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Acute myeloid leukemia with monosomal karyotype at the far end of the unfavorable prognostic spectrum

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The treatment of acute myeloid leukemia (AML) is among the most dose-intensive approaches in clinical oncology and involves variable therapeutic options with highly diverse consequences in terms of toxicities and anti-leukemic effects. One illustrative example is the choice between consolidation chemotherapy and stem cell transplantation in first remission and also the choice among highly diverse types of stem cell transplantation such as autologous, allogeneic-sibling, haplo-identical, unrelated donor or umbilical cord blood grafting. Prognostic factors provide guidance in clinical practice in these complex treatment management dilemmas. An average 40% of adult patients up to the age of 60 will have long-term survival prospects; for older patients this is only 10-15%. Among these estimates there is considerable variation in outcome between individual patients. Patient related factors (e.g. age, comorbidity conditions) and hematologic factors (e.g. '*de novo*' *vs.* secondary AML) impact on individual treatment outcome. Most prominently, particular leukemia-specific somatic genetic alterations furnish essential prognostic determinants. These genomic abnormalities in the leukemic blasts are assessed with classical cytogenetic techniques (banding, fluorescence *in situ* hybridization) or a range of molecular methods. There is no question that cytogenetics, more than any other genetic source of information, has become solidly established in the diagnostic work up of patients with AML.[1-3] Cytogenetics unravels the highly variable clinical biology of AML and thus allows for sharp clinically useful diagnostic and prognostic distinctions. Recent studies have revealed that AML with so called monosomal karyotypes are at the extreme unfavorable end of the prognostic spectrum and predict one of the worst possible outcomes. This issue of the journal contains a report by Xie *et al.* that examined the significance of residual karyotypically normal cells in monosomal karyotype AML (MK-AML).[4]

Monosomal karyotype AML: what is it about?

During the past 25 years several large clinical trial groups, such as the Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) and the Swiss Group for Clinical Cancer Research (SAKK), have collected cytogenetic diagnostics at baseline in patients with AML enrolled in their treatment protocols. This has generated data sets in large series of comparatively homogeneously treated patients in whom the prognostic contribution of various cytogenetic abnormalities such as complex karyotypes (i.e. multiple chromosomal aberrations) could be evaluated. Statistical analysis revealed that loss of a complete autosomal chromosome conferred profound negative prognostic impact (Figure 1A), whereas structural abnormalities negatively influenced prognosis in association with an autosomal monosomy.[5] Extra chromosomes

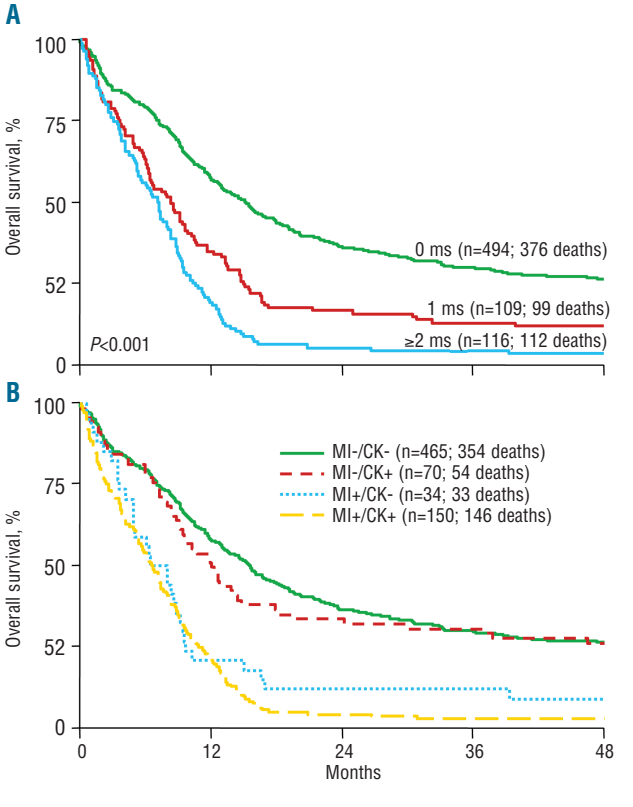

Figure 1. Overall survival of patients with acute myeloid leukemia (AML) and non-core-binding-factor chromosomal abnormalities. (A) Survival in relation to numbers of autosomal chromosomal monosomies (none, 1, and ≥2 ms). (B) Survival in relation to 'monosomal karyotype' (in figure designated as MI) as defined by Breems *et al.*[5] and/or 'complex karyotype with ≥3 cytogenetic clonal abnormalities' (CK). *Reprinted with permission. ©2008 American Society of Clinical Oncology. All rights reserved."* Breems D et al. J Clin Oncol 2008;26(29):4791-7.

