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Management of Older or Unfit Patients with Acute Myeloid Leukemia

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Abstract

Acute myeloid leukemia (AML) is primarily a disease of older adults, for whom optimal treatment strategies remain controversial. Because of the concern for therapeutic resistance and, in particular, excessive toxicity or even treatment-related mortality, many older or medically unfit patients do not receive AML-directed therapy. Yet, evidence suggests that outcomes are improved if essentially all of these patients are offered AML therapy, ideally at a specialized cancer center. Medical fitness for tolerating intensive chemotherapy can be estimated relatively accurately with multiparameter assessment tools; this information should serve as basis for the assignment to intensive or non-intensive therapy. Until our accuracy in predicting the success of individual therapies improves, all patients should be considered for participation in a randomized controlled trial. Comparisons between individual trials will be facilitated once standardized, improved response criteria are developed, and standard treatment approaches have been defined against which novel therapies can be tested.

Keywords

Acute myeloid leukemia (AML); older adult; resistance; therapeutic fitness; treatment; treatment-related mortality

INTRODUCTION

Acute myeloid leukemia (AML) primarily affects older adults (Figure 1A), for whom outcomes have not substantially improved in the last 4 decades.^{1–3} Recent data indicate a median survival of 3 months for patients >65 years – with slightly higher estimates for 66–75 year olds (~6 months) than 76–89 year olds (~2.5 months) – and merely ~5% alive 5 years after initial diagnosis (Figure 1B).^{1, 4–7} Considering that the average life expectancy at age 65 approaches 20 years and is still >5 years at age 85 (Figure 2),⁸ the AML-attributable years of life lost are enormous.

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Conflict of Interest

The authors declare no competing financial interests.

AML in older adults brings two challenges. First, the disease commonly has features associated with therapeutic resistance, including adverse genetic or epigenetic abnormalities, drug transporter activity, and history of antecedent hematologic disorder or prior chemo/radiotherapy.^{9, 10} And second, older patients are on average more likely to be intolerant of intensive chemotherapy and to experience treatment-related mortality (TRM) than younger individuals. The presumption that potential risks are not commensurate with potential benefits often leads physicians and/or patients to shy away from AML-directed therapy. Indeed, less than half of Americans aged >65 years with newly diagnosed AML, and as few as 10–20% of those aged >80 years, receive specific chemotherapy, and only a minority does so in specialized cancer centers.^{5, 6} Herein, we review the evidence suggesting that AML therapy improves survival relative to supportive care-only strategies in most older adults. We also discuss means of quantifying the risks of TRM and treatment failure should standard therapies be administered. This information will enable physicians to better advise older patients about their fundamental options: standard or investigational intensive therapy (herein defined as “3+7” regimens or those of higher intensity), or standard or investigational non-intensive therapy.

VALUE OF SUCCESSFUL AML THERAPY

U.S. and European population-based registry data support the use of intensive chemotherapy in most AML patients up to age 80.^{4, 5} Swedish data indicated that early death rates were lower in patients receiving remission induction rather than palliative or no chemotherapy regardless of age. Even after stratification by performance status, survival was longer in regions where a higher proportion of patients received intensive therapy.⁴ American data very similarly indicated lower early death rates if therapy was given within one month of diagnosis, possibly except in individuals >age 80 or those with substantial co-morbidities. Furthermore, up to age 80, overall survival was significantly better with treatment.⁵

While suggesting merits of intensive therapy for many older adults, these observations must be interpreted cautiously as information on exact regimens and individual dose reductions is usually not available and significant bias due to non-random assignment to intensive therapy is possible. Furthermore, benefits from chemotherapy cannot be separated from those associated with the attendant supportive care. Differences in the latter, e.g. more diligent use of transfusions or antimicrobials in patients receiving intensive therapy, could at least partially account for the outcome differences noted. Although randomization to examine this hypothesis is not feasible, the importance of supportive care is suggested by the observation that short- and long-term outcomes appear better in patients who are referred to a specialized cancer center, even after adjustment for age, comorbidities, and receipt of chemotherapy.¹

