Dismal Prognostic Value of Monosomal Karyotype (MK) in Elderly Patients with Acute Myeloid Leukemia (AML): a GOELAMS Study of 186 Patients with Unfavorable Cytogenetic Abnormalities

Running head: Poor prognosis of monosomies in elderly with AML


1Clinical Hematology, University Hospital Nancy Brabois, Vandœuvre-lès-Nancy, France; 2Hematology Laboratory, University Hospital Robert Debré, Reims, France; 3Clinical Hematology, University Hospital Haut Levêque, Bordeaux, France; 4Hematology Laboratory, University Hospital du Bocage, Dijon, France; 5Clinical Hematology, University Hospital Hôtel Dieu, Nantes, France; 6Centre René Gauducheau, Saint Herblain, France; 7Clinical Hematology, University Hospital Bretonneau, Tours, France; 8Clinical Hematology, University Hospital Michallon Grenoble, France; 9Clinical Hematology, University Hospital Larrey, Angers, France; 10Clinical Hematology, University Hospital Robert Debré, Reims, France; 11Clinical Hematology, University Hospital Purpan, Toulouse, France; 12Institut Paoli Calmettes, Marseille, France; 13Clinical Hematology, University Hospital Larrey Purpan, Strasbourg, France; 14Clinical Hematology, General Hospital, Mulhouse, France; 15Clinical Hematology, University Hospital La Seyne, Montpellier, France; 16Clinical Hematology, University Hospital Brest, France; 17Clinical Hematology, University Hospital La Milétrie, Poitiers, France; 18Immunology Laboratory, University Hospital Nancy Brabois, Vandœuvre-lès-Nancy, France.

Correspondence to: Aurore Perrot, Service d’Hématologie et Médecine Interne, CHU de Brabois, Rue du Morvan, 54500 Vandœuvre-lès-Nancy. Phone: +3383153282 - Fax: +3383153558. E-mail: Aurore.Perrot@medecine.uhp-nancy.fr
ABSTRACT

The prognosis of AML is very poor in elderly patients, especially in those classically defined as having unfavorable cytogenetics. The recent monosomal karyotype (MK) entity defined as two or more autosomal monosomies or combination of one monosomy with structural abnormalities has been reported to be associated to a worse outcome than the traditional complex karyotype (CK). In this retrospective study of 186 AML patients over 60 years, the prognostic influence of MK was used to further stratify elderly patients with unfavorable cytogenetics. CK was observed in 129 patients (69%) and 110 exhibited abnormalities according to the definition of MK (59%). MK+ patients had a complete response (CR) rate significantly lower than MK- patients: 37% (41/110) versus 64% (49/76) (p = .0008), and their 2-year overall survival (OS) was also significantly decreased at 7% versus 22% (p < .0001). In multivariate analysis, MK appeared as the major independent prognostic factor related to CR achievement (OR: 2.3, CI: 1-5.4, p = .05) and OS (HR: 1.7, CI: 1.1-2.5, p = .008). In the subgroup of 129 CK+ patients, survival was dramatically decreased for MK+ patients: 8% versus 28% at 2 years (p = .03). These results demonstrate that MK is a major independent factor of very poor prognosis in elderly AML.
INTRODUCTION

Major advances in the treatment of adult patients with acute myeloid leukemia (AML) have been obtained with intensive postremission therapies including high-dose chemotherapy and/or allogeneic hematopoietic stem cell transplantation. However, AML occurs more frequently after the age of 60 years, and such options are not adapted for elderly patients because they frequently present a poor clinical condition or severe comorbidities. Treatment results remain unsatisfactory even in the cohort of older AML patients eligible for intensive chemotherapy for two main reasons: i) an increased incidence of adverse disease-related factors, such as an unfavorable karyotype, which may explain a low complete remission (CR) rate and a short response duration; and ii) suboptimal postremission treatment in comparison with younger adults because these patients cannot be offered repeated consolidation courses with high dose chemotherapy.

