Future ONCOLOGY

EDITORIAL

Toward a better management of older patients with acute myeloid leukemia

"...besides the scientific challenges to be met, we ought to focus on the optimal use of currently available tools to ensure excellent clinical care."

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• acute myeloid leukemia
• azacitidine • older patients

The median age at presentation for patients with acute myeloid leukemia (AML) is 67 years [1]. This translates into roughly more than three-fourths of the patients being older than 65 years. In our daily practice we use 65 years of age as a margin to delineate older patients from younger patients with AML. Whereas significant progress has been made in the treatment of younger patients, survival rates among older patients remain poor with a median survival of only a few months [2]. This difference is related to the biology of the disease and to the progressive functional decline of organs and tissues associated with ageing. On clinical grounds, aging frequently translates into frailty – in other words, poor tolerance of cytotoxic chemotherapy. More than two-thirds of older patients have adverse prognostic features such as adverse cytogenetics and pre-existing myelodysplastic syndrome (MDS) so that disease tends to be chemotherapy-resistant [1–3]. Yet intensive treatment in older patients leads to an overall probability of complete response (CR) of 50%, median remission duration of 9 months and leukemia-free survival at 3 years of 15% [3,4]. Withholding chemotherapy generally results in low survival rates and a poor quality of life. There is an evidence from the Swedish registry that the outcome among older patients with AML is better in geographic regions where intensive chemotherapy is offered than in regions where it is not [5]. Despite major improvements in supportive care, there is a substantial risk of early death (up to 25%) and the potential for serious harm in older patients after induction chemotherapy which means that the risks and benefits of treatment must be weighed carefully when formulating a treatment plan.

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Much of the controversy in the treatment of AML centers on which older patients are suitable for intensive treatment [6]. Researchers have developed predictive scores for estimating the likelihood of CR or early death associated with chemotherapy but these have not infiltrated clinical practice in most centers [7,8]. In making this judgment, we wait for the cytogenetic and mutational-analysis results. Support for this comes from a study where delaying

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chemotherapy until the cytogenetic findings were known had no impact on the outcome in older patients [9]. The presence of adverse karyotypes and secondary AML indicate a low likelihood of CR: patients with adverse karyotypes have a CR rate of 40% and an estimated 12-month survival of 19%, whereas patients with both adverse karyotypes and secondary AML have a CR rate of only 24% [3,10]. Furthermore, a basic clinical assessment for comorbid illnesses, disabilities and frailty provides critical information about the patient's ability to tolerate chemotherapy – bedridden patients and patients older than 80 years tend to die early after chemotherapy (median survival 5 weeks) [3]. By these means, we customarily classify our patients on the basis of simple criteria as to whether they are eligible for intensive treatment or not. We believe that the risk-benefit ratio of intensive chemotherapy is unfavorable among older patients with adverse cytogenetic or molecular lesions [11], pre-existing MDS or high probability for treatment-related death (i.e., performance status 3–4, age over 80 years or severe comorbidities) and a different therapy should be offered. By contrast, fit patients (or vulnerable patients with reversible impairment after medical intervention) with cytogenetically favorable-risk or intermediate-risk AML should be considered eligible for induction chemotherapy. The regimen that we use is the standard cytarabine and daunorubicin combination (DA60). Attempts to increase CR rates with the use of additional agents and daunorubicin escalation have generally failed, although there is some evidence that the addition of gemtuzumab ozogamicin to induction chemotherapy may lead to longer survival [12]. Many questions remain to be resolved such as the optimal number of post-induction courses and the role of maintenance therapy. Considerable data indicate that highly selected patients might benefit from reduced intensity allogeneic transplantation from a suitable stem-cell donor [13,14]. Clearly, chemotherapy alone is unlikely to improve the cure rates in this large subset of patients and therefore new approaches to therapy are needed.

The burden of disease in the bone marrow may provide practical information about decision-making. Slowly progressive AML (*de novo* or MDS-related) is seen in some older patients with 20–30% bone marrow blasts in whom cytopenia is the main symptom. Use of the hypomethylating agent azacitidine has become standard treatment in these patients based on data from a randomized trial in which the median survival was 24.5 months for azacitidine group versus 16.0 months for conventional care group [15]. Beyond this straightforward choice, treatment modifications may be needed according to an individual patient's characteristics.

Outside of clinical trials, older patients with more than 30% bone-marrow blasts who are not deemed suitable or fit for intensive chemotherapy are currently treated with supportive care or low-dose cytarabine. In a clinical trial in patients who were thought unfit for induction chemotherapy, low-dose cytarabine led to a longer survival than best supportive care [16]. Although low-dose cytarabine has been adopted as standard care, it is inadequate for the vast majority of patients – the median survival is 4 months, at least 80% of patients die within 1 year and patients with adverse karyotypes do not benefit. A natural consequence of the success of azacitidine in MDS-related AML was the question of whether it could be used in patients with higher blast counts. Therefore, a Phase III, multicenter, randomized trial was undertaken to compare outcomes in older patients with newly diagnosed AML who received either azacitidine or conventional care regimens (CCRs, which included one of the following: standard induction chemotherapy, low-dose cytarabine or supportive care) [17]. All patients had bone-marrow blasts over 30%, white-cell count less than 15×10^9/l and either intermediate-risk or unfavorable-risk karyotypes. Compared with patients who received CCRs, patients who were treated with azacitidine experienced longer median survival (the primary end point; 10.4 months vs 6.5 months; $p = 0.082$) and higher 1-year survival rates (47 vs 34%; $p = 0.001$). The lack of statistical significance in overall survival rate might be explained by the fact that the two curves converged after a follow-up of 2 years, perhaps because conventional chemotherapy might be curative for rare patients. After censoring for subsequent AML therapy, the benefit of azacitidine became significant (12.1 vs 6.9 months; $p = 0.019$). CR was achieved in 28% of patients who received azacitidine and in 25% of those who received CCRs. This important observation suggests that azacitidine benefits patients beyond the achievement of CR. The findings of this study are consistent with the largest overall and 1-year survival benefit seen with a low-intensity therapy among older patients with AML [16–18]. There is no doubt that this trial generates data to inform and to reform medical thought

and practice. However, the entry criteria of the trial leaves unanswered the important question what is the role of azacitidine in older patients who have proliferative-type AML (white cells above 15 × 10^9/l). Because of the lack of molecular data, there is also some controversy over which factors influence the effectiveness of treatment.

Current efforts in clinical research focus on the discovery of new treatments that are intended to provide an improvement in efficacy over existing therapies. Trials are under way to determine whether epigenetic modulation of leukemic blasts with use of azacitidine and vorinostat, or azacitidine maintenance therapy after chemotherapy, might be beneficial in older patients with AML. Notably, molecularly targeted therapies are increasing within new drug regimens. For example, investigational agents undergoing development for use in AML include FLT3 inhibitors, polo-like kinase inhibitors, farnesyltransferase inhibitors, HSP90 inhibitors, Mdm2 inhibitors, anti-CD123 and anti-CD47 antibodies, and novel nucleoside analogs.

Certainly the clinician who consults patients with AML would welcome the addition of azacitidine to the current options for older patients who are not eligible for intensive chemotherapy. Findings from cancer registries suggest that up to 70% of older patients are not offered any treatment other than supportive care [19]. Many patients do not undergo cytogenetic studies and only a minority of older patients enroll in clinical trials [20]. Thus, besides the scientific challenges to be met, we ought to focus on the optimal use of currently available tools to ensure excellent clinical care. As pointed out by William Osler, "The best preparation for tomorrow is to do today's work superbly well."

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