How I treat the older patient with acute myeloid leukemia

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Abstract
Acute myeloid leukemia (AML) in patients of older age presents a notable therapeutic challenge to the clinical hematologist. The clinical biology of AML among patients is highly heterogeneous. The inter-patient variations are relevant for prognosis and treatment choice. Outcome of treatment at 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. These vignettes are specifically discussed in light of the perspective of the patient with leukemia at older age. 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 as regards personalized therapy recommendations. The dilemmas in tailoring treatment selection in this category of patients with AML are the central theme in this discussion.

Abbreviations: AML – acute myeloid leukemia; Ara-C – cytarabine; ASXL1 – oncogene mutation in general with unfavorable prognostic value in AML; CEBPA or CEBP-alpha gene mutations (gene for the transcription factor CAAT binding protein) – with favorable prognostic value in AML; CBF- core binding factor leukemias; CN normal cytogenetics or normal karyotype; CR or CRi – complete remission or CR with incomplete neutrophil or platelet recovery; DNMT3A - DNA methyltransferase 3A gene; EVI-1 – ecotropic viral integration-1 oncogene when mutated or overexpressed with unfavorable prognostic value in young adults with AML, FLT3-ITD - internal tandem duplications of the fms-like tyrosine kinase gene may have adverse prognostic value; HCT-CI – hematopoietic cell transplantation comorbidity index; HOVON – Dutch-Belgian Cooperative Leukemia Group; HSCT – hematopoietic stem cell transplantation; LDAC – low dose cytarabine; MDS – myelodysplastic syndromes; MK – monosomal karyotype; p53 – mutated oncogene with unfavorable prognostic value; MRC – Medical Research Council; NPM1 – nucleophosmin-1 gene has favorable prognostic value mainly in the context of non-mutant FLT3; SAKK – Swiss Cancer Cooperative Group; WBC – white blood cell count;
The median age of patients with acute myeloid leukemia (AML) is around 70 years.\textsuperscript{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, while old age as such is not a feature that defines a disease entity, it is of significant clinical relevance because it confers profound prognostic impact on disease outcome. Treatment outcome in patients with AML continuously declines with progressively increasing age.\textsuperscript{2} Some of the key questions for clinical hematologists in daily practice are: ‘Which patient at older age can receive intensive treatment and not experience prohibitive toxicity?’ ‘Secondly, even in those that 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 at age 65 years is still around 15-20 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 age segment of patients with the objective of improving their treatment outcome. Clinical trials for practical reasons have usually applied age cutoffs above age 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 50-60\% will successfully attain a complete remission (CR). However, such fairly high rates of good response translate into a two year survival of only of 15-20\%.\textsuperscript{3} These outcome results have only very modestly improved in the last decade, in particular in patients below 75 yrs.\textsuperscript{4, 5, 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.\textsuperscript{3, 4} The determinants of success and failure nevertheless remain only partly understood.

These determinants are clearly multifold and include a combination of patient-related and specific disease-related factors.\textsuperscript{7}

\textit{-Patient related prognostic factors.} Comorbid conditions are more frequent at older age. These and performance status are among the most critical patient-related factors. Pharmacokinetic and pharmacodynamic changes results 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 due to more toxicity of the treatment. Also psychosocial factors like cognitive decline, social
isolation and often lack of caretakers are factors influencing the outcome. The patient-related determinants may create hurdles to sufficiently safely deliver dose-intensive chemotherapy

-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 hematological disorders are all more common among the aging population. They correlate markedly with treatment failure, ie, primary resistance and relapse after induction therapy. Distinct gene expression profile noted for older compared to younger patients supports a molecular basis for poor outcomes in elderly patients.

In this article we will present four selected clinical vignettes that highlight our treatment approach in clinical practice in light of the biology of the disease and we will discuss some of the common practical issues and dilemmas that we encounter in the therapeutic management of patients with AML at older age.