The value of “response” to AML therapy is well documented. Shortly after the introduction of chemotherapy for acute leukemia, it was observed that patient survival was better if some hematologic response was obtained. This improvement resulted almost entirely from the time spent in response, suggesting that the responders lived longer because of their response rather than an inherently better prognosis.¹¹ We recently confirmed improved outcomes for contemporary patients who obtained a response with initial intensive chemotherapy, with longest survival in those achieving complete remission (CR), but with those achieving CR

with incomplete platelet recovery (CRp) living longer than those who were resistant, even after accounting for various prognostic factors.¹² Survival beyond 3 years after diagnosis was exceedingly unlikely if CR was never achieved.¹² Our study included a significant proportion of patients aged >60 years, reinforcing that some older individuals benefit from intensive induction chemotherapy, as also observed by others.^{13, 14} The value of response to non-intensive therapy was shown in the NCRI/MRC AML 14 trial, which randomized 217 patients aged >65 considered unfit for intensive chemotherapy between low-dose cytarabine or supportive care with use of hydroxyurea as necessary. The CR rate was superior and survival longer in the cytarabine arm, with the improvement being entirely accounted for by the achievement of CR, while toxicity and supportive care needs did not differ between the treatment arms.¹⁵

ESTIMATING TREATMENT TOXICITY AND SUCCESS

These data suggest that a response to AML therapy is beneficial in older individuals. Less clear is which patients should be treated intensely and which non-intensely. Three widely cited studies illustrate this uncertainty. In the first, the EORTC randomized 60 patients aged 65 years to either intensive induction chemotherapy or supportive care with hydroxurea or low-dose cytarabine as necessary and found significantly higher CR rates and better survival for intensely treated patients, whereas the proportion of days spent in hospital was similar.¹⁶ In contrast, a randomized ECOG study conducted in 45 patients aged 70 years showed that lower doses of daunorubicin, cytarabine, and 6-thioguanine resulted in fewer deaths within 60 days of treatment initiation, superior survival, and better quality of life (QOL) than full doses, while remission rates were similar.¹⁷ Yet another conclusion can be reached using data from a French trial randomizing 87 AML patients aged 65 years between low-dose cytarabine or intensive chemotherapy: while the more intensive therapy yielded more remissions, survival was similar because the duration of these remissions was insufficient to offset an increased early death rate; furthermore, the less intensive therapy required less supportive care and shorter hospital stays.¹⁸

These trials highlight the delicate balance between competing positive (treatment efficacy) and negative (resulting toxicity) effects. Randomized investigations would be ideal to determine the value of intensive vs. non-intensive therapy for older patients, but these are very difficult to conduct. For example, although the NCRI/MRC AML 14 trial was designed to randomize between higher and lower intensity treatments, only 8 of the 1,485 recruited patients were randomized between the 2 approaches.¹⁵ Furthermore, while randomized studies assume that all patients share the same potential for benefit and risk from a given therapy, the probabilities of TRM and treatment efficacy differ widely among patients. For instance, TRM with standard induction chemotherapy is <5% in many patients but >50–75% in others; similarly, the CR likelihood can exceed 80–90% in certain patients but may not reach 30% in others.^{19–21}

Estimating fitness for intensive chemotherapy

Numerous factors are associated with TRM, including age and covariates that may serve as surrogates for biological (rather than chronological) age. Such factors underlie several scoring systems aimed at identifying patients at high risk for TRM with intensive

chemotherapy (Table 1).^{22–29} While differing in particulars, each system indicates that decisions about fitness for intensive AML therapy should not be based on a single factor (such as age) but a combination of factors to optimize predictive accuracy. Similarly, recent studies have highlighted the importance of comprehensive geriatric assessments as independent predictors of TRM in older patients with AML.^{30, 31} In conjunction with other factors, these may refine our ability to forecast excess toxicity. This said, the rate of early death following intensive induction chemotherapy has declined considerably over the last 20 years despite relatively unchanged therapeutic regimens.³² Although not specifically obtained in older individuals, these data suggest that intensive therapies can now be given more safely because of better supportive care. Thus, TRM scoring systems will need to be re-assessed and re-calibrated periodically. Nonetheless, they offer an empiric approach of identifying older patients who will likely survive intensive AML chemotherapy.

