment of Cancer Therapy-General or other scales) and their understanding of potential complications associated with treatment options being considered. Because patient perceptions of outcome are generally more optimistic than those of the physician, clear advice should be given regarding the risk of early death, expected remission rate and overall survival likely from an intensive, nonintensive, or supportive care approach.

Apart from age, a multitude of factors influence outcome after IC in AML.[4] Poor performance status, increasing frailty, concurrent comorbidities, and poorer AML prognosis are collectively perceived as reducing the risk-benefit ratio associated with IC. Patients may also have subjective views on the length of time they are prepared to spend in hospital, as well as the impact on QOL and physical and social function they are prepared to risk in pursuit of survival. Many physicians use an end-of-the-bed assessment in determining reduced fitness in older patients. Recommendations for less intensive treatment are often based on retrospective data, suggesting that the higher initial responses associated with IC fail to translate into improved overall survival (OS), compared with less intensive approaches. Data on this topic, however, remains contentious.[5,6]

Unfortunately, no standardized method exists for identifying which older patients would be best served by NIC. In recent clinical trials involving older/unfit AML,

age ≥75 years, or if below this age threshold, presence of at least 1 organ comorbidity or Eastern Cooperative Oncology Group (ECOG) 2-3 function has defined incompatibility for IC. However, in an attempt to validate this model, a retrospective study in 703 patients receiving IC found that 4% were ≥75 years, 5% had an infection-related complication, 4% had ECOG ≥3, and <5% had any of the defined organ comorbidities (cardiac, liver, renal, cognitive, or other).[7] Although 21% had a respiratory function test abnormality, this was within a subset of patients (52%) that already had respiratory function tests performed. Therefore, physicians had already excluded patients with most of these criteria from receiving IC.

Sorror et al therefore studied whether a quantitative AML risk score could identify patients at higher risk of inferior OS and QOL if given IC, compared with NIC. They applied the "AML composite model" (AML-CM), which quantifies comorbidities using an "augmented" hematopoietic cell transplant comorbidity index, that incorporates baseline

age, albumin, platelet count, and lactate dehydrogenase, along with cytogenetic and molecular risk according to the European LeukemiaNet 2017 classification.[8] The authors retrospectively analyzed 1292 patients receiving AML therapy and surprisingly found that patients receiving IC had superior OS compared with those receiving NIC options, regardless of the AML-CM score. However, when limited to those ≥65 years, OS was in favor of IC if the AML-CM score was 7 to 9, but not for those with a score of 4 to 6 or ≥10. When the cohort was restricted to patients 70 to 79 years (n = 245), OS benefit in favor of IC if the AML-CM score was ≥4 was marginal. Notably, median OS was <9 months for both IC and NIC cohorts, suggesting poor outcome, despite IC.

The authors then sought to validate their findings using a prospective cohort of 692 patients, of whom 43% were ≥65 years and 23% 70 to 79 years. In patients with AML aged 70 to 79 years, there was no impact of chemotherapy intensity on survival outcome, regardless of the AML-

CM score. Among patients ≥65 years, there were no longitudinal QOL outcomes (Functional Assessment of Cancer Therapy-General, EuroQol-5D, Patient Health Questionnaire 9, instrumental activities of daily living, activities of daily living, or walk test) that suggested an advantage for NIC. The median number of days spent in hospital during the first 3 months was 50% lower for recipients of NIC vs IC (17 vs 37 days). Counterintuitively, when patients were asked to rank their chance of cure, 48% receiving NIC thought their chances were "good" and 69% ranked this as their main objective of treatment. In contrast, physician assessment of the chance of cure was only 1% and 7%, for IC and NIC, respectively. This highlights the abysmal correlation between patient and physician expectations from treatment and the need for improved communication methods. The work by Sorror et al provides important perspectives regarding the impact of IC in older patients. First, patients receiving IC may have superior outcomes over NIC options, although less likely for patients ≥70 years. Second, the negative impact on quality of life from IC vs NIC is not as large as we might expect, although length of hospitalization from IC is longer. Third, patient expectations of cure are overly optimistic. The main limitation of the study was the lack of randomization and the relatively small proportion of patients with advanced age who actually received IC. Despite the many assessment tools used, perhaps the treatment decision had already been predetermined by the physician or patient.

For the majority of older patients with AML, the choice between IC or NIC remains complex and multifactorial. Although several randomized studies comparing IC with hypomethylating agents are pending, results have yet to be published. Furthermore, recent studies showing improved remission rate and OS from venetoclax in combination with azacitidine make it likely that any comparisons between IC and NIC will need to be reevaluated in light of this new regimen.[9] So, how should patients be counseled today? The figure outlines some factors to consider when evaluating older patients for appropriateness for IC or NIC. No single tool is perfect; therefore, the physician should gather information using a range of measures to enable an objective assessment of the patient's physical and functional status. Ultimately,

the final decision rests with the patient and the hematology team should ensure a structured approach is in place to provide the patient with clear, accurate and objective information, with verification that the patient's expectations of outcome are aligned with those of the assessing physician.

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PLATELETS AND THROMBOPOIESIS

Comment on Guo et al, page 401

Platelets modulate T-cell activity

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In this issue of *Blood*, Guo et al[1] demonstrate by a combination of ex vivo human and in vivo mouse model experiments that platelets modulate CD8+ T-lymphocyte response during sepsis, causing diminished specific CD8+ T-cell counts and function (eg, cytokine release). In a murine model of polymicrobial sepsis, this platelet-mediated downregulation of CD8+ T lymphocytes is associated with reduced survival. This finding is surprising, because platelets induced an increase in CD8+ T-lymphocytes and cytokine release in a mouse model of cerebral malaria and in murine infections with lymphocytic choriomeningitis arenavirus,[2,3] raising the possibility that the role of platelets differs, depending on whether the pathogen is a bacterium, a virus, or a parasite.

Using a cecal ligation and puncture polymicrobial sepsis model, the authors convincingly show that platelets upregulate expression of major histocompatibility complex class I (MHC-I, HLA-I) during

sepsis. These MHC-I molecules on platelets seem to be responsible for downregulation of specific CD8+ T lymphocytes. In a platelet-lineage–specific mouse model where β2 microglobulin (required for