**Which patient qualifies as candidate 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 generally older patients with AML fare markedly better on intensive chemotherapy than on palliative treatment. Performance status rather than age in the strict sense is predictive of early mortality. Yet, a particular proportion of AML patients won’t tolerate the use of intensive chemotherapy. Those patients may be offered demethylating agents (eg decitabine, azacitidine) as a less intensive modality of treatment. The recognition of patients who might more likely benefit from an intensive treatment approach should ideally be based on baseline assessments. It is and has remained a challenge to identify those patients prior to the start of treatment and define their features. A variety of composite multifactorial risk algorithms have been proposed in which patient specific factors (performance, comorbidity scores) together with disease specific factors (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. An inherent limitation of all these risk algorithms is that they have been derived from data of a patient population who had already been selected for intensive treatment and thus they do not reflect the average real world of
older patients with AML who 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 co-morbidities. The HCT-CI (Haematopoietic Cell Transplantation Comorbidity Index) scoring system that is based only on co-morbidities 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 as it provides a reflection of their concomitant diseases. For example a relatively high HCT-CI score ≥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. 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 AML. 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 have 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. Additional research on the developments of measurements solidly validated and preferably quite easily applicable in clinical practice is ongoing.

On the other hand particular disease-specific biological characteristics of AML may be associated with such a poor outcome that even though patients are considered to be medically fit, they will unlikely 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 instance: overexpression of the oncogene EVI-1, ASXL1 gene mutations, biallelic FLT3-ITDs, p53 gene mutations, complex and/or monosomal karyotypes. We would consider intensive treatment in such patients only in case an allogeneic HSCT is foreseen as a possible prospective option following 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 $25 \times 10^9/L$. Cytological examination of the marrow showed dysplastic signs in various cell lineages and an abnormal karyotype with 45, XY, 1p-, -17, 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). Molecular analysis revealed high EVI1 transcript expression and -17 and 17q+, two other adverse signs. He exhibited a 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 bronchial disease, atrial fibrillation, hypertension. Two years ago he had received a coronary stent for angina pectoris and coronary stenosis. His cardiac left ventricular function however was normal. According our general approach, remission induction chemotherapy was undertaken with the intention to lead the patient to a complete remission (CR) and subsequently try to lead him to an allogeneic hematopoietic stem cell transplantation (HSCT). The first remission induction cycle with daunorubicin ($45 \text{ mg/m}^2$ on each of 3 days) and cytarabine ($200 \text{ mg/m}^2 \text{ ci}, 7 \text{ days}$) was complicated by fever and coagulase negative staphylococcus septicemia. A CR with incomplete platelet recovery (platelet count of 45000) (CRi) ensued. Subsequently a consolidation cycle with intermediate dose cytarabine (cytarabine at $1000 \text{ mg/m}^2$ twice daily given intravenously over the course of 6 hours on days 1-6) initiated after an interval of 32 days following 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 arms and back which originated from spondylodiscitis (C5-C6) caused by an infection with staphylococcus epidermidis and citrobacter freundii which required intravenous treatment with antibiotics. 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 ½ months after the start of treatment at age 69 our patient received an allograft following a reduced intensity conditioning regimen with fludarabine and 2Gy TBI (total body irradiation) and postransplant immunophylaxis with mycophenolate and cyclosporine. There was early engraftment with full hematological recovery within 2 weeks, complete donor chimerism ensued with no apparent signs of graft-versus-host disease. Mycophenolate was discontinued at 3 months and cyclosporin 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 an allogeneic transplant. Clinicians with a treatment goal in mind that has been defined in advance, should obviously be prepared to adjust their plan according the course of medical developments. There is no basis for an absolute ‘a priori’ fatalism, even not when there are various unfavorable signs although a favorable outcome as described here will be relatively uncommon. This leukemia carried three types of adverse genomic abnormalities that each define poor outcome. The AML exhibited chromosomal abnormalities additional to a single monosomy and thus fulfilled the criterium of a monosomal karyotype and the AML also exhibited high expression of the oncogene \textit{EVI1}, a known unfavorable feature in younger adults with AML. Furthermore the loss of chromosome 17 also is 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. If the direction towards intensive chemotherapy is chosen, the older patient deserves adequate dose intensified chemotherapy rather than a chemotherapy regimen with unsubstantiated dose level reductions. Physicians nowadays also often deviate to a default of the use of demethylating agents but we should bear in mind that a huge body of data is available about intensive chemotherapy. Intensive chemotherapy data indicate a substantial probability of CR and prolonged survival in responders while the accumulating evidence arguing in favor of demethylating agents in AML with high blast count is still limited. Whereas the relation between CR and overall survival in patients treated with hypomethylating agents as well as mitigated chemotherapy may be less clear-cut than for intensive chemotherapy. Recent MRC trials with either clofarabine or gemtuzumab as adjuncts to low dose ARA-C revealed a higher CR rate but no better OS. 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. Whenever possible it may make sense to try and lead these patients to an allogeneic HSCT in a way that is similar to the approach that is pursued in younger and middle-aged adults. 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 towards allogeneic HSCT rescue treatment. In recent years allogeneic HSCT is more commonly applied at higher age since long term data indicates that allogeneic HSCT after reduced intensity conditioning is
associated not only with reduced mortality but it also exhibits significant anti-leukemic effectiveness in a range that is very similar to that of ablative allogeneic HSCT. 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 above 75 yrs) deserve a careful discussion about the alternative options (type of remission induction therapy and level of dose intensity in relation to CR probability and expected toxicities, leukemia-specific prognostic risk, consideration of the option of HSCT for consolidation) according a tailored individualized approach.

