How I treat the older patient with acute myeloid leukemia

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Acute myeloid leukemia (AML) in older patients presents a notable therapeutic challenge to the clinical hematologist. The clinical biology of AML among patients is highly heterogeneous. Interpatient variations are relevant for prognosis and treatment choice. Outcome of treatment for patients of advanced age is often compromised by comorbid conditions and an enhanced susceptibility to toxicities from therapy. Here we present selected clinical vignettes that highlight distinct representative situations derived from clinical practice. The vignettes are specifically discussed in light of the perspective of treating older patients with leukemia. We review the clinical significance of various cytogenetic and molecular features of the disease, and we examine the various currently available treatment options as well as the emerging prognostic algorithms that may offer guidance in regard to personalized therapy recommendations. The dilemmas in tailoring treatment selection in this category of patients with AML are the central theme in this discussion. (Blood. 2015; 125(5):767-774)

Introduction

The median age of patients with acute myeloid leukemia (AML) is around 70 years.1 Calendar age reflects an absolute value but it ignores the “biological age” that is representative of the physical condition, which may vary considerably among older people of the same age. In any event, although old age is not a feature that defines a disease entity, it is of significant clinical relevance because it confers a profound prognostic impact on disease outcome. Treatment outcome in patients with AML continuously declines with progressively increasing age.2 Some of the key questions for clinical hematologists in daily practice are: (1) Which patient of an older age can receive intensive treatment and not experience prohibitive toxicity? and (2) Even in those who can tolerate such chemotherapy, would disease features make the likelihood of benefit so low that non-intensive therapy would be a better option?

In industrialized societies, the average life expectancy of a person at age 65 years is still approximately 15 to 20 more years, which underscores the considerable lifetime that can be gained if AML at that age could be cured. Specific clinical trials have been dedicated to the older-aged segment of patients with the objective of improving their treatment outcome. Clinical trials for practical reasons have usually applied age cutoffs above ages 60 to 70 years as operational definitions for older patients. Enrollment in such trials usually implies that the investigator assumes that the patient will tolerate intensive chemotherapy. On average, a significant proportion of about 50% to 60% of patients will successfully attain a complete remission (CR). However, such fairly high rates of good response translate into a 2-year survival of only about 15% to 20%.3 These outcome results have only very modestly improved in the last decade, in particular in patients younger than 75 years.4-6 However, there is a significant individual heterogeneity that likely accounts for a substantial variation in treatment outcome among patients (eg, in relation to leukemia cytogenetics and molecular genetics).3,4 The determinants of success and failure nevertheless remain only partly understood.

These determinants are clearly multifaceted and include a combination of patient-related and specific disease-related factors.1

- Patient-related prognostic factors: Comorbid conditions are more frequent in patients at an older age. These and performance status are among the most critical patient-related factors. Pharmacokinetic and pharmacodynamic changes result in decreased drug clearance, causing extended prolonged exposure to chemotherapeutics. The decreased immune competence of elderly patients results in less tolerability of infections. This all influences outcome because of increased toxicity of the treatment. In addition, psychosocial factors like cognitive decline, social isolation, and, often, lack of caretakers are factors that influence the outcome. The patient-related determinants may create hurdles to sufficiently deliver dose-intensive chemotherapy safely.

- Disease-related prognostic factors: Higher frequencies of adverse cytogenetics and unfavorable molecular aberrations, multidrug-resistant abilities of the leukemia cells to expel the chemotherapeutics that had initially entered the cell, and antecedent hematologic disorders are all more common among the aging population. They correlate markedly with treatment failure (ie, primary resistance and relapse after induction therapy).4 A distinct gene-expression profile noted for older compared with younger patients supports a molecular basis for poor outcomes in elderly patients.8,9

In this article we present 4 selected clinical vignettes that highlight our treatment approach in clinical practice in light of the biology of the disease, and we discuss some of the common practical issues and dilemmas we have encountered in the therapeutic management of older patients with AML.

