

# Leucemia mieloblástica aguda del adulto

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## Presentación

En la actualidad, uno de los grandes retos de los hematólogos es el tratamiento de la leucemia mieloide aguda (LMA). Durante más de 20 años, los avances en el tratamiento han sido mínimos. Sin embargo el progreso en el conocimiento fisiopatogénico y molecular de la enfermedad ha sido impresionante. En este simposio los doctores Schelenk, Sanz y Faderi nos hablarán del futuro, que ya es presente, del tratamiento de la leucemia mieloide aguda, tanto en sujetos jóvenes como en ancianos.

La gran cantidad de alteraciones moleculares presentes en esta enfermedad y su heterogeneidad nos hace clasificar a estos enfermos en pequeños subgrupos que van a necesitar un tratamiento muchas veces diferenciado. Basados en estos hechos, se abre una gran avenida en su tratamiento, el tratamiento adaptado al riesgo e incluso lo que venimos a llamar la medicina personalizada; el doctor Shelenk nos pondrá al día los interesantes trabajos que realiza el grupo alemán para el tratamiento de la LMA. En esta línea, el doctor Sanz nos hablará de los nuevos fármacos que vamos a poder disponer dentro del armamento terapéutico contra la LMA; algunos de ellos ya son una realidad.

Finalmente, el doctor Faderi nos hablará del tratamiento de la LMA de los ancianos, otra de las grandes cenicientas de la hematología. Sin embargo, en los últimos años se han producido pequeños avances, como el uso de los agentes hipometilantes, que nos hace tener cierta esperanza en la mejoría del pronóstico de este grupo de enfermos.



## Taylored therapy for young patients with acute myeloid leukemia

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During recent years, considerable progress has been made in deciphering the molecular genetic and epigenetic basis of acute myeloid leukaemia (AML) and in defining new diagnostic, prognostic and even more important predictive markers.<sup>1</sup> The recent WHO classification reflects the fact that an increasing number of AML can be categorized based upon their underlying cytogenetic or molecular genetic abnormalities, and that these genetic changes form clinico-pathologic-genetic entities.<sup>2</sup> In total, more than two thirds of all AML cases can now be classified according to the underlying cytogenetic or molecular genetic lesions.<sup>1</sup> Thus the WHO 2008 classification represents an enormous progress in terms of reliability, validity and objectivity in comparison to morphological criteria used in the former FAB classification.

Novel therapies are now being developed that target some of the genetic lesions. However, so far this concept of targeted therapy has only been successfully applied in the therapy of acute promyelocytic leukemia (APL) by introducing all-trans retinoic acid (ATRA) and/or arsenic trioxide to conventional chemotherapy.<sup>3</sup>

New biomarkers enter more and more clinical practice with regard to prognostication but even more important to genotype-specific treatment approaches. Fast molecular screening beyond *PML-RARA* has been introduced by the international CALGB 10603 trial evaluating the impact of midostaurin as an adjunct to intensive chemotherapy (ClinicalTrials.gov: NCT00651261) in patients with AML being characterized by activating *FLT3* mutations subsuming internal tandem duplication (*FLT3* -ITD) and tyrosin kinase domain mutations (*FLT3* -TKD). A prerequisite and challenge of this study are that the *FLT3* mutational status has to be known before intensive chemotherapy gets started. To be clinically applicable this necessitates i) diagnostic laboratories being available 7 days a week, ii) laboratory turn around times of maximally 48 hours, iii) well organized sample logistics including overnight shipment by courier, iv) a clinical trials offices

being again 7 days a week available, v) transmission of laboratory results in combination with a genotype-specific trial recommendation and finally vi) an efficient system (primarily web-based) for patient trial-registration.

The German-Austrian AML Study Group (AMLSG) has extended the genotype-specific approach by including additional molecular markers into the screening and by offering additional genotype-specific treatment trials (Figure 1). The fast molecular screening within 48 hours of AMLSG currently comprises *PML-RARA*, *RUNX1-RUNX1T1*, *CBF $\beta$ -MYH11*, *FLT3*-ITD, *FLT3*-TKD and *NPM1*; testing for *CEBPA* mutations and *MLL-AF9* is supplemented within 2 weeks. In the same time period (2 weeks) karyotyping is available. All results are transmitted rapidly by a web-based system as well as by automatized fax messages without time delay to the clinician.