Patient 2 - A 64-year-old male 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 x 10^9/L and a WBC of 9.3 x 10^9/L with 90% blasts in the differential and a normal hemoglobin value. The marrow showed a 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-alpha genes (ie, mutations in both alleles of the gene for the transcription factor CAAT binding protein). The immunophenotype of the blasts was consistent with acute myeloid leukemia. 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 leukemia of favorable risk. The patient began treatment with an induction regimen consisting of cytarabine 200 mg/m² qd for 7 days and idarubicine 12 mg/m² on each of days 1, 2 and 3 and he promptly entered a CR. After 6 weeks he received consolidation chemotherapy that included amsacrine and intermediate dose cytarabine (1000 mg/m2 q 12 hrs for 6 days) and after 12 weeks he received a final cycle of consolidation with mitoxantrone and etoposide. The subsequent course was uneventful but after 2 ½ years following the 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 reinduce the patient with an anthracyclin-cytarabine 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
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, i.e., a normal karyotype with biallelic mutant CEBPA. These ‘favorable’ leukemias show an average probability of about 70% survival at 3 yrs among adults less than 60 yrs of age.\textsuperscript{35,36} Also elderly patients with a favorable risk profile have a distinctly better outcome as compared with the other cytogenetic and molecular risk groups (Fig1 derived from the HOVON/SAKK study (HOVON 43) investigating the value of high dose Daunorubicin shows overall survival according to cytogenetic risk in patients above 60 years.)\textsuperscript{3,37}. In this regard it is of note that in younger adults with favorable genotypes overall survival is similar between those who receive an allogeneic HSCT in first CR and those who do not so that in the good-risk patients the option of an allogeneic HSCT is usually reserved in case the leukemia will recur\textsuperscript{33,38,39}. Also autologous stem cell transplant applied in CR1 reduces the probability of relapse with similar overall survival results\textsuperscript{39}. 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 a relapse.\textsuperscript{40} This probably holds similarly for patients with any favorable genotype, in particular the core-binding AMLs, AML with NPM1 mut/FLT3-ITD neg (nucleophosmin-1 gene mutation and absence of fms-like tyrosine kinase gene internal tandem duplications)\textsuperscript{39}, AML with biallelic CEBPA mutants\textsuperscript{38}. While autologous HSCT and allogeneic HSCT in younger and middle-aged adults with favorable subtypes of AML offer about similar probabilities of overall survival, strictly speaking it is unknown whether these relationships can be extrapolated and hold up the same way in older patients. Thus in the patient presented here there are two defendable therapeutic strategies for consolidation in CR1, i.e., to apply chemotherapy or autologous HSCT and keep the option of an allogeneic HSCT as a back up for relapse, or immediately proceed to an allogeneic HSCT. The downside of an allogeneic HSCT in CR1 obviously involves the risks of allo-immune mediated complications and greater mortality but on the other hand completion of the entire treatment within a single one-time concentrated intensive approach with a reduced risk of recurrence might be seen as an advantage. In any event, there is no compelling argument for guiding patients with low-risk AML to an early allogeneic HSCT in first CR. In the patient presented here based on the then available
knowledge the choice was made in favor of chemotherapy as first line treatment without a HSCT. Fortunately, our patient following the relapse readily entered a second CR which is quite characteristic for patients with favorable cytogenetic or molecular features\textsuperscript{41}.