Which patients qualify as candidates for intensive treatment?

Population data from the Swedish Acute Leukemia Registry suggest that the majority of older patients should be regarded...
as candidates for intensive chemotherapy. These national registry data show that, in general, older patients with AML fare markedly better receiving intensive chemotherapy than palliative treatment. Performance status rather than age in the strict sense is predictive of early mortality.\textsuperscript{10,11} Yet a particular proportion of AML patients will not tolerate the use of intensive chemotherapy. Those patients may be offered demethylating agents (eg, decitabine, azacitidine) as a less-intensive modality of treatment.\textsuperscript{12} The recognition of patients who may more likely benefit from an intensive treatment approach should ideally be based on baseline assessments. It remains a challenge both to identify those patients before the start of treatment and to define their features. A variety of composite multifactorial risk algorithms have been proposed in which patient-specific factors (eg, performance, comorbidity scores) together with disease-specific factors (eg, [cyto]genetics, white blood cell counts, percent marrow blast count, secondary leukemias) have been taken into account to predict treatment effectiveness and lend support to a documented choice between intensive treatment and various other treatment possibilities.\textsuperscript{13-15} An inherent limitation of all of these risk algorithms is that they have been derived from data of a patient population that had already been selected for intensive treatment, and thus they do not reflect the average real world of older patients with AML who normally present in our consulting room. For instance, in the French ALFA 9803 trial (elderly AML trial), no more than 5% of the included 416 patients had 3 or more comorbidities.\textsuperscript{16} The Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) scoring system, which is based only on comorbidities and was developed for estimating transplant-related mortality, has also been evaluated for patients with AML treated with intensive chemotherapy. It appears of some use for selecting patients for intensive chemotherapy because it provides a reflection of their concomitant diseases.\textsuperscript{17} For example, a relatively high HCT-CI score of $\geq 3$ is associated with an early death rate that may be as high as 30%. More recently, another prediction model for early mortality after induction therapy that is based on age, performance status, and platelet count has been introduced and validated in independent cohorts of patients.\textsuperscript{18} Geriatric assessments with a focus on cognitive and physical functions have also been demonstrated to express predictive value for outcome of induction treatment in elderly patients with AML.\textsuperscript{19,20} Nevertheless, the reality of clinical trials implies that a certain proportion of older patients will always be excluded from intensive chemotherapy trial participation irrespective of these assessments because of their inability to meet the eligibility criteria. As yet, none of these risk algorithms has become widely accepted. However, the decreased rate of treatment-related mortality in intensively-treated patients recently described could be partly explained by a better selection of patients suitable for this intensive therapy.\textsuperscript{21} Additional research on the developments of measurements that are solidly validated and (preferably) quite easily applicable in clinical practice is ongoing. Conversely, particular disease-specific biological characteristics of AML may be associated with such a poor outcome that even though patients may be considered medically fit, they will not likely benefit from intensive treatment and therefore should perhaps rather be offered a less intensive or investigational approach. The biological characteristics of these high-risk AMLs include, for example, overexpression of the oncogene EVI-1,\textsuperscript{22,23} ASXL1 gene mutations, biallelic FLT3-ITDs, p53 gene mutations,\textsuperscript{24} and complex and/or monosomal karyotypes.\textsuperscript{3,25} We would consider intensive treatment in such patients only in case an allogeneic hematopoietic stem cell transplantation (HSCT) is foreseen as a possible prospective option after attainment of CR.