Such a complex process which parallelizes fast molecular screening and trial-recommendation needs stringent criteria with respect to data protection, data privacy and good clinical practice. AMLSG has implemented for this purpose a procedure, in which only a trusted third party has access to the personnel data of patients. All other communications between clinicians, laboratories and the clinical trials office is based on the uniform AMLSG identifier (AMLSG BiO-ID) which guaranties proper allocations (Figure 2). In consequence, the informed consent process of molecular screening is dissected from that of the subsequent genotype-specific treatment trial. Therefore, AMLSG has activated a clinical study, AMLSG BiO, where molecular screening, biobanking and gen-

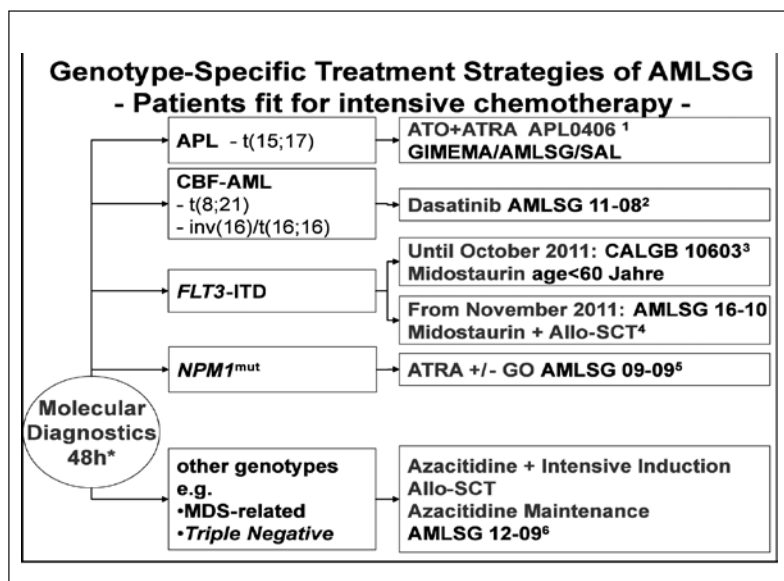


Figure 1. <sup>1</sup>ClinicalTrials.gov, NCT00482833; <sup>2</sup>ClinicalTrials.gov, NCT00850382; <sup>3</sup>ClinicalTrials.gov, NCT00651261; <sup>4</sup>planning phase; <sup>5</sup>ClinicalTrials.gov, NCT00893399; <sup>6</sup>ClinicalTrials.gov, NCT01180322; \* seven days a week.

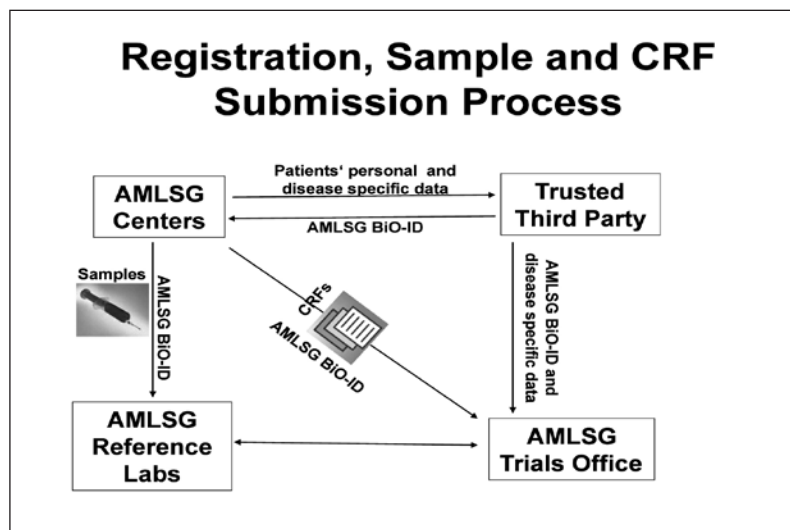


Figure 2. Abbreviations: ID, identifier; CRF, case report forms.

eral clinical data collection are covered (ClinicalTrials.gov, NCT01252485).

There is growing evidence, that genotype-specific approaches have to be integrated already during induction therapy. In patients with AML and activating *FLT3* mutations the addition of *FLT3*-inhibitors such as midostaurin to intensive induction therapy seems to substantially increase CR rates.<sup>4</sup> Similarly, gemtuzumab ozogamicin (GO) as adjunct to intensive induction therapy in patients with core binding factor leukemia was associated with an improvement of relapse-free and overall survival.<sup>5</sup> Of note, the integration of GO into consolidation<sup>5</sup> or maintenance<sup>6</sup> therapy seems to have no impact on survival endpoints. The addition of ATRA immediately after intensive induction therapy significantly increased CR rates and event as well as overall survival in older AML patients.<sup>7</sup> This beneficial effect was restricted to AML characterized by mutated *NPM1* in the absence of *FLT3*-ITD.<sup>8</sup> Taken together, these examples strongly supports the use of specific agents in specific genetically defined subgroups for induction therapy and this necessitates fast molecular screening.