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

A patient of 73 yrs old was admitted to our hospital with Hgb 5.9 mmol/l, platelets 53x10\(^9\)/l, WBC 3.5x10\(^9\)/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 while no molecular abnormalities (\textit{NPM1} (nucleophosmin-1) gene mutation, \textit{EVI-1} overexpression, \textit{FLT3}-ITD (internal tandem duplications), \textit{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 like chronic obstructive bronchial disease, arterial vascular occlusive disease, 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 about 30\%. Our team felt that there were too many medical issues and hurdles to confidently recommend an intensive treatment approach. Patient started on treatment with azacitidine 75mg/m\(^2\)/s.c. /day1-7 every 28 days in an outpatient setting. Prophylactic antibiotics were administered. The therapy was quite well tolerated, only mild gastro-intestinal disturbances and local reactions at the injection site were noted. After the 4\(^{th}\) cycle the transfusion dependency declined and peripheral blood counts began to recover. Bone marrow examination showed a decrease of blasts to 7\% with persisting dysplastic features. Treatment was continued and after 8 cycles less than 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 due to progressive disease.

**Comments about patient 3.**

In this case the therapeutic decisions were dictated by performance status and co-morbidities. The diagnosis of AML with myelodyplasia-related changes does not a priori classify as a bad prognostic leukemia. AML with myelodysplasia-related changes is very heterogenous and as
such it lacks independent prognostic significance. The prognosis is determined by underlying cytogenetic and molecular abnormalities.\textsuperscript{42,43} What are the possibilities in case a patient classifies as unfit or will not likely benefit from dose-intensive chemotherapy? Low dose cytarabine (LDAC) (20 mg s.c. BID /10 days/4-6 weeks) is quite commonly employed 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\%).\textsuperscript{44} While the overall survival for the LDAC treated group has been demonstrated to be statistically significantly better, we should keep in mind that in absolute terms the therapeutic advantage is marginal and corresponds with a prolongation of overall survival of just a few months only. The benefit is restricted to the minority fraction of patients who achieve a CR (median survival 19 months versus 2 months in non-responders).\textsuperscript{44} Furthermore, patients with adverse cytogenetics do not seem to benefit from LDAC. Thus the overall survival 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 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 III trial azacitidine (75 mg/m\textsuperscript{2} s.c. /7 days/ 28-days) was compared to various conventional care regimens (ie low dose cytarabine, intensive chemotherapy or supportive care) in patients with intermediate-2 and high-risk myelodysplasia. As a matter of fact 113 patients among this series had bone marrow blast percentages of 20-29\%, thus the trial included AML with low blast counts only. CR rates were similar for azacitidine when compared to conventional care treatments (18\% versus 16\%).\textsuperscript{45} Recently azacitidine has also been compared with a mix of conventional care regimens (ie supportive care only, cytoreduction with hydroxyurea and anthracyclin-cytarabine based remission induction chemotherapy) in a study in elderly patients with AML with any blast count. Although azacitidine demonstrated a slight improvement in median OS (10.4 months versus 6.5 months) no statistical significance for the study’s primary endpoint of OS (p=0.08) was achieved. However a pre-planned sensitivity analysis censored for subsequent AML treatment showed a benefit in terms of median overall survival of 12.1 months versus 6.9 months for azacitidine (Dombret, EHA 2014 abstract).

Also decitabine 20 mg/m\textsuperscript{2} daily for 5 days per cycle has been compared with conventional care (either supportive care or LDAC) in a phase III trial of 485 patients aged 65 years or older with AML unfit for intensive chemotherapy. Treatment with decitabine resulted in a
higher response rate (CR+ CRi 17.8% versus 7.8%) and better survival that reached statistical significance on further follow-up in an unplanned analysis (median overall survival 7.7 v 5.0 months). However one should appreciate that as yet in none of these low intensity regimens a trend to a plateau in the survival curves has been apparent. Improvement in performance status and organ function following 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 20-30% blasts cell count and decitabine for patients with AML of 65 years and above who are not considered candidates for standard induction therapy. Both azacitidine and decitabine have been approved in the USA by the Food and Drug Administration (FDA) for all types of MDS including refractory anemia with excess of blasts and thus also for AML with 20-30% of blasts according the current WHO classification of myeloid neoplasms. Early correlative studies suggest that particular AML genotypes, especially TET2 and DNMT3A mutated AML’s, might benefit from the use of these epigenetic agents.