**Patient 1: AML with unfavorable features in a 68-year-old man**

This 68-year-old man was diagnosed with AML with a relatively low blast count (marrow blast infiltrate 21%) with normocytic anemia (Hgb 5.5 mmol/L), a white blood cell count (WBC) of $3.5 \times 10^{9}$/L, and a severe thrombocytopenia of $25 \times 10^{9}$/L. Cytologic examination of the marrow showed dysplastic signs in various cell lineages and an abnormal karyotype with 45,XY,1p-,17q-,20q-,~22, +mar1 (4). Thus, the patient presented with a notably unfavorable type of AML that included a complex karyotype ($\geq 3$ clonal cytogenetic aberrations) and a monosomal karyotype (multiple monosomies and also additional structural aberrations).\textsuperscript{25} Molecular analysis revealed high EVII transcript expression and $-17$ and $17q^{-}$, 2 other adverse signs.\textsuperscript{22,23} He exhibited good physical performance but, as is quite common among older patients, he had multiple comorbid conditions including prior surgery for benign prostate hypertrophy, chronic obstructive pulmonary disease, atrial fibrillation, and hypertension. Two years prior he had received a coronary stent for angina pectoris and coronary stenosis. His left ventricular function, however, was normal. According to our general approach, remission-induction chemotherapy was undertaken with the intent to lead the patient to a CR and subsequently try to progress to allogeneic HSCT. The first remission-induction cycle with daunorubicin (45 mg/m$^2$ on each of 3 days) and cytarabine (Ara-C) (200 mg/m$^2$ ci, 7 days) was complicated by fever and coagulase-negative *Staphylococcus* septicemia. A CR with incomplete platelet recovery (platelet count of 45 000) (CRi) ensued. Subsequently, a consolidation cycle with intermediate-dose Ara-C (1000 mg/m$^2$ twice daily IV over 6 hours on days 1-6) initiated after an interval of 32 days after the start of induction cycle I was complicated by considerable gastrointestinal toxicity and diarrhea. At 3 months from diagnosis, he presented with severe pain in his arms and back, which originated from spondylodiscitis (C5-C6) caused by an infection with *Staphylococcus epidermidis* and *Citrobacter freundii*, which required IV antibiotic treatment. Thus, because of the latter intercurrent medical problems, additional antileukemia treatment in this older patient had to be postponed. Meanwhile, the CRi continued. In the absence of an available HLA-identical family donor, an unrelated donor search had yielded a 12/12 HLA-matched donor. At 5.5 months after the start of treatment at age 69, our patient received an allograft after a reduced-intensity conditioning regimen with fludarabine and 2Gy total body irradiation (TBI) and posttransplant immunophrophylaxis with mycophenolate and cyclosporine. There was early engraftment with full hematologic recovery within 2 weeks, and complete donor chimerism ensued with no apparent signs of graft-versus-host disease. Mycophenolate was discontinued at 3 months and cyclosporin discontinued at 6 months. Currently, the patient survives in good performance and remains disease-free at 24 months after diagnosis.