Cytogenetic features of the blasts at diagnosis have been identified as a major prognostic factor in AML in all age groups, leading to the AML cytogenetic classification. A complex karyotype (CK), described as the combination of multiple structural abnormalities was demonstrated as unfavorable, associated with a poor outcome. CK was first defined by the Medical Research Council AML Working Group (MRC) as the combination of at least five cytogenetic abnormalities but a Cancer and Leukemia Group B (CALGB) study showed subsequently a similar prognostic influence whether CK was defined by $\geq 3$, $\geq 4$ or $\geq 5$ abnormalities. Several studies have investigated the prognostic impact of cytogenetics in elderly AML patients. The MRC assessed the cytogenetic classification in a cohort of 1065 patients older than 55 years of age. Almost 20% of these patients had abnormalities classifying them in the unfavorable group and their outcome strongly correlated with cytogenetics. Subsequently, the Eastern Cooperative Oncology Group (ECOG), the CALGB and the German Austrian AML Study Group (AMLSG) also analyzed the impact of cytogenetics on the CR rate and survival in cohorts of patients older than 55 or 60 years of age and showed cytogenetics to be a strong and independent prognostic factor in multivariate analysis (together with age and/or leukocytosis).

In 2008, Breems et al. proposed the concept of monosomal karyotype (MK), defined by the presence of at least two autosomal monosomies or one monosomy plus one or more structural abnormalities. In 733 AML patients under 60 years old with cytogenetic abnormalities, MK was shown to be associated with a very poor prognosis and a more powerful prognostic predictor than CK. MK status was not investigated in elderly patients in this study. The recent large SWOG study included a subgroup of 457 elderly AML patients older than 60 years of age. In this subgroup, 90 patients had a MK that appeared to be associated with a shorter survival.
Since elderly AML are characterized by a higher prevalence of poor-risk cytogenetic abnormalities than adult AML,\textsuperscript{15} with less favorable abnormalities (CBF-type), more frequent monosomies and comparatively less abnormalities such as t(6;9), 3q abnormalities or 11q23/MLL abnormalities, an improvement in the prognostic stratification of cytogenetic subgroups might be of particular interest in order to optimize therapeutic decisions. The identification of a very poor risk cytogenetic subgroup should lead in elderly patients to consider an alternative therapeutic approach, either experimental or palliative, rather than standard intensive chemotherapy.

In order to further investigate the incidence, features and specific prognostic relevance of MK in this elderly population, we conducted on behalf of the Groupe Ouest Est des Leucémies Aiguës et Autres Maladies du Sang (GOELAMS) a retrospective study of 186 AML patients older than 60 years of age with classically defined unfavorable cytogenetics AML.
METHODS

Patients and treatment protocols
Eligibility for this study was limited to patients with previously untreated AML and unfavorable cytogenetics, enrolled between 1996 and 2006 (after obtaining written consent according to Helsinki declaration) in one of three successive prospective trials focused on AML in elderly patients (older than 60 years of age). Standard intensive chemotherapy with cytarabine and idarubicin was used in all three trials for induction. Postremission treatment comprised monthly or quarterly reinduction courses associated with maintenance chemotherapy. Treatment schedules of the 3 trials are presented in Figure 1. Of note, poor cytogenetics patients were well-balanced between the treatment arms.

- The SA4 GOELAMS study was designed to directly compare by randomization the potential effects of fludarabine given in association with Ara-C during induction and postremission treatment in patients aged 60 to 75 with de novo AML.16 Two-hundred and ninety four eligible patients were enrolled, including 63 with high-risk cytogenetics (24% of 260 patients with available data).

- The SA2002 randomized trial, aimed to assess whether the addition of androgens to postremission therapy, was associated with an improved outcome in elderly patients (≥ 60 years old) with de novo AML.17 This trial included 330 patients, aged between 60 and 86 years old. Eighty out of 308 with available cytogenetics presented with high-risk AML. Leukemia-free survival and OS were improved in the androgen arm.

- The R04 trial (43 patients) was a phase II study which assessed the combination of gemtuzumab ozogamycin with intensive induction chemotherapy and was restricted to patients aged 60 to 75 years with de novo or secondary AML and unfavorable karyotype.18 Together with the 43 patients enrolled in the R04 trial, this study included 186 patients, 143 being issued from the 568 AML patients with available cytogenetic data treated in the SA4 and SA2002 trials (25.2%).

The trial hypotheses tested did change neither the CR rate nor the 2-year OS except for the favorable impact of androgen maintenance on the 5-year leukemia-free survival and OS in the SA2002 trial.17 This allowed us to compile data from different trials together in one cohort. This cohort was approved by the institutional review boards of all participating institutions.