A more intensified regimen of decitabine (20 mg/m² daily for 10 days) was applied to 53 patients (median age 74 years) who were unsuitable for standard chemotherapy and resulted in encouraging outcomes. The CR rate was 47% and CRi 17%, with a 30- and 60-day mortality of 2% and 15%, respectively. Overall survival and disease-free survival durations were 55 and 46 weeks (median). Responses were present in all subgroups, regardless of age, cytogenetics, leukocyte count, and antecedent myelodysplasia. The data from this small single arm study are encouraging but at this stage far from definitive. The sparse comparative data on demethylating agents versus intensive chemotherapy that have been published failed to show a clear advantage for intensive treatment. However no long term survival data have been reported after therapy with hypomethylating drugs. A prospective study comparing these agents with intensive treatment is yet to be conducted.

Patient 4- A patient of 72 yrs old presenting with intermediate risk AML declining a recommended intensive chemotherapy approach

This woman, 72 yrs old at the time of diagnosis, presented with recurrent upper airway infection. She was a widow and had no children and lives a solitary life. Her medical history was unremarkable. A complete blood cell count included a WBC of $3.8 \times 10^9/l$, neutrophils $0.4 \times 10^9/l$, Hgb $5.7\text{mmol/l}$ and platelets $23 \times 10^9/l$. Morphological 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 which 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 now lasts for more than 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 participate in decision making based on accurate information about the risks and benefits of all available treatment options. Apart from chances of cure and treatment-related mortality, it should also include discussions on living and social circumstances, quality of life issues and personal expectations in relation to either choice\(^51\). In our patient individual socio-economic factors determined her decision and these then had to be taken into account to define the appropriate treatment. Since our patient was interested in receiving a less intensive treatment, there was an opportunity to enroll her in a clinical trial which whenever possible we would consider a priority option.

Final considerations
Today patients with AML at older age can be offered one of the following treatment options:
- standard induction treatment consisting mostly of a 3+7 regimen of an anthracyclin and cytarabine
- hypomethylating agents
- investigational drugs within a clinical trial
- low dose cytarabine
- best supportive care with oral cytostatic drugs like hydroxyurea, and/or transfusions

Obviously the assessment of the clinical performance and medical condition about whether or not intensive chemotherapy can be recommended remains a subjective approach that largely depends on the judgment of the medical doctor. Risk scoring
systems as discussed above could be instrumental in this regard. Geriatric assessments
with a focus on cognitive and physical function either by objective measurements or
self-reported measures have not been widely studied. However, early studies suggest
that they have added value in comparison to performance status and comorbidity
evaluations and thus they may improve the prediction of survival in older patients
receiving intensive chemotherapy.20, 52
What in general can we learn from the clinical vignettes presented above? First, we should
always, also in patients of older age, make a deliberate therapeutic plan that makes sense in
the individual circumstances and try to adhere to the defined plan as much as possible even
though intercurrent problems may urge for 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 less than 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 two decades most
probably due to better supportive care.21 A wait-and-see approach with supportive care and
cytoreduction with hydroxyurea does not furnish a significantly better perspective for the
patient with AML in terms of improving quality of life or prolonging survival since none of
the basic medical problems will be tackled.28
Third, nonmyeloablative allogeneic HSCT being reasonably well tolerated in terms of early
toxicity have shifted the age limit of the applicability alloHSCT upwards. Allogeneic HSCT
following reduced intensity conditioning nowadays provides antileukemic effectiveness that
is not much different from ablative alloHSCT.
Fourth, in a general sense the molecular features that characterize risk of AML in middle
aged adults also apply to AML at older age37, 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 along the way of the therapeutic management in an individual patient. For
instance good-risk cytogenetics (core-binding factor leukemias) express a distinctly favorable
impact in older patients with AML.3, 9 And this background information may be reassuring in
our management approach when we encounter intercurrent medical hurdles during the
treatment in an older patient. On the other hand monosomal karyotypes at the unfavorable end of the cytogenetic spectrum carry adverse prognostic value \(^3\) (fig1). Various studies have established that the favorable effect of the NPM1 mutant genotype in the absence of FLT3 gene mutations for patients treated on intensive chemotherapy protocols also holds up in AML at advanced age \(^3,9,53,54\). This genotype exerts a strong positive effect on outcome that is much more apparent than that of individual NPM1 or FLT3 genotypes. On the other hand 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 \(^55,56,57\).