**Comments about patient 1**

This patient illustrates that in a fit elderly patient with AML, even with unfavorable risk characteristics and various comorbid conditions, it may be useful to embark on a treatment plan with curative intent with intensive chemotherapy followed by allogeneic HSCT. Clinicians with a treatment goal in mind that has been defined in advance should obviously be prepared to adjust their plan according to the course of medical developments. There is no basis for an absolute a priori fatalism, not even when there are various unfavorable signs, although a favorable
outcome as described here will be relatively uncommon. This leukemia carried 3 types of adverse genomic abnormalities that each define poor outcome.23 The AML exhibited chromosomal abnormalities additional to a single monosomy and thus fulfilled the criterion of a monosomal karyotype.25,26 and the AML also exhibited high expression of the oncogene EVII, a known unfavorable feature in younger adults with AML.22 Furthermore, the loss of chromosome 17 is also a high-risk prognostic marker in AML. A recent analysis from an international study consortium has confirmed the generally poor outcome of patients with AML with various abnormalities that involve 17p and include −17, so-called “abn(17p),” where the P53 gene is located.27 If a direction toward intensive chemotherapy is chosen, the older patient deserves adequate dose-intensified chemotherapy rather than a chemotherapy regimen with unsubstantiated dose-level reductions.3,28 Physicians currently also often deviate to a default of the use of demethylating agents, but it should be considered that a large amount of data are available addressing intensive chemotherapy. Intensive chemotherapy data indicate a substantial probability of CR and prolonged survival in responders, whereas the accumulating evidence arguing in favor of demethylating agents in AML with high blast count is still limited. However, the relation between CR and overall survival (OS) in patients treated with hypomethylating agents as well as mitigated chemotherapy may be less clear-cut than it is for intensive chemotherapy. Recent Medical Research Council trials with either clofarabine or gemtuzumab as adjuncts to low-dose Ara-C (LDAC) revealed a higher CR rate but no better OS.29,30 Nevertheless, it is generally accepted that achieving CR is a first necessary positive step on the way to improved outcome. Survival beyond 3 years is unlikely if CR has not been achieved.31 Whenever possible, it may make sense to try and lead these patients to allogeneic HSCT in a way that is similar to the approach that is pursued in younger and middle-aged adults.4,32,33 In a fraction of patients, a CR may be achieved with demethylating agents. The use of these agents is associated with less toxicity and may also lead the way toward allogeneic HSCT rescue treatment.14 In recent years, allogeneic HSCT has been more commonly applied at higher ages because long-term data indicate that allogeneic HSCT after reduced-intensity conditioning is not only associated with reduced mortality but also exhibits significant antileukemic effectiveness in a range that is very similar to that of ablative allogeneic HSCT.34 Thus, the options in older patients with AML for consolidation with allogeneic HSCT have increased in recent years. Clearly, the decisions regarding treatment choices, in particular in patients of very advanced age (eg, >75 years), deserve a careful discussion about the alternative options (ie, type of remission in older adults). The probability of attaining a second CR in AML with a favorable genetic profile is comparatively high, which enhances the feasibility of salvage with an allotransplant in case of relapse. The probability of attaining a second CR in AML with a favorable genetic profile is comparatively high, which enhances the feasibility of salvage with an allotransplant in case of relapse.

**Comments about patient 2**

This patient has an estimated prognosis that markedly contrasts from that of patient 1. He has AML with a relatively favorable genotype (ie, a normal karyotype with biallelic mutant *CEBPA*). These “favorable” leukemias show an average probability of ~70% survival at 3 years among adults younger than 60 years of age. In addition, elderly patients with a favorable risk profile have a distinctly better outcome compared with the other cytogenetic and molecular risk groups (Figure 1). In this regard, it is of note that in younger adults with favorable genotypes, OS is similar between those who receive an allogeneic HSCT in first CR (CR1) and those who do not, so that in the good-risk patients, the option of an allogeneic HSCT is usually reserved in case leukemia recurs. Also, autologous stem cell transplant applied in CR1 reduces the probability of relapse, with similar OS results. The probability of attaining a second CR in AML with a favorable genetic profile is comparatively high, which enhances the feasibility of salvage with an allotransplant in case of relapse. Although autologous HSCT and allogeneic HSCT in younger and middle-aged adults with favorable subtypes of AML offer similar probabilities of OS, it is unknown whether these relationships can be extrapolated and be maintained the same as in older patients. Thus, in the patient presented here, there are 2 defendable therapeutic strategies for consolidation in CR1 (ie, to apply chemotherapy or autologous HSCT and keep the option of an allogeneic HSCT as a backup for relapse, or to immediately proceed to an allogeneic HSCT). The downside of an allogeneic HSCT in CR1 obviously involves the risks of alloimmune-mediated complications and greater mortality; but alternately, completion of the entire treatment within a one-time, concentrated, intensive approach with a reduced risk of recurrence might be seen as an advantage. In any