Currently, there are several clinical trials expanding the genotype specific induction approach. Exemplarily, two genotype specific induction approaches are described:

A) Based on the high frequency of *KIT* mutations and high expression levels of the *KIT* receptor in core binding factor (CBF)-AML, two collaborative trials (AMLSG, ClinicalTrials.gov Identifier: NCT00850382; CALGB, ClinicalTrials.gov Identifier: NCT01238211) evaluate feasibility and efficacy of dasatinib, a potent inhibitor of mutated and wild-type *KIT*, in combination with conventional induction and consolidation therapy followed by a one-

year dasatinib maintenance therapy in patients with CBF-AML.

B) The constitutionally high expression of CD33 in AML with mutated *NPM1* brings up GO as a specific agent in these patients. A subset analysis in the MRC-15 trial failed to show a beneficial effect in this group of patients.<sup>5</sup> However, one has to be aware of the complex design of the study (5 by 6 by 2 factorial design resulting in 60 treatment-arms) and the low number of cases studied for the mutational status of *NPM1* and *FLT3* (39% and 37%, respectively). Therefore, careful interpretation of results is warranted. In contrast to the data from MRC a French study evaluating the addition of GO to salvage therapy revealed a extremely favourable overall response rate of 85% and excellent overall survival after 5 years of 80% in AML with mutated *NPM1* without concurrent *FLT3*-ITD.<sup>9</sup>

Encouraged by our own results in primary refractory patients<sup>10</sup> and the before mentioned French study, AMLSG currently evaluates GO within a randomized study for AML with mutated *NPM1* (ClinicalTrials.gov, NCT00893399).

Risk-adapted consolidation therapy is nowadays the standard of care. Based on recommendations from an international expert panel on behalf of the European LeukemiaNet four risk groups could be defined by cyto- and molecular-genetics.<sup>11</sup> So genotype-specific consolidation therapy is already implemented in that low risk patients were recommended to receive high-dose cytarabine-based consolidation chemotherapy and high risk patients an allogeneic hematopoietic stem cell transplantation (HSCT). For these to extremes there are rarely discussions about the risk-benefit ratio of the respective treatment strategy.<sup>12</sup> However, for the two intermediate risk groups, intermediate-1 and intermediate-2, there is some controversy whether the higher rate of treatment related mortality after allogeneic HSCT is outweighed by a substantially lower relapse risk in individual subgroups. A matter of debate was also whether allogeneic HSCT from matched related donors (MRD) and from a matched unrelated donors (MUD) were equally with respect to outcome. Several retrospective cohort and register studies have shown similar results.<sup>13</sup> In high risk AML patients defined either by unfavourable cytogenetics or induction failure this equivalence has recently been demonstrated also prospectively.<sup>14</sup> In a large prospective study (AMLHD98A) of 870 patients 267 were classified as high risk and of these 62% actually received an allogeneic HSCT from MRD (n=62), MUD (n=89) and hap-

loidentical or cord blood donor (n=11). By using adequate statistical methods to include allogeneic HSCT as a time dependent variable into multivariable models a marked and significant risk reduction could be demonstrated for allogeneic HSCT from MUD (31%) and MRD (37%). A secondary analysis focussed on transplanted patients revealed no difference in allogeneic HSCT between MRD and MUD.

Except for APL in patients with AML maintenance chemotherapy was not a widely accepted standard.<sup>11</sup> However, the introduction of tyrosin kinase inhibitors into the treatment of AML has led to the renaissance of maintenance therapy. In the CALGB 10603 (ClinicalTrials.gov: NCT00651261) trial a one year maintenance therapy is an integral part of the concept due to frequent and early relapses in patients with FLT3-ITD positive AML after consolidation therapy. In addition, prolonged inhibition of FLT3 signalling may be of importance.<sup>15</sup> Similarly, both trials using dasatinib in CBF-AML (AMLSG, ClinicalTrials.gov Identifier: NCT00850382; CALGB, ClinicalTrials.gov Identifier: NCT01238211) integrate a one year single agent maintenance after consolidation therapy.