Quantifying the benefit of standard therapy

With supportive care improvements, primary failure of induction chemotherapy or disease recurrence after short remission duration (“therapeutic resistance”) has become the principal life-limiting problem in AML even in older adults. When large groups of patients are considered, several factors are associated with therapeutic resistance.³³ However, it is important to distinguish “association”, as quantified by p-values, from “prediction”, as quantified by area under receiver operating characteristic curves (AUCs). Prediction is more relevant for patient management, and this ability is more limited than perhaps commonly appreciated. We recently used data from >4,500 adults with newly diagnosed AML to quantify our ability to predict therapeutic resistance with multiparameter models. Because resistance is more complex than TRM, AUCs for resistance models were lower (typically 0.71–0.78) than those previously obtained for TRM models (0.80–0.83).^{27, 34} This finding of only a fair ability to predict CR is consistent with a recent study by Krug *et al.* who observed AUCs of 0.72 and 0.68 with multivariable models in their study cohort.²⁵ Predictive accuracy might be improved by incorporating additional pre-treatment data (e.g. from sophisticated genetic/molecular analyses or from functional signaling pathway assessments of AML cells) or post-treatment data (e.g. early disease clearance or assessment of minimal residual disease [MRD]). Nonetheless, these relatively low AUCs suggest caution to avoid overestimating our ability to predict resistance following standard therapy of AML, which is closer to a coin-flip than certainty in many instances when commonly utilized factors are considered.

BALANCING THE RISKS AND BENEFITS OF INDIVIDUAL THERAPIES AS BASIS FOR TREATMENT ASSIGNMENT

The ability to accurately predict TRM and treatment efficacy (i.e. responses of sufficient length to yield improvements in survival) in older patients with AML following standard therapy would permit more informed decisions about appropriate treatment intensity by weighing anticipated TRM against the benefit of intensive therapy and the use of standard versus investigational therapy. A possible decision process would be: 1) patients with low probability of both TRM and therapeutic resistance would be appropriate for standard intensive therapy; 2) patients with low probability of TRM and high probability of

therapeutic resistance would be appropriate for investigational intensive therapy; 3) patients with high probability of TRM and low probability of therapeutic resistance would be candidates for reduced-intensity standard therapy; and 4) patients with high probability of both TRM and therapeutic resistance would be appropriate for investigational reduced-intensity therapy. The exact criteria for high/low likelihood of TRM/therapeutic resistance would be based on “acceptable” levels of these outcomes in each individual patient or trial. For example, a higher risk of TRM might be more acceptable in a patient with favorable-risk cytogenetics or normal karyotype than a similarly aged patient with very poor risk AML. Underlying this paradigm is the formally unproven assumption that intensive therapy leads to better outcomes than non-intensive therapy if the former can be tolerated.

CHOICE OF STANDARD VERSUS INVESTIGATIONAL TREATMENT

Although in need of refinement, the currently available TRM prediction tools appear accurate enough for decision-making regarding treatment intensity. This leaves the fundamental question as to whether an established (standard) treatment or an investigational therapy should be given. Since the outcome of investigational therapies is inherently unknown, this decision must be based on the anticipated outcome of standard treatment. Usually, there is time to assess pre-treatment prognostic factors. Although physicians and patients often believe that treatment cannot be delayed by 1–2 weeks until cytogenetic and molecular profiles are determined, increasing evidence suggests that such delays are unlikely to be harmful in older patients, in particular if presenting with low white blood cell count.³⁵ Nonetheless, the current limitations in predicting therapeutic resistance complicate rational assignment to standard versus investigational therapy and may place physicians in a difficult ethical quandary. For example, for patients with cytogenetic abnormalities associated with very poor outcome, it is natural to recommend investigational therapy but the relative uncertainty about treatment outcomes will require the continued use of trials randomizing between standard and new therapies. Several strategies may partially alleviate this problem, including use of adaptive randomization or less restrictive stopping rules.