Patient 2: A 64-year-old man with AML with a favorable molecular genotype

A 64-year-old man was admitted for fever. The hematology laboratory had reported a reduced platelet count of $52 \times 10^9/L$ and a WBC of $9.3 \times 10^9/L$ with $90\%$ blasts in the differential and a normal hemoglobin value. The marrow showed $87\%$ infiltrate with blasts that were almost entirely Sudan Black–positive ($99\%$ of blasts). Cytogenetic examination of 21 metaphases exhibited normal 46,XY cytogenetics, but molecular analysis revealed biallelic mutations of both *CEBPA* or *CEBP-α* genes (ie, mutations in both alleles of the gene for the transcription factor CAAT-binding protein). The immunophenotype of the blasts was consistent with AML. Thus, the patient was diagnosed with AML with mutated CEBPA (an entity in the classification WHO2008). The *CEBPA* biallelic mutant, a recurrent gene abnormality, designates this a leukemia of favorable risk. The patient began treatment with an induction regimen consisting of Ara-C $200 \text{mg/m}^2$ daily for 7 days and idarubicin $12 \text{mg/m}^2$ on each of days 1, 2, and 3, and he promptly achieved CR. After 6 weeks, he received consolidation chemotherapy that included anthracycline and intermediate-dose Ara-C ($1000 \text{mg/m}^2\text{every}12\text{hours}\text{for}6\text{days}$), and after 12 weeks he received a final cycle of consolidation with mitoxantrone and etoposide. The subsequent course was uneventful, but 2.5 years after his initial diagnosis, $6\%$ circulating blasts reappeared in the blood and the marrow showed an infiltrate with $11\%$ blasts. The same *CEBPA* mutations were noted and chromosomal examination now also showed cytogenetic evolution of the disease with newly acquired cytogenetic abnormalities (ie, 46,XY.del(11)(q13q23), idic(17)(p11)(5)/46,XY[15]). Because of the comparatively long interval between the emerging relapse and diagnosis, it was decided to reduce the patient with an anthracycline–Ara-C regimen, and the patient attained a second CR within 5 weeks with restoration of normal cytogenetics and molecular genetics. There was no matched family donor, and the patient (then at age 66 years) proceeded to an unrelated HLA-matched HSCT according a protocol similar to that in patient 1. Currently at 18 months after relapse, the patient continues in unmaintained second CR.
that were Sudan Black – a second CR, which is quite characteristic for patients with favorable blast in the differential. His bone marrow was in remission, which revealed a trisomy 8, and no molecular abnormalities. The choice was made in favor of chemotherapy as first-line treatment without HSCT. Fortunately, after relapse, our patient readily entered a second CR, which is quite characteristic for patients with favorable cytogenetic or molecular features.

**Patient 3: A 73-year-old man with AML with myelodysplasia-related changes: medical doubts about the feasibility of intensive chemotherapy**

A 73-year-old man was admitted to our hospital with blood counts of Hgb 5.9 mmol/L, platelets 53 × 10⁹/L, WBC 3.5 × 10⁹/L, and 12% blasts in the differential. His bone marrow was infiltrated with blasts (27%) that were Sudan Black–positive and showed >50% dysplastic changes in the megakaryocytic and erythroid series. The immunophenotype was consistent with myeloid leukemia. Cytogenetic analysis revealed a trisomy 8, and no molecular abnormalities (NPM1 [nucleophosmin-1] gene mutation, ETV1 overexpression, FLT3-ITD [internal tandem duplications], CEBPA gene mutations) were detected. Thus, the leukemia was classified as AML with myelodysplasia-related changes. The patient’s performance status was 2, but he had multiple comorbidities such as chronic obstructive pulmonary disease, arterial vascular occlusive disease, and diabetes mellitus, and he had also recently been diagnosed with Alzheimer disease. His HCT-IC score was 4, which correlates with an estimated average early death rate on remission-induction chemotherapy of ~30%. Our team felt that there were too many medical issues and hurdles to confidently recommend an intensive treatment approach.

The patient started treatment with subcutaneous (SC) azacitidine 75 mg/m² for days 1 to 7 every 28 days in an outpatient setting. Prophylactic antibiotics were administered. The therapy was tolerated well, with only mild gastrointestinal disturbances and local reactions at the injection site noted. After the fourth cycle, the transfusion dependency declined and peripheral blood counts began to recover. Bone marrow examination showed a decrease of blasts to 7% with persistent dysplastic features. Treatment was continued, and after 8 cycles <5% blasts were noted in the marrow smear. He did not show full recovery of his platelet counts to normal values and thus he achieved a CRi. Unfortunately, after cycle 12, the leukemia recurred. At that point, treatment was discontinued and the patient died at 14 months after the initial diagnosis as a result of progressive disease.