Finally, molecular disease persistence has been shown to be a highly predictive factor for relapse and overall survival.<sup>16</sup> In particular, CBF-AML and AML with mutated *NPM1* as well as *MLL*-AF9 positive AML exhibit an excellent molecular marker for disease assessment.<sup>17-19</sup> Consistent prognostic time points for assessment of relapse risk based on the level of molecular disease persistence seems to be after induction therapy but even more at the end of consolidation therapy. Although, no prospective data are available in AML of treatment intensification based on level of molecular disease persistence after consolidation therapy, allogeneic HSCT should be considered in this situation even in formally low risk patients.

In conclusion, the continuous discovery of molecular markers with important prognostic and, more importantly, predictive significance on treatment will lead in conjunction to their role as potential targets to a stepwise replacement of standard risk-adapted therapy to genotype-specific treatment strategies. This development will necessitate international large collaborative group efforts to perform clinical trials even in small genetic subgroups.

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Dose Cytarabine and Etoposide with or without All-Trans Retinoic Acid in Older Patients not Eligible for Intensive Chemotherapy with Acute Myeloid Leukemia and *NPM1* Mutation AMLSG 15-10] from the Bundesministerium für Bildung und Forschung (BMBF).

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## Nuevos fármacos para el tratamiento de la leucemia mieloblástica aguda

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En estos últimos años se ha producido un impresionante desarrollo del conocimiento de la biología y de la genética molecular en la leucemia mieloblástica aguda (LMA), habiéndose identificado un número considerable de mutaciones cuyo papel patogénico en la leucemogénesis está aún por determinar en la mayoría de ellas. Esquemáticamente, estas mutaciones se clasifican en dos grupos, las que intervienen en los mecanismos de transducción de señal y los que alteran los factores de transcripción. Mientras las primeras propiciarían una ventaja proliferativa a las células con dichas mutaciones, no afectando a la diferenciación celular, las últimas alterarían el proceso de diferenciación y de auto-renovación. Ejemplos de mutaciones que afectarían a la proliferación serían las mutaciones de FLT3, como FLT3-ITD y FLT3-TKD, de c-KIT y las mutaciones oncogénicas en RAS, entre otras. En cambio, entre las mutaciones más frecuentemente implicadas en el bloqueo de la diferenciación estarían los reordenamientos de RAR $\alpha$  (retinoic acid receptor alpha) y de MLL (myeloid-lymphoid or mixed-lineage leukemia), así como factores de transcripción como los *core binding factors* (CBF), RUNX1, GATA1, y C/EBP alpha. La capacidad que ha demostrado el ácido holo-trans reti-

noico de revertir el bloqueo de la diferenciación que caracteriza a la leucemia promielocítica, en la que RAR $\alpha$  generalmente se reordena con PML, representa la mejor evidencia de un posible cambio de paradigma en el tratamiento de la LMA y, por qué no, de otras enfermedades neoplásicas. Bajo la perspectiva de este cambio de paradigma, en los últimos años se han desarrollado estrategias terapéuticas dirigidas contra diversas dianas con resultados muy variables que intentaremos analizar en esta ponencia. Un número importante de nuevos agentes dirigidos o no contra dianas moleculares han sido explorados (Tabla 1). Entre éstos se incluyen los anticuerpos anti-CD33 e inmunoconjugados, los inhibidores de proteínas como la P-glicoproteína implicadas en la resistencia múltiple a fármacos, los inhibidores de farnesil transferasa, los inhibidores de tirosina quinasa, los agentes anti-Bcl-2 y los inhibidores de mTOR (*mammalian target of rapamycin*). Otros nuevos agentes alquilantes y análogos de las purinas, tales como cloretazina y clofarabina, que interfieren el ADN y las ribonucleósido reductasas, respectivamente, han sido también ensayados recientemente. Algunos de estos agentes se han mostrado prometedores en pequeños estudios en fases precoces, pero precisan de ensayos amplios en fases más avanzadas para determinar mejor su eficacia. La combinación de agentes dirigidos a dianas con quimioterapia también podría aumentar la eficacia antileucémica.

Algunos de los agentes mencionados, como larmustina y rapamicina, han demostrado actividad en pacientes con LMA resistente o en recaída y están siendo investigados para la inducción a la remisión, especialmente en pacientes de edad avanzada, dado su perfil de toxicidad. Aunque algunos datos son prometedores, el papel de estos agentes en el tratamiento de la LMA está aún por determinar.