(e.g. trisomies) had a minor effect on prognosis. Based on these observations, the 'monosomal karyotype' as a predictor for very poor prognosis of AML was identified. MK-AML, referring to at least two autosomal monosomies or a single autosomal monosomy plus an additional structural cytogenetic abnormality were, therefore, postulated as a more homogeneous distinguishable subset of AML representative with an extremely adverse outcome.[5] In direct comparisons, MK provided significantly better prognostic prediction than the traditionally defined complex karyotype that considers any 3 or more, 4 or more, or 5 or more clonal cytogenetic abnormalities.[5] As a matter of fact, it also became apparent that complex karyotype AML is by no means prognostically different from any generally cytogenetically aberrant AML if karyotypes with deletions of complete chromosomes (monosomies) were excluded from the complex karyotypes (Figue 1B).[5] Thus, MK-AML, in addition to AML with normal cytogenetics and core-binding-factor abnormalities, represents a new distinct aggregate of cytogenetically abnormal AML (Figure 2).[5]

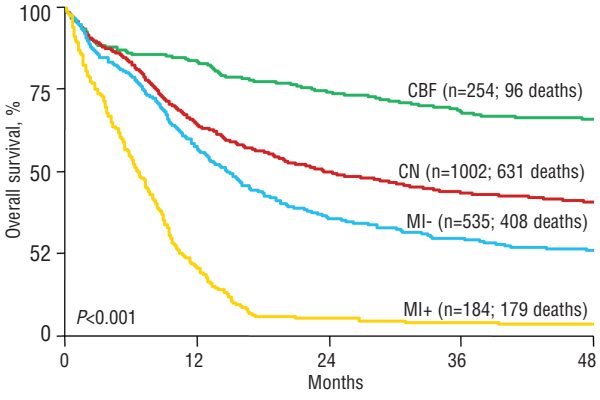

Figure 2. Overall survival of four prognostic subcategories of acute myeloid leukemia (AML) aggregated according to cytogenetics. Core-binding-factor (CBF) abnormalities. Normal karyotype (CN). Non-CBF abnormalities but 'monosomal karyotype' negative (in figure designated as MI-) and non-CBF abnormalities but 'monosomal karyotype' positive (in figure designated as MI+). MK refers to ≥2 autosomal monosomies or one autosomal monosomy with at least one structural abnormality. Breems D et al. J Clin Oncol 2008; 26(29):4791-7.

What do we currently know about monosomal karyotype AML?

It is notable that AML with complex karyotypes have for long been accepted for their unfavorable prognosis while only recently has it become clear that the unfavorable impact of the complex karyotypes is predominantly due to the fact that they are heavily admixed with monosomal karyotypes.[5] In the original HOVON-SAKK report, the MK-AML was prevalent in about 9% of AML patients between 15 to 60 years of age.[5] In subsequent studies, MK-AML has been reported in about 6-10% among patients with newly diagnosed AML although the prevalence goes up with increasing age.[6-9] For example, Medeiros *et al*. reported a frequency of MK-AML of about 20% in newly diagnosed patients with AML over the age of 60 years[8] (Table 1). AML with MK has poor outcome in patients in any age group and even young patients show a comparatively poor complete remission (CR) rate and survival estimate when they present with MK-AML.[5] Subsequent studies have confirmed these findings (Table 1). In the recent HOVON-SAKK studies, the CR rates for MK-AML were no more than 52% in patients between 18 to 60 years[9] and only 34% in patients with MK-AML older than 60 years.[6] A study from the South West Oncology Group (SWOG) reported exceptionally low CR rates of only 50% in patients under the age of 31 years, 27% in patients 31-40 years, 14% for patients 41-50 years, 24% for patients aged 51-60 years and 13 % for patients with MK-AML aged over 60.[8] In addition to CR rates, the survival estimates in AML with MK are universally poor (Table 1). In the original study for patients up to 60 years of age, the 4-year overall survival (OS) was estimated at only 4%. These highly unfavorable results have also been noted in subsequent studies. The SWOG study reported an OS of 3% at four years[8] and the HOVON-SAKK group in their recent prospective studies reported 7% OS at five years in patients under 60 years of age[9] and 4% OS at two years in patients over 60 years of age.[6] In the SWOG study, patients with AML between 41 to 88 years of age showed an estimated survival of less than 1% at four years[8] and in the HOVON-SAKK study in patients 60 years and older there were no long-term survivors at five years.[6] The very poor prognosis of MK-AML was also apparent in a large-scale study in more than 5,500 patients with AML in patients between 16 to 59 years of age by the United Kingdom Medical Research Council (10-year OS: 5%).[7] Not only in AML, but also in patients with high-risk myelodysplastic syndrome (MDS), the presence of MK appears to confer a notably poor outcome. An analysis of the Mayo Clinic database showed that in adult MDS with complex karyotype the MK is also a predictor for very unfavorable survival (2-year OS: 23% in MK- and 6% in MK+ MDS).[10]