In this case, the therapeutic decisions were dictated by performance status and comorbidities. The diagnosis of AML with myelodysplasia-related changes does not a priori classify it as a bad prognostic leukemia. AML with myelodysplasia-related changes is very heterogeneous, thus it lacks independent prognostic significance. The prognosis is determined by underlying cytogenetic and molecular abnormalities. What are the possibilities in the case a patient is classified as unfit or will not likely benefit from dose-intensive chemotherapy? LDAC (20 mg SC 2× for 10 days for 4-6 weeks) is quite commonly used in these patients in some countries but is less popular in other countries. Treatment with LDAC does not confer considerable toxicity and it produces a higher CR rate than best supportive care (18% vs 1%). Although the OS for the LDAC-treated group has been demonstrated to be statistically significantly better, it should be considered that in absolute terms, the therapeutic advantage is marginal and corresponds with a prolongation of OS of only a few months. The benefit is restricted to the minority fraction of patients who achieve a CR (median survival 19 months vs 2 months in nonresponders). Furthermore, patients with adverse cytogenetics do not seem to benefit from LDAC. Thus, the OS in patients receiving LDAC is still highly unsatisfactory (median 5 months).

Hypomethylating drugs are considered by many clinicians as an attractive strategy for this patient group. Accumulated experience in myelodysplastic syndromes (MDS) have paved the way for the use of these agents in AML. Two hypomethylating agents—azacitidine and decitabine—have been studied in elderly patients with AML who are not considered candidates for intensive chemotherapy. In a phase 3 trial, azacitidine (75 mg/m² SC per 7 days for 28 days) was compared with various conventional care regimens (ie, LDAC, intensive chemotherapy, or supportive care) in patients with intermediate-2 and high-risk myelodysplasia. In fact, 113 patients among this series had bone marrow blast percentages of 20% to 30%, and thus the trial included AML with low blast counts only. CR rates were similar for azacitidine when compared with conventional care treatments (18% vs 16%). Recently, azacitidine has also been compared with a mix of conventional care regimens (ie, supportive care only, cytodestruction with hydroxyurea, and anthracyclin-Ara-C–based remission-induction chemotherapy) in a study of elderly patients with AML with any blast count. Although azacitidine demonstrated a slight improvement in median OS (10.4 months vs 6.5 months), no statistical significance for the study’s primary end point of OS (P = .08) was achieved. However a preplanned sensitivity analysis censored for subsequent AML treatment showed a benefit in terms of median OS of 12.1 months vs 6.9 months for azacitidine.
In addition, decitabine 20 mg/m² daily for 5 days per cycle has been compared with conventional care (either supportive care or LDAC) in a phase 3 trial of 485 patients aged 65 years or older with AML who were considered unfit for intensive chemotherapy. Treatment with decitabine resulted in a higher response rate (CR + CRi 17.8% vs 7.8%) and better survival that reached statistical significance on further follow-up in an unplanned analysis (median OS 7.7 vs 5.0 months). However, as yet, no trend to a plateau in the survival curves has been apparent in any of these low-intensity regimens. Improvement in performance status and organ function after a successful low-intensity regimen may create a possibility for a curative reduced-intensity allogeneic HSCT. Currently, azacitidine has licensed approval from European Medicines Agency Committee for Medicinal Products for Human Use (EMA) for intermediate-2 and high-risk MDS and AML with 20% to 30% blast cell count, and decitabine has been approved for patients of 65 years and above with AML who are not considered candidates for standard induction therapy. Both azacitidine and decitabine have been approved by the US Food and Drug Administration for all types of MDS including intermediate-risk AML who declined a recommended intensive chemotherapy approach.