El mayor conocimiento de los mecanismos moleculares subyacentes en la LMA está estimulando el diseño de estrategias dirigidas a determinadas dianas. En este sentido, FLT3 representa una de las dianas terapéuticas más atractivas, entre otras cosas porque las mutaciones de este gen afectan a casi una cuarta parte de los pacientes con LMA y se asocian con un peor pronóstico. Aunque los inhibidores de FLT3 han mostrado una eficacia modesta cuando se usaron en monoterapia, estudios *in vitro* sugieren una sinergia de estos agentes con la quimioterapia. Por ello, estudios en fase III están actualmente explorando esta vía de terapia combinatoria en pacientes con LMA portadores de una mutación FLT3.<sup>1</sup>

Tipifarnib es un potente inhibidor de la farnesil-transferasa que ha demostrado actividad, tanto *in vivo* como *in vitro*, contra diversas neoplasias y particularmente en la LMA. Debido a que la actividad de este agente interfiere una variedad de vías implicadas en la leucemogénesis, y dado su favorable perfil de toxi-

Tabla 1. Nuevos agentes en el tratamiento de la LMA

Anti-CD33 conjugado con quimioterapia (gemtuzumab ozogamicina)
Inhibidores de la resistencia múltiple a fármacos (zosuquidar)
Inhibidores de farnesil transferasa (tipifarnib)
Inhibidores de FLT3 (lestaurtinib, midostaurin, tandutinib)
Oligonucleótidos antisentido Bcl-2 (oblimersen sodium)
Agentes antiangiogénicos (lenalinomida)
Inhibidores de histona deacetilasas
Agentes hipometilantes (azacitidina, decitabina)
Agentes alquilantes (laromustina)
IL-2 plus histamine
Análogos de deoxiadenosina (clofarabina)
Inhibidores de mTOR quinasa (rapamicina)
Inhibidores de múltiples receptores de quinasas (XL999)

cidad y su administración oral, la investigación clínica de este fármaco ha sido muy atractiva, especialmente en pacientes viejos. Desafortunadamente, las expectativas con este fármaco aún no se han visto satisfechas. Así, un reciente ensayo clínico en fase III, en el que se comparaba tipifarnib frente al mejor cuidado de soporte, no pudo demostrar ninguna ventaja.<sup>2</sup> Otro estudio en el que este agente fue combinado con bajas dosis de citarabina resultó en un exceso de muertes que llevaron a un cierre prematuro del estudio.<sup>3</sup> El papel de este agente en el mantenimiento o en combinación con quimioterapia estándar de inducción está siendo investigado.

En relación con el tratamiento de mantenimiento, diversas estrategias han sido propuestas en los últimos años, pero vale la pena destacar que, mientras diversos estudios no demostraron ventaja de administrar interleucina-2 (IL-2) en esta fase terapéutica, un estudio aleatorizado llevado a cabo en 320 pacientes mostró un beneficio significativo de la administración post-consolidación de un mantenimiento con IL-2 e histamina.<sup>4</sup> Otros fármacos dirigidos a dianas como tipifarnib, inhibidores de tirosín quinasas o agentes hipometilantes están siendo objeto de ensayos clínico en fase III para determinar su utilidad en el tratamiento de pacientes con LMA.

Con respecto a clofarabina, un análogo de la deoxiadenosina que fue diseñado para combinar propiedades de fludarabina y cladribina es un fármaco realmente interesante y prometedor que está actualmente siendo evaluado en diversos ensayos clínicos en fases II y III en pacientes con LMA. Estos y otros ensayos con otros agentes mostrados en la Tabla 1 serán objeto de un análisis más detallado en la presentación en el simposio.

El desarrollo de nuevos agentes dirigidos a dianas implicadas en los mecanismos de la leucemogénesis

es un área en continuo desarrollo y progreso. Aunque muchos nuevos agentes antileucémicos tienen actualmente un gran potencial, su papel definitivo en el tratamiento de la LMA está en su mayoría pendiente de ser confirmado en ensayos clínicos. No obstante, para el futuro se vislumbra que las estrategias terapéuticas serán más específicamente dirigidas a la biología de la enfermedad.

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## Treatment of older patients with acute myeloid leukemia

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### Abstract

Acute myeloid leukemia (AML) in patients over 60 years of age has a poor prognosis. Whereas most patients only receive supportive care, the remaining one third has better overall survival and quality of care following leukemia-specific therapy. However, compared to younger patients, outcome with standard therapy remains suboptimal. For most of the older patients with AML, investigational therapies are appropriate. These therapies may include low- or higher-intensity strategies. Many novel agents have been introduced and are being explored in clinical trials. Although promising, there is no general agreement about the best treatment strategy. Prognostic models have been proposed to help decide appropriate therapies. Stem cell transplant can improve the outcome of a select group of patients but donor availability and a high treatment-related mortality remain signif-

icant barriers to success. Frontline therapy of older patients with AML remains one of the most active areas of clinical research within leukemia.