Cytogenetic analyses
At diagnosis, bone marrow samples were provided to local cytogenetics laboratories of the various centers for karyotypic analyses. Standard banding techniques were used on the mitoses obtained. All cytogenetic data were centrally reviewed by the GOELAMS Cytogenetics Committee and annotated.
according to the International System for Human Cytogenetic Nomenclature. An abnormality was considered clonal when at least two metaphases had the same aberration in case of a structural abnormality or an extra chromosome. Monosomy had to be present in at least three metaphases to be considered significant. A minimum of 20 normal metaphases was required to define a normal karyotype. The presence of t(8;21) or inv(16)/t(16;16) defined the favorable group. Cytogenetic abnormalities defining the unfavorable group were -5/del(5q), -7/del(7q), 3q26/EVI1, t(6;9), t(9;22), 11q23/MLL [except t(9;11)] and complex rearrangements with 3 clonal abnormalities or more. The intermediate group included normal karyotype and other abnormalities. Karyotypes were further analyzed to delineate three categories respectively with no monosomy, one monosomy (associated or not with other structural abnormalities) and two or more monosomies. The MK status was assessed retrospectively according to Breems' definition: presence of at least two autosomal monosomies or one monosomy plus one structural abnormality.

Evaluation of treatment
The efficacy of induction therapy was evaluated after one course: CR was defined according to Cheson’s revised recommendations as a normocellular bone marrow containing less than 5% blasts associated with a neutrophils count over 1x10^9/L and a platelets count over 100x10^9/L in peripheral blood. Response assessment did not rely on cytogenetics. Persistent leukaemia was defined as a partial response or no response and mortality at induction by early death during the first seven days of treatment or subsequent chemoinduced hypoplasia.

Statistical analyses
Overall survival (OS) was the main objective of the study. Secondary objectives were to evaluate CR and leukaemia persistence rates. The Fisher exact test was used for comparison of binary variables between cytogenetic groups. OS was calculated from the time of inclusion until the date of death or last contact and alive patients were censored at the time of last contact. Survival curves for OS were estimated by the Kaplan-Meier method and comparisons were made by the log-rank test. In multivariate analyses, outcome comparisons were adjusted with the Cox model and tested by the likelihood-ratio test. P-values lower than .05 were considered of statistical significance. Hazard ratios were given with 95% confidence intervals (CI). All calculations were performed using MedCalc® software (Mariakerke, Belgium).
RESULTS

Patients’ characteristics, overall outcome and cytogenetic abnormalities

The median age in this high-risk cohort of 186 patients was 68 years-old (range: 60-79) and the M/F ratio was 1.04. A vast majority of patients (176/186) presented de novo AML. Ten out of 43 patients (23%) enrolled in R04 trial had secondary AML. Of these 186 patients assessable for post-induction response and survival, 90 (48%) achieved CR. There were 31 deaths (17%) during induction course and 65 patients (35%) showed persistent leukemia. After a median follow-up of 43 months for survivors, the OS was 13.7% at 2 years [CI: 12.4-14.9]. The CR rate was not significantly different between patients aged 60 to 69 and patients older than 69: 46% and 51%, respectively (p=.6). There also was no significant difference in 2 year-OS between these two age categories (p=.87). There was no influence of the treatment protocol for either CR (p=.17) or 2-year OS rate (p=.24).

Distribution of the different unfavorable cytogenetic abnormalities among the 186 patients and their relationship to outcome are summarized in Table 1. Poor cytogenetic features included monosomy 5 or del(5q) in 85 patients (46%) and monosomy 7 or del(7q) in 76 (41%). Only 9 patients (4.8%) had 11q23/MLL abnormalities, 15 (8%) 3q21q26 abnormalities and 3 patients presented a t(6;9) translocation. A CK as defined by 3 or more clonal abnormalities was noted in 129 patients (69%). CR rates ranged from 41% in patients with del(5q) to 53% in patients with 3q abnormalities and 2-year OS between 6% in patients with monosomy 5 and 16% in patients with del(7q). Patients with CK had lower rates of CR and 2-year OS at 39% and 12%, compared to patients without CK (CR rate at 68% and 2y-OS at 17%, p<.002 and p<.005, respectively).

Incidence and prognostic influence of autosomal monosomies

At least one autosomal monosomy was observed in 119 patients (64%) (Table 2). The most frequent monosomies were -7 (n=46) and -5 (n=30) followed by -17, -16 and -18. These patients had a CR rate of 39% and a 2-year OS of 8%.

The outcome was more favorable in patients showing a single monosomy without other structural chromosomal abnormality (n=9) with a 77% CR rate and 2-year OS of 18%. Conversely, patients with either one monosomy associated with at least one structural abnormality or with 2 or more monosomies had a lower CR rate (from 37 to 40%) and a reduced 2-year OS (7%). These differences in outcome are statistically significant (p<.004 and p<.003 respectively). Survival data are shown in Figure 2. Of note, the 2-year OS of patients with a single monosomy without structural chromosomal
abnormality was similar to that of patients without autosomal monosomy (18% and 22%, respectively, p=.79).