Patient 4: A 72-year-old woman with intermediate-risk AML who declined a recommended intensive chemotherapy approach

At the time of diagnosis, this 72-year-old woman presented with recurrent upper airway infection. She was a widow and had no children and lived a solitary life. Her medical history was unremarkable. A complete blood cell count included a WBC of 3.8 × 10⁹/L, neutrophils 0.4 × 10⁹/L, Hgb 5.7 mmol/L, and platelets 23 × 10⁹/L. Morphologic examination of the bone marrow revealed an AML without maturation, with 85% Sudan Black–positive blasts and immunophenotypic examination consistent with a myeloid leukemia. Cytogenetic evaluation showed a normal 46,XX karyotype. Molecular analysis did not reveal mutations of the NPM1, FLT3, or CEBPA genes, nor EVI-1 overexpression. Thus, the AML was prognostically classified as intermediate risk.

After extensive discussions with this intelligent and fit woman, she declined the proposed option of intensive treatment. She elected to participate in a clinical study that enabled her to be treated in an outpatient setting. She was included in a pharmaceutical-sponsored trial that prospectively compared LDAC alone with LDAC plus an investigational drug. She achieved a CR after 2 treatment cycles that persists for >12 months while she continues to receive treatment. She does not report any significant side effects.

Comments about patient 4

Although this patient would in our view have been suitable for intensive treatment, she deliberately declined this option. Patients should be encouraged to make decisions based on accurate information about the risks and benefits of all available treatment options. Aside from the chances of cure and treatment-related mortality, decisions should also include discussions on living and social circumstances, quality of life issues, and personal expectations in relation to either choice.
patient, individual socioeconomic factors determined her decision
and these then had to be taken into account to define the appro-
priate treatment. Because our patient was interested in receiving
a less-intensive treatment, there was an opportunity to enroll her
in a clinical trial that, whenever possible, we consider a priority
option.

**Final considerations**

Today, older patients with AML can be offered one of the following
treatment options:

- Standard induction treatment consisting mostly of a 3+7 regi-
men of an anthracyclin and Ara-C;
- Hypomethylating agents;
- Investigational drugs within a clinical trial;
- Low-dose Ara-C;
- Best supportive care with oral cytostatic drugs like hydroxyurea
and/or transfusions.

Obviously, the assessment of the clinical performance and medical
condition about whether intensive chemotherapy can be recommended
remains a subjective approach that largely depends on the judgment
of the medical doctor. Risk-scoring systems as we have discussed could
be instrumental in this regard. Geriatric assessments with a focus
on cognitive and physical function by either objective measurements or self-
reported measures have not been widely studied. However, early studies
suggest that they have added value in comparison with performance status
and comorbidity evaluations, and thus they may improve the prediction
of survival in older patients receiving intensive chemotherapy.19,20

What in general can we learn from the clinical vignettes presented
here?

First, we should always, also in patients of older age, make a
deliberate therapeutic plan that makes sense to the individual circum-
stances and try to adhere to the defined plan as much as possible, even
though intercurrent problems may urge the modification and temporary
deviation from the original intentions.

Second, as an initial priority, it seems useful to follow the same
therapeutic principles that we apply in younger adults provided the
medical situation of the patient allows for intensive induction
chemotherapy. This implies that intensive remission induction
chemotherapy is the first choice whenever this is considered realistic
and feasible on clinical grounds. Early death is in most studies <15%
and does not seem to play a major role in the inferior outcome of
elderly patients with AML. In this regard, it is of note that the early
death rate in intensively-treated patients has decreased considerably
over the last 2 decades, most probably owing to better supportive
care.21 A wait-and-see approach with supportive care and cytor-
eduction with hydroxyurea does not provide a significantly better
perspective for the patient with AML in terms of improving quality
of life or prolonging survival because none of the basic medical
problems will be tackled.28

Third, nonmyeloablative allogeneic HSCT being reasonably
well tolerated in terms of early toxicity has shifted the age limit of
the applicability of allogeneic HSCT upward. Allogeneic HSCT
after reduced-intensity conditioning currently provides antileukemic
effectiveness that is not much different from ablative allogeneic
HSCT.