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## Introduction

Acute myeloid leukemia (AML) is a rare hematopoietic neoplasm with a median age of presentation of 65 to 70 years. Even though rare, its aggressive nature, rapid progression, universally fatal outcome if left unattended to, and often complicated clinical course continue to present formidable challenges.

An evolution in the understanding of the biology of AML has led to the identification of several cytogenetic and molecular abnormalities highlighting the heterogeneity of AML not as one but many diseases. Accordingly, there has been a re-definition of prognostic models in addition to what was established in the past based on karyotype alone.<sup>1</sup> These discoveries and the description of pathophysiologically relevant signaling pathways resulted in numerous small molecules and other drugs that are being developed for targeting these pathways.

Progress in AML therapy is nowhere more needed than in older patients with AML where response rates to standard induction therapy decrease with each decade of increasing age and long-term disease free survival remains below 10%. Therapy of older patients with AML not only faces the obvious hurdles of having to deal with multiple co-morbidities and decreasing tolerance to myelosuppression and immunosuppression. AML in the elderly also appears to be a biologically different disease to what is encountered in the younger population. There is reason to hope that the ever increasing number of therapeutic molecules and the design of novel therapeutic regimens will change the decade old treatment paradigm of cytarabine plus anthracyclines and lead to a better prognosis for these patients in the future.

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## The particular challenges of older patients with AML

The general approach to AML therapy is guided by AML subtype (acute promyelocytic leukemia [APL], core binding factor [CBF] leukemias, and others) as well as age and performance status of the patient (high-intensity versus low-intensity therapy). APL, whose treatment differs most substantially from that of other types of AML, and CBF leukemias, which are uniquely sensitive to cytarabine, are rare in older patients. Given the particular challenges in this patient group, there is a growing trend to separate treatment of older patients from younger patients.

Although arbitrary, “older” usually refers to patients who are above 60 years. In an analysis of Surveillance, Epidemiology, and End Results (SEER) cancer registries and Medicare administrative claims, the estimated median survival of 2657 elderly patients with AML was 2 months with a 2-year survival rate of 6%.<sup>2</sup> It is important to note however, that only one third of the patients received treatment at all as often times therapy was considered futile for most and palliation thought to be more appropriate. The results for therapy in older patients are inferior for a number of reasons: 1) more frequent co-morbidities; 2) the performances status is more likely to be reduced; 3) tolerance to intensive chemotherapy is diminished as older patients are less likely to tolerate prolonged myelo- and immunosuppression. In addition there are differences intrinsic to the biologic behavior of AML blasts between older and younger patients. The older age group is far more likely to present with secondary AML (following a preceding phase of myelodysplastic syndrome [MDS] or any other antecedent hematologic disorder [AHD]), express unfavorable cytogenetics, are less sensitive to anthracyclines, and more often express multidrug resistant phenotypes.<sup>3</sup> Nevertheless, older patients still do better with therapy. As the SEER analysis also demonstrated, patients who received therapy lived on average 6 months longer. This observation is also reflected in other studies where the benefits of therapy included longer survival and better quality of life.<sup>4,5</sup>

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## Induction therapy

Once the diagnosis of AML is established, there are three options: conventional chemotherapy, investigational therapy, and palliative care. The rare occurrences of APL and CBF leukemias for older patients should probably be approached in a way similar to the strategies applied in younger patients. Although there is evidence that the response rates for CBF leukemias are lower in older patients, these patients should not be bereft of the benefits that they may still gain from more conventional therapy under these circumstances. Given the poor outcome in the remaining subtypes of AML with conventional therapy (median survival time of 10 months; induction mortality of around 20% which easily exceeds 50% for patients with a poor performance status), a convincing case can be made that conventional therapy not be recommended.<sup>6</sup> Yet older patients are not a homogeneous group and therefore prognosis remains highly variable with some (even though only a few) doing well with standard chemotherapy whereas others are better served with alternative therapies. Several prognostic models have been described to provide