STANDARD INTENSIVE AND NON-INTENSIVE TREATMENT APPROACHES

As discussed below, the optimal standard treatment strategy remains uncertain in many situations, and several approaches can be considered.

Standard treatment algorithms for older, medically fit adults with newly diagnosed AML

For 4 decades, 3 days of an anthracycline or the anthracenedione mitoxantrone in combination with 7 days of continuously infused cytarabine (“3+7” regimen) has remained the mainstay of remission induction therapy for younger adults.³³ While results are not as satisfactory as in younger patients, these regimens can be considered as standard for older patients with low TRM probability, although benefits are greater in patients with favorable- and intermediate-risk disease than in those with adverse-risk disease.^{9, 10} Recent data suggest that improvements can be achieved in some patients with escalated doses of anthracyclines, additional of gemtuzumab ozogamicin, or high-dose cytarabine-containing regimens such as FLAG-idarubicin.^{20, 36, 37} Nonetheless, most remissions will last <6–12 months. In contrast to younger patients, the value of post-remission therapy is not

established, and there is no generally accepted post-remission treatment. Little efficacy has been noted with repeated cycles of low- to intermediate-dose cytarabine, which may improve disease-free but not overall survival, while escalation of cytarabine doses, increasing the number of post-remission cycles, or addition of cytotoxic agents to cytarabine typically has not improved survival while often producing increased toxicity. Perhaps as another reflection of the balance between efficacy and toxicity, repeated doses of ambulatory chemotherapy may be equivalent or better than intensive consolidation.^{9, 10}

Reduced-intensity or nonmyeloablative conditioning regimens have extended the age range of patients suitable for allogeneic hematopoietic cell transplantation (HCT) to 70–75 years and perhaps older. As with induction chemotherapy, models that focus on factors other than age (e.g. comorbidities) have been used to select patients unlikely to incur TRM after HCT,³⁸ but recent population-based data indicate that only about 2–3% of adults with AML aged 65–74 years undergo allogeneic HCT.^{5, 6} In these highly selected patients, however, allografting with various stem cell sources can produce long-lasting remissions, with age per se not having any effect on transplant outcomes,^{39–41} although the exact value of HCT relative to conventional post-remission chemotherapy is difficult to determine given the highly selected nature of HCT patients. A Markov decision analysis found that older adults with intermediate- or unfavorable-risk AML lived longer with allogeneic HCT, but this benefit became less impressive after adjusting for QOL.⁴² Preliminary data from the CIBMTR and the CALGB revealed that, in adults ≥60 years, reduced-intensity HCT was associated with a significantly reduced risk of relapse and a trend toward longer relapse-free survival (RFS) relative to conventional chemotherapy; however, HCT was associated with more TRM, resulting in an overall survival (OS) that was not significantly different,⁴³ again emphasizing the intricate balance between disease control and TRM in this patient population.

Standard treatment strategies for medically unfit adults with newly diagnosed AML

For many years, low-dose cytarabine served as non-toxic standard regimen for older, often medically unfit, patients with newly diagnosed AML. However, CR and survival rates, while statistically significantly better than those with supportive care and hydroxyurea, are relatively modest and may not extend to patients with unfavorable-risk disease.¹⁵ Today, the DNA methyltransferase inhibitors azacitidine or decitabine are probably most commonly used in the U.S. for older patients, even for those considered fit. In 113 patients with AML and 20–30% blasts randomized to azacitidine 75 mg/m² for 7 days every 4 weeks or physicians' choice of conventional care (supportive care-only, low-dose cytarabine, or intensive chemotherapy), azacitidine was associated with longer median survival (24.5 vs. 16 months) and less time in hospital than conventional care regimens,⁴⁴ although the number assigned to intensive therapy was too small to draw firm conclusions. A similar trial randomizing 485 patients with > 20% blasts to decitabine (20 mg/m² daily for 5 days every 4 weeks) or physicians' choice of supportive care-only or low-dose cytarabine found superior median survival with decitabine (7.7 vs. 5 months);⁴⁵ whether longer courses of decitabine⁴⁶ have better risk/benefit profiles is currently under investigation. Generalization of these results is hampered because the median survival difference in the conventional care arms in the two studies is greater than that between conventional care and either azacitidine