In this regard it should be noted that the frequencies of these genotypes are considerably less common in older patients \(^58\) while the incidence of particular unfavorable genotypes (eg ASXL1 and TET2 gene mutations) appear to increase with progressively higher age \(^57,59,60,61\). Also gene expression levels have been evaluated for their prognostic value. They employ relative cutoff values (high versus low) rather than absolute 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, it is to be noted that numerous new drugs are currently emerging from the development 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 in close collaboration rational and complementing trials to accelerate the treatment development of AML that is so urgently needed.

Sixth, we would recommend whenever possible to include the older AML patients in well designed clinical trials. This furnishes some guarantee for quality of treatment (eg protocolized treatment according 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 contain 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 upfront context in fit elderly AML and in distinctly genomic defined AML where the effect of drugs specifically targeting components of key signal transduction pathways can be investigated.

The treatment outcome in patients of older age is comparatively reduced as compared to younger and middle-aged adults with AML, but this should not at all be a reason to approach the patient with a fatalistic approach. The patient with AML irrespective of his/her age deserves the opportunity of adequate diagnostics including molecular genetics that provides a documented substrate for a thoughtfully considered treatment plan.

Author statement: GO and BL both wrote the article
Conflict of interest disclosure:
BL: No disclosures
GO: Consultancy: J&J, Novartis, Celgene, ARIAD; Research Funding: Novartis, Celgene.

References:


37. Friederike Pastore, Annika Dufour, Tobias Benthaus, Klaus H. Metzeler, Kati S. Maharry, Stephanie Schneider, Bianka Ksienzyk, Gudrun Mellert, Evelyn Zellmeier, Purvi M. Kakadia, Michael Unterhalt, Michaela Feuring-Buske, Christian Buske, Jan Braess, Maria Cristina Sauerland,


64. Estey E. Clinical trials in AML of the elderly: should we change our methodology? *Leukemia*. 2004;18(11):1772-4

**Legends for the figures**

**Fig 1** Overall survival according to cytogenetic risk in patients above 60 years. Data derived from the HOVON/SAKK study (HOVON 43) investigating the value of high dose Daunorubicin.\(^3\) Abbreviations: CBF: Core binding factors; CN: normal karyotype (including -Y, -Y); CA rest: Other cytogenetic abnormalities; Unfav,MK-: complex cytogenetic abnormalities (at least three unrelated cytogenetic abnormalities), monosomies or partial deletions of chromosome 5 or 7 (del(5q), del(7q), -5, -7), abnormalities of the long arm of chromosome 3 (q21;q26), t(6;9) (p23;q34), t(9;22)(q34;q11.2), or abnormalities involving the long arm of chromosome 11 (11q23); MK: monosomal karyotype.

N: numbers; F: failures (death)

**Fig 2** General algorithm for the treatment of patients at older age with AML. This algorithm serves as a global guideline and should not be applied dogmatically but with thoughtful consideration of the individual circumstances. Patients who are eligible for intensive treatment are considered for remission induction chemotherapy following which depending on the response and the risk profile of the leukemia an allogeneic HSCT as consolidation therapy can be considered. For patients with an unfavorable risk AML intensive chemotherapy is mainly considered when a donor for an allogeneic HSCT is available and a subsequent alloHSCT can be foreseen. Otherwise these unfavorable risk patients and also patients noneligible for intensive chemotherapy will more likely be considered for less intensive treatment approaches or sometimes a clinical trial with an interesting investigational agent. A minority of these patients may eventually still proceed to an alloHSCT in case they would show an exceptionally good response to treatment and their general performance status at that point appears to show sufficient improvement so that an alloHSCT is considered feasible. For reasons discussed in the text, we recommend to include patients in a clinical trial whenever possible. Medical criteria and dilemmas regarding patient eligibility for intensive chemotherapy are also discussed in the manuscript.
Algorithm for the treatment of patients at older age with AML

Complete work up including cytogenetics/molecular classification of AML, co-morbidities/socio-economic situation of patient

Identify clinical trial

Considered eligible for intensive treatment

Standard remission induction therapy

No

Consider alloHSCT

Yes

Unfavorable prognostic risk profile

Donor? 

No

standard remission induction treatment plus alloHSCT

Non-intensive treatment (eg with hypomethylating agents)

Investigational drug (clinical trial)

Not considered eligible for intensive treatment
How I treat the older patient with acute myeloid leukemia

Gert Ossenkoppele and Bob Löwenberg