Table 1. Frequencies, complete remission rates and overall survival estimates of newly diagnosed patients with acute myeloid leukemia and monosomal karyotype in relationship to age.

Age	Frequency*	Complete remission	Overall survival	Reference
≤ 30 years	nr	nr	17% at 4 years	Breems *et al.*[5]
	4%	50%	40% at 4 years	Medeiros *et al.*[8]
≤ 60 years	9%	48%	4% at 4 years	Breems *et al.*[5]
	6%	nr	5% at 10 years	Grimwade *et al.*[7]
	10%	24%	3% at 4 years	Medeiros *et al.*[8]
	10%	52%	7% at 5 years	Löwenberg *et al.*[9]
> 60 years	13%	34%	4% at 2 years	Löwenberg *et al.*[6]
	20%	13%	1% at 4 years	Medeiros *et al.*[8]

*nr: not reported. *indicates frequency of monosomal karyotype acute myeloid leukemia among all patients.*

In this issue of the journal, investigators report an effort to identify prognostic heterogeneity among MK-AML.[4] They looked at the significance of residual normal karyotypes in 176 patients with MK in a multivariate analysis. Previously, Estey *et al.* had reported in another context that a subgroup of AML and MDS with chromosome 5 and/or 7 abnormalities exhibit a somewhat more favorable prognosis when these abnormali-

ties are found in combination with more than one residual normal metaphase.[11] In the study reported here, MK-AML shows statistically a slightly better survival at two years of follow up when normal metaphases are apparent, although the survival of even those patients remained very poor.[4]

Therapeutic implications of monosomal karyotype AML?

The excessively poor prognostic subgroup of AML with MK is explained by resistance against current treatment modalities resulting in a low CR percentage. CRs achieved following 3+7 anthracyclin-cytarabine induction chemotherapy in MK-AML are of poor quality which is evident from the high and early relapse rate after CR. This high relapse rate is also apparent in an analysis of the University of Minnesota showing a relapse rate of 62% at four years of patients with MK-AML who had been treated with an allogeneic stem cell transplantation in their first CR.[12] On the other hand, preliminary data from the HOVON-SAKK cooperative group suggest that patients submitted to an allogeneic stem cell transplantation have a better prognosis than those submitted to chemotherapy programs (HOVON-SAKK cooperative group, unpublished results). Thus, an allogeneic stem cell transplantation, which is the currently recommended consolidation treatment for poor-risk AML in general,[13,14] also seems to be the treatment of choice in patients with MK-AML as one of few available treatment options. Meanwhile, novel more active therapies are evidently badly needed for MK-AML. This means that MK-AML represents a subtype of AML that is heavily dependent on investigational explorative approaches and particularly suitable for new drug development even in front-line treatment situations.

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Therapy-related acute promyelocytic leukemia

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Success in the treatment of cancer has led to an expanding population of survivors with their attendant long-term complications. Treatment with cytotoxic, DNA-interactive drugs and radiation is well known to predispose to the development of secondary tumors, in particular secondary myelodysplasia and acute myeloid leukemia (AML).[1] Such therapy related neoplasms have been associated with recurring chromosomal abnormalities such as translocations involving the *MLL* gene (commonly seen within a few years after therapy with topoisomerase II inhibitors) and loss of part or the whole of chromosomes 5 and 7 (frequently observed several years after treatment with the alkylating agents).[1] The occurrence of these recurring chromosomal aberrations and their association with specific chemotherapeutic agents is suggestive of a specific interaction between these drugs and the genome.[1]