or decitabine, perhaps reflecting various biases and/or the exclusion of patients with >30% blasts from the azacitidine trial. While responses with azacitidine and decitabine are seen across all risk subgroups, validated predictive tools to identify patients particularly likely to benefit from these drugs based on pre-treatment characteristics have not yet been introduced in the clinic.⁴⁷

Standard treatment strategies for relapsed/refractory disease

Although many studies have been conducted in older adults with relapsed or refractory AML, no treatment algorithms have been established. A major difficulty in interpreting relevant studies is that they are, typically, small, uncontrolled single arm studies, and it remains unknown whether results are better than an older therapy.

CONSIDERATIONS FOR TESTING OF NEW THERAPIES

Progress in the treatment of older adults with AML will require the conduct of trials that are relevant to daily practice, devoid of selection bias, and comparative to currently available (standard) therapy. With these requirements, it is not difficult to point out challenges for drug evaluation in this patient population.⁴⁸ Perhaps foremost is the risk of selection bias. AML patients enrolled on clinical studies tend to have better performance status and organ function and more favorable disease characteristics,⁴⁹ such common trial eligibility criteria select subsets of older patient with significantly better survival expectations than other patients of the same age.³ A second challenge is the choice of control group. Today, many AML trials include no control group or use “historic” patient cohorts for comparison. Recent reductions in TRM may render results in “historic” controls unrepresentative of results that would be obtained should contemporary patients receive the historic therapies. Although ethically problematic in some instances, controls would thus ideally be concurrently randomized to standard treatment, at least until we are able to more accurately predict outcome if a given patient received the control treatment. Biological heterogeneity constitutes a third challenge. Emphasis on average results leads to ignorance of discordant findings in specific subgroups, with the overall conclusion that a drug is “promising” (not promising) merely reflecting the relatively favorable (unfavorable) patients treated. As therapy becomes more individualized, this heterogeneity will further increase, and it may be impossible to retain conventional false positive and false negative rates as trials otherwise become inordinately lengthy.

Critically important is the choice of trial endpoint(s). Many phase 2 studies have used CR rates as primary endpoint, assuming that they tightly correlate with survival. Although remission achievement has unique value as a necessary precursor of long-term survival,¹² and may be valuable in its own right, investigational therapies that significantly increase CR rates do not necessarily prolong survival,^{50, 51} probably because many patients relapse quickly and fail salvage therapies. More stringent definitions of CR (e.g. CR without evidence of MRD) may render CR more relevant as endpoint, but focus on event-free survival (EFS) and/or RFS may be advisable. Unlike OS, EFS and RFS are not affected by subsequent salvage therapy; they also occur earlier than OS, thus shortening the study duration. As a potential disadvantage, these survival endpoints are composite endpoints that can be affected by competing events that are non-cancer related (e.g. death from comorbid

diseases),⁵² a fact that will become more relevant in this older patient population once more efficacious AML therapies are available.

So far neglected are endpoints of QOL, which is greatly impaired in AML patients on many levels^{53,54} and may be the most important consideration along with life expectancy.

Unfortunately, the lack of validated measures of QOL specific to AML and methodological limitations have hampered use of such endpoints⁵⁴ although they can lead to drug approval in the U.S.⁵⁵ Since focus on single outcomes ignores the complexity of medical practice, consideration should be given to statistical approaches that formally monitor multiple outcomes, with early trial stopping when it becomes likely that improvement in at least one outcome is improbable. Given the balance between therapeutic efficacy and treatment-related toxicity, monitoring multiple endpoints appears ideal for older or “unfit” adults with AML.