Table 1. Prognostic Models

Group	Outcome	Unfavorable Prognostic Markers
Study Alliance Leukemia <sup>7</sup>	Survival Disease-free survival	CD34 expression > 10% WBC > 20x10 <sup>9</sup> /L Age > 65 years LDH > 700 U/L NPM1, wild-type*
UKMRC <sup>8</sup>	Survival	Unfavorable cytogenetic group High WBC <sup>#</sup> Poor performance status <sup>#</sup> Older age <sup>#</sup> Secondary AML
ALFA <sup>9</sup>	Survival	Unfavorable cytogenetics ± Age ≥ 75 years Performance status ≥ 2 WBC ≥ 50x10 <sup>9</sup> /L
MDACC <sup>10</sup>	Remission rate Induction mortality Survival	Age ≥ 75 years Secondary AML <sup>^</sup> AHD duration ≥ 6 <sup>^</sup> (12) months Treatment outside LAFR Unfavorable cytogenetics WBC ≥ 25x10 <sup>9</sup> /L <sup>^</sup> Hemoglobin ≤ 8 g/dL <sup>^</sup> Creatinine > 1.3 mg/dL Performance status > 2 LDH > 600 U/L <sup>&amp;</sup>
HCTCI <sup>11</sup>	Early mortality Survival	Dyspnea Coronary artery disease, CHF, MI, or EF < 50% Chronic hepatitis, elevation of bilirubin and/or transaminases Cirrhosis Elevations of creatinine, dialysis, renal transplant Secondary AML Depression/anxiety requiring therapy Continued use of anti-microbial therapy after day 0 BMI > 35 kg/m <sup>2</sup>

\* Favorable and high-risk groups were defined solely by cytogenetic aberrations. Above factors served to further divide the intermediate risk group into good intermediate versus adverse intermediate; <sup>#</sup> as continuous variables; <sup>^</sup> only significant for prediction of remission; <sup>&</sup> only significant for prediction of survival; UKMRC, United Kingdom Medial Research Council; ALFA, Acute Leukemia French Association; MDACC, MD Anderson Cancer Center; HCTCI, Hematopoietic Cell Transplantation Comorbidity Index; WBC, white blood cell count; LDH, lactic dehydrogenase; AHD, antecedent hematologic disorder; LAFR, laminar air flow room (isolation floor); CHF, congestive heart failure; MI, myocardial infarction; EF, ejection fraction; BMI, body mass index

objective guidelines of who may do better with standard therapy and who is “unable and unfit” for it and better off with investigational treatments (Table 1).<sup>7-</sup>

<sup>11</sup> Most of these models are built upon easily accessible clinical information and can provide useful guidance as to what to expect with standard therapeutic strategies. As these models are virtually all based on retrospective analyses they still require validation in prospective clinical trials.

Within conventional therapy, the options include low-intensity and intensive (i.e. at least standard dose cytarabine) therapy. Low-intensity therapy should be considered in the unfit patients (see models; in general

these patients are older [e.g. > 70 to 75 years] and have a limited performance status) without any disease features with a high likelihood of resistance (adverse karyotype, treatment-related AML). It should always be remembered, however, that these parameters only serve as aides and are not to be taken as absolutes. In the National Cancer Research Institute (NCRI) AML 14 Trial, 217 patients considered unfit for intensive chemotherapy were randomized to low-dose cytarabine at 20 mg subcutaneously twice daily for 10 days or hydroxyurea.<sup>12</sup> Both survival and remission rate (18% versus 1%; p<.001) were significantly superior in the low-dose cytarabine arm with the notable exception of patients with adverse cytogenetics who had a poor response with any treatment. This study establishes low-dose cytarabine as an accepted standard of care against which other investigational agents may be evaluated.<sup>13</sup> The use of hypomethylating agents is so widespread that they may be counted among the standard armamentarium for elderly patients with AML (although they are not approved for this indication by regulatory authorities in Europe and in the US). Azacitidine 75 mg/m<sup>2</sup> subcutaneously daily for 7 days was compared to conventional care (best support-

ive care, low-dose cytarabine, intensive chemotherapy) in 113 elderly patients with a median age of 70 years.<sup>14</sup> Median overall survival was 24.5 months in the azacitidine group compared to 16 months in the conventional care group (p=.005). In a couple of single-arm trials, decitabine at 20 mg/m<sup>2</sup> intravenously daily for up to 10 days achieved complete remission rates from 24 to 47% and overall median survival times ranging from 7.7 months to slightly longer than one year.<sup>15,16</sup> Induction mortality was low and responses also occurred in patients with unfavorable karyotypes, an important difference to low-dose cytarabine.