Patients’ characteristics and outcome according to the MK status

Out of the 186 patients with unfavorable cytogenetics in this cohort, 110 (59%) had abnormalities in agreement with MK criteria as defined by Breems et al.13 Patients’ characteristics of both MK-negative (MK-) and MK-positive (MK+) groups are summarized in Table 3. The proportion of MK+ patients was similar in the different trials (p=.3). The median age of MK- and MK+ patients was similar at 68 years (p=.2). Only 5 of 10 patients with secondary AML presented a MK. The incidence of hyperleukocytosis over 30x10^9/L was similar in MK- and MK+ groups at 17 and 14%, respectively (p=.7).

MK+ patients had a significantly lower CR rate at 37% (41/110) than MK- patients (64% (49/76), p=.0008). The 2-year OS was also significantly impaired in MK+ patients at 7% versus 22% (p<.0001) (Figure 3). For comparison, results observed in other cytogenetic subgroups when considering the 538 pts of the SA4 and SA 2002 trials were as follows: CR rates 83%, 74%, 60% and 2-year OS 70%, 45% and 40% in patients with favorable (n=23), normal (n=280) and intermediate karyotype (n=92), respectively.

MK+ patients had a quite similar CR rate at 37% and 2-year OS rate at 7% whether they were aged between 60 and 69 or 70 and 79 years old (p=.45). The outcome of MK- patients was not significantly different in these two age categories in terms of CR rate or 2-year OS (58% versus 73% for CR, 21% versus 26% for OS, respectively, p=.09 and p=.46).

All patients with monosomy 5 belonged to the MK+ group, had a 43% CR rate and an average 2-year OS of 6%. The CR rate was lower in MK+ patients with del(5q) (30% versus 59%) and 2-year OS was abysmal (0% versus 18%).

Prognostic influence of MK in comparison with CK

CK was confirmed to confer a negative prognostic impact. The CR rate was significantly lower in CK+ patients, at 39% (51/129) compared to 68% (39/57) in CK- patients (p=.002). The 2-year OS also was significantly decreased in patients with CK, at 12% versus 17% in patients with poor-risk CK- AML (p<.005) (Figure 4). CK defined by 5 or more abnormalities (CK5) was also a predictive factor for very poor prognosis in this cohort. The 2-year OS was dramatically impaired in patients with CK5 at 6% versus 22% for other poor-risk AML patients (p<.0002). The more recently described21 threshold of CK4 (n=111) showed intermediate results with a CR rate of 39% and OS of
11% significantly different compared to CK4- patients who displayed a CR rate of 63% and 19% OS at two years (p=.003).

The majority of the 110 patients with MK also had a CK. CK+ patients experienced a very poor outcome when they also belonged to the MK+ group: CR rate, 38% versus 44% (p=.41) and 2-year OS, 8% versus 28%, respectively (p=.03). There were discrepancies between MK and CK presentations in 39 patients. Ten patients had MK without CK (MK+CK- group) and experienced the same very poor prognosis as other patients with MK (2-year OS, 0% and 8%, p=.59). Conversely, 29 patients had CK without MK (MK-CK+ group) and had a similar outcome as all other patients without MK (2-year OS, 28% and 22%, p=.8).

With regard to the definition of CK5, 28 patients belonged to the MK+CK5- group and 9 patients were MK-CK5+. Although there was a trend for a better outcome for these patients not cumulating both risk factors, this was not statistically significant, probably owing to the small size of the subgroups.

In multivariate analysis using a Cox model including MK and CK variables only (since age, leukocytosis and treatment arm had no significant influence in univariate analysis), MK appeared as the major independent prognostic factor for CR (OR 2.3, CI: 1-5.4, p=.05) and for OS (HR 1.70, CI: 1.1-2.5, p=.008), as summarized in Table 4. In comparison to CK, MK appeared to be a more robust predictor of CR and OS.
DISCUSSION

The negative prognostic impact of autosomal monosomies on AML outcome, especially of MK was first demonstrated by Breems et al. in a large cohort of adult patients less than 60 years of age. This description has been recently confirmed by the SWOG in a study including patients between 16 and 88 years of age.