Fourth, in a general sense, the molecular features that characterize
the risk of AML in middle-aged adults also apply to older adults with
AML,27 although the incidence of unfavorable genotypes is significantly
more frequent among older adults. These genetic disease-related features
of the leukemia furnish clinically informative prognostic insights and
thus may offer useful guidance during the therapeutic treatment of an
individual patient. For instance, good-risk cytogenetics (core-binding
factor leukemias) express a distinctly favorable impact in older patients
with AML.3,9 This background information may be reassuring in our
treatment approach when intercurrent medical hurdles during the
treatment of an older patient are encountered. Conversely, monosomal
karyotypes at the unfavorable end of the cytogenetic spectrum carry
adverse prognostic value3 (Figure 1). Various studies have established
that the favorable effect of the NPMI-mutant genotype in the absence
of FLT3 gene mutations for patients treated with intensive chemother-
apy protocols also holds up in older patients with AML.19,35,53 This
genotype exerts a strong positive effect on outcome that is much more
apparent than that of individual NPM1 or FLT3 genotypes. Alternately,
in some studies, FLT3-ITD, DNMT3A, and ASXL1 gene mutations
seem to confer a negative effect on response and survival estimates in
older patients with normal cytogenetics.55,56 In this regard, it should
be noted that the frequencies of these genotypes are considerably
less common in older patients,58 whereas the incidence of particu-
larly unfavorable genotypes (eg, ASXL1, TET2 gene mutations) appear
to increase with progressively higher patient age.57,59-61 In addition,
gene-expression levels have been evaluated for their prognostic
value. They use relative cutoff values (high vs low) rather than abso-
late values and therefore are more difficult to apply as a reference in
clinical practice.62 These accumulating genomic data mark the
beginning of efforts to better understand and predict responsiveness
and refractoriness to antileukemic drugs in individual patients.

Fifth, numerous new drugs are currently emerging from the de-
velopment pipeline. For example, small drugs targeting a specific oncogenic
pathway, a variety of drugs with novel mechanisms of action and/or
affecting novel intracellular targets, as well as monoclonal antibodies
and antibody conjugates are in clinical development, and some of these
may likely enrich the therapeutic arsenal in the near future.

Testing so many emerging new drugs poses a real challenge and
urges for new trial designs like the “Pick-a-Winner” concept that
should offer the possibility of rationally designed combinations of new
drugs.63,64 It would be desirable that major AML trial groups combine
efforts in designing rational and complementing trials in close collab-
oration to accelerate the treatment development of AML that is so
gerently needed.

Sixth, we recommend whenever possible to include older AML
patients in well-designed clinical trials. This furnishes some guarantee
for quality of treatment (eg, protocolized treatment according to state-
of-the-art standards), but it also offers the opportunity to contribute to
progress in this still devastating disease.65 Especially the elderly unfit
and relapsing population of patients with AML are often selected for
clinical trials with new therapeutic agents. Many new drugs have failed
approval, in part perhaps because the setting in which these drugs are
tested has been suboptimal. The study population of relapsed/refractory
AML in the older patient population by definition contains some of the
most notoriously resistant leukemias. Early clinical trials on new drugs
could and should also be actively pursued effectively and informatively
in the up-front context in fit, elderly patients with AML and in distinctly
genomic-defined AML in which the effect of drugs specifically
targeting components of key signal transduction pathways can be
investigated.

The treatment outcome in older patients is reduced compared with
that of younger and middle-aged adults with AML, but this should not
be a reason for a fatalistic approach in the older patient. The patient with
AML, irrespective of his or her age, deserves the same opportunity for
adequate diagnostics—including molecular genetics—that provide a
documented substrate for a thoughtfully considered treatment plan (Figure 2).

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