Table 2. Investigational Treatments

Regimens	N	Median age (y) (range)	OR (%)	CR (%)	Median survival (m)	Induction mortality (%)
Clofarabine <sup>18</sup>	112	71 (60-88)	46	38	9.8	9.8
Clofarabine + low-dose cytarabine <sup>19</sup>	54	70 (60-82)	67 <sup>#</sup>	63 <sup>#</sup>	11.4	19
Tipifarnib + etoposide <sup>20</sup>	84	77 (70-91)	40	25	5.3	11
Laromustine <sup>21</sup>	85	72 (60-87)	32	23	3.2	14
Idarubine/cytarabine + lomustine <sup>22</sup>	508	70 (60-86)	68	68*	12.7*	16
High-dose lenalidomide <sup>23</sup>	33	71 (60-88)	30	NA	4	24

<sup>#</sup> significantly higher than with clofarabine alone

\* significantly higher than with idarubicin plus cytarabine alone

Conventional intensive therapy typically means 3 days of an anthracycline with 7 to 10 days of cytarabine 100 to 200 mg/m<sup>2</sup>/dose (mostly “3+7”). If one decides to use this approach, doses should not be attenuated based on age alone. The choice of anthracycline has no significance as long as they are used at equitoxic doses. In a recent large randomized trial, higher dose daunorubicin (90 mg/m<sup>2</sup> daily x 3 days) was compared to daunorubicin 45 mg/m<sup>2</sup> daily x 3 days in combination with standard dose cytarabine.<sup>17</sup> The higher dose daunorubicin arm achieved higher rates of CR, notably after only one course, than the standard dose group. A survival benefit was also seen in the subgroup of patients between 60 and 65 years. Addition of other drugs in a three drug combination (such as mitoxantrone or etoposide) does not improve outcome.

As the number of older patients who benefit from standard therapy remains limited, investigational therapy can be recommended for the majority of elderly patients with AML. The attraction of investigational treatments is not only limited to the unfit as described above, but particularly increases with the accumulation of unfavorable prognostic factors. Investigational for older patients therefore does not a priori indicate low-intensity therapy. Patients with an excellent performance status but high-risk disease (unfavorable karyotype, preceding MDS, therapy-related AML) may be appropriate candidates for high-intensity programs whereas low-intensity protocols are the better choice for patients with a more fragile performance status, multiple co-morbidities, or those who do not want to undergo intensive chemotherapy. Many investigational approaches are being pursued in clinical trials (Table 2).<sup>18-23</sup>

Patients with a performance status of 3 or 4, severely abnormal organ function, or who are very old (> 80 years) may benefit more from supportive care as their expected treatment-related mortality is likely to be high and any gains will be minimal with currently available means. As always, these decisions need to be made on an individual basis.

## Postremission therapy

There is no one generally agreed upon postremission therapy for older patients. To administer repetitive cycles of modest dose consolidation therapy is a reasonable strategy for patients with a good performance status and absence of adverse cytogenetics. Unlike in younger patients, high-dose cytarabine is less effective and given its worse toxicity in older patients (neurological and pulmonary toxicities in addition to myelosuppression and gastrointestinal adverse events) also less likely to be feasible. There remains uncertainty as to the number of post-remission cycles (4 have been equal to 1), the intensity of postremission treatments (1 intensive consolidation cycle was better than one year of oral maintenance but in another study 6 cycles of outpatient consolidation were superior to one short but more intense inpatient course), and whether or not a more prolonged maintenance could be beneficial (as suggested in one study).<sup>1</sup> It can be expected that identification of gene mutations may impact on the choice of postremission therapy, but to date little experience exists how this will best be accomplished. It remains the general consensus though that postremission therapy consisting of any permutations of anthracyclines with cytarabine are unsatisfactory for most patients with AML who are older than 60 years.<sup>24</sup>

Hematopoietic stem cell transplant (HSCT) has been hampered by lack of suitable donors in most cases and high treatment-related mortalities that are associated with standard transplant procedures. Reduced-intensity conditioning (RIC) regimens have opened this treatment modality to a wider range of older patients as demonstrated by a recent analysis that revealed no significant impact of age on non-relapse mortality, relapse, disease-free and overall survival.<sup>25</sup> Selection of patients for HSCT would presumably follow similar guidelines as in younger patients with the caveat that for older patients long-term disease control is far more difficult to achieve.

## Conclusions

Treatment of AML in older patients remains a challenging endeavor. Whereas standard therapy carries a dismal prognosis for most patients, some will still benefit from it. Prognostic models have been designed to estimate response, induction mortality and/or overall survival of older patients based on experience with conventional chemotherapy and are therefore helpful tools to identify the most appropriate therapeutic approach to patients. Many investigational therapies are being explored in the frontline therapy of older patients with AML including novel targeted molecules and cytotoxic chemotherapeutic agents. Reduced intensity conditioning regimen have extended to age range for HSCT to at least 70 years of age whereas there is very little experience with HSCT for patients older than that. Donor availability remains an issue. There is no well defined role for maintenance therapy and the role of minimal residual disease remains to be explored.

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