In addition to the evaluation of new therapies in patients with active AML, consideration should be given to testing in those in remission. The latter not only have lower disease burdens, but also have demonstrated at least some sensitivity to chemotherapy, thus reducing the risk of false negative conclusions regarding drug efficacy. Many patients in CR will have MRD, which can serve to rapidly identify active drugs. A final issue to consider is the number of courses that should be given before patients can be considered “refractory”. With 3+7, up to 2 courses should be given.⁵⁶ With new drugs, the appropriate number of courses required before failure is assumed is by definition unknown but must strike a balance between declaring failure too early and continuing too long in the face of non-response to permit trials of other new therapies.

New drugs and drug combinations are being introduced at ever accelerating rates. This is problematic given the length and cost of the traditional drug development process.⁴⁸ Several approaches may render this process more efficient, including the use of randomized phase 2 studies or selection (“pick-the-winner”) designs to screen several new therapies in a relatively small number of patients with the goal of prioritizing them for examination in phase 3, the use of Bayesian designs to allow for adaptive randomization or accounting for prognostic heterogeneity, and the monitoring of multiple endpoints.⁵⁷ Many of these designs can be criticized as “inadequately powered”. However, numerous drug discoveries have been serendipitous, and the worst false negative may result if a drug is not tested at all.

CONCLUSIONS

Outcomes for older adults with AML are typically unsatisfactory. The available data suggest that essentially all older patients should be considered for specific chemotherapy, preferably at a specialized cancer center. Medical fitness should then be determined with multiparameter assessment tools, and the estimated TRM probability used to assign to intensive or non-intensive therapy based on the toxicity risk that is considered acceptable. Until the accuracy to predict the success of individual therapies improves, all patients should be considered for participation in a randomized controlled trial, although treatment with a standard regimen may be appropriate in certain circumstances, e.g. if the response to standard therapy is thought to be very likely or a clinical trial is not available. Comparisons

between individual trials will be facilitated if standardized response criteria are used, and, as e.g. done in Germany, the research community reaches consensus on what constitutes standard AML treatment.

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Figure 1. Incidence and Mortality of AML

Surveillance, Epidemiology, and End Results (SEER) Cancer Registry estimates of incidence and mortality of AML in the U.S.⁷ (A) Age-specific incidence rates, SEER 18 areas, 2007–2011. Rates are given per 100,000 and are age-adjusted to the 2000 U.S. Standard Population. (B) 5-year relative survival for men and women of all races, SEER 18 areas, 2004–2010.

Figure 2. Life Expectancy of Older Adults

U.S. Social Security Administration estimates of the average remaining number of years expected prior to death for man or woman of that exact age, born on January 1, using the mortality rates for 2009 over the course of his/her remaining life in the Social Security area population (period life table).⁸

TABLE 1

Tools to Estimate Treatment-Related Mortality with Intensive Induction Chemotherapy

Study	Covariates
Kantarjian <i>et al.</i> (2006) ²²	Age, PS, cytogenetics, duration of AHD, treatment outside laminar flow room, abnormal organ function
Giles <i>et al.</i> (2007) ²³ Savic <i>et al.</i> (2012) ²⁸	HCT-CI
Malfuson <i>et al.</i> (2008) ²⁴	Age, PS, infection, HCT-CI, WBC, cytogenetics
Kantarjian <i>et al.</i> (2010) ²⁶	Age, PS, cytogenetics, creatinine
Krug <i>et al.</i> (2010) ²⁵ *	Body temp, Hb, platelets, fibrinogen, LDH, age, cytogenetics
Walter <i>et al.</i> (2011) ²⁷ **	Age, PS, platelets, albumin, 2 nd AML, WBC, creatinine, PB blast%
Valcárel <i>et al.</i> (2012) ²⁹	Age, WBC, creatinine

Abbreviations: AHD, antecedent hematologic disorder; Hb, hemoglobin; HCT-CI, hematopoietic cell transplantation-comorbidity index; LDH, lactate dehydrogenase; PB, peripheral blood; PS, performance status; WBC, white blood cell count

* Calculator available online: <http://www.aml-score.org>

** Calculator available online: <http://cstaging.fhcrc-research.org/TRM/Default.aspx>