The study we present here analyzed the prognostic influence of MK in a cohort comprising exclusively elderly patients (older than 60 years of age) with unfavorable cytogenetics AML. In order to test a large and homogeneous cohort of patients, we restricted our analysis to patients with an unfavorable karyotype. The cohort could therefore also include the 43 patients enrolled in the RO4 trial which had been designed for high-risk patients only. On the other hand, MK is a very rare event outside the context of unfavorable AML in the elderly: only one patient out of 568 with available cytogenetic data enrolled in SA4 and SA2002 trials showed a MK without any associated criterion for unfavorable karyotype. Our results suggest that the definition of MK is well adapted in elderly AML too, because elderly patients with no monosomy or one single monosomy without other structural abnormality experienced a better outcome than those with MK. This result is consistent with the observations from Breems et al. in adult AML patients. Moreover, the high incidence of cytogenetic abnormalities and particularly monosomies must be underlined in elderly AML. The incidence of MK is indeed higher in this population than in younger adult AML patients: 16% of the 568 elderly patients included in SA4 and SA2002 trials showed a MK without any associated criterion for unfavorable karyotype. The SWOG also showed that the proportion of MK+ patients increased with age: 4% in patients younger than 30 years old, 12% in patients between 30 and 60 years of age and 20% in patients older than age 60.

The influence of MK on treatment outcome was at least as important in our elderly cohort as in younger adult patients: here, we demonstrated that MK was associated with a significantly lower CR rate, at 37% versus 64%, and a significantly impaired 2-year OS, at 7% versus 22%. By comparison, the 4-year OS was significantly decreased at 4% versus 21% in the MK+ group of Breems’ adult cohort and at 3% versus 13% in the SWOG study. Although these three studies were performed at different times and with different schedules, these figures are amazingly similar, underscoring the relevance of the prognostic value of MK. Our results might even suggest that MK definition is more adapted to elderly than adult AML patients, because the prognostic influence of MK overcomes in our elderly cohort the impact of other classical prognostic factors, such as age, leukocytosis and classical poor-risk cytogenetic abnormalities including CK. The MK status had a similar prognostic influence in our cohort of elderly patients without difference between the two age groups (60-70 years and >70 years old). To note, MK+ was associated with a statistically significant decrease of OS.
in patients with del(5q): 2-year OS impaired at 0% in MK+ patients, versus 18% in MK- (p=.0002). Our results were different to those of the whole cohort of the SWOG study, in which MK was not associated with an impaired OS in the subgroup with del(5q).

The most important observation of our study is that MK retains a prognostic impact within the subgroup of CK patients, since 2-year OS was impaired to 8% in CK+MK+ patients, as compared to 28% in CK+MK- patients (p=.03). This observation in elderly patients is concordant with Breems’ results in adult patients\textsuperscript{13} and with the results of the whole cohort of the SWOG.\textsuperscript{14} However, while CK remained an independent prognostic factor for OS in the latter (HR 1.5 [1.1-1.9]), MK is the only independent factor influencing CR rate and OS in our study (OR 2.3 [1.0-5.4] and HR 1.7 [1.1-2.5]).

In our study, CK and CK5 had a different prognostic impact, CK5 being a better indicator of patients with very poor outcome (12% OS at 2 years for CK+ patients and 6% for CK5+ patients). Regarding CK and CK5, Breems \textit{et al.}\textsuperscript{13} reported 4-year OS at 26% and 25% in CK+MK- and CK5+MK- patients respectively, and 3% in both CK+MK+ and CK5+MK+ groups. We consider that MK is not only better than CK for stratifying elderly unfavorable AML patients, but also better than CK5 since it applied to a higher number of patients in our cohort (110 versus 91 patients with MK and CK5, respectively).

Although caution should be exerted with such small series, it is interesting to note that considering the 10 patients with MK but without CK (MK+CK-), five of them had a 3q21q26 abnormality associated with a monosomy 7. These patients showed a particularly poor prognosis, perhaps related to high EVI1 expression.\textsuperscript{22} The 5 other patients had a monosomy 7 associated with translocations such as t(2;3), t(9;22) or with deletions del(5q), del(6q).

A few other groups have investigated the prognostic impact of MK status in several clinical conditions. An American study by Oran \textit{et al.}, concerned 212 patients aged 18 to 68 years treated by allogeneic hematopoietic stem cell transplantation for AML, including 23 patients with MK.\textsuperscript{23} In multivariate analysis, MK was the only factor associated with shorter relapse-free survival in patients in first CR.\textsuperscript{23} In three other studies including 68, 18, and 16 MK+ patients respectively, the worse prognostic effect of MK was confirmed in patients under 60 years.\textsuperscript{24-26}

Our results showed that none of the hypotheses tested in the clinical trials had modified the outcome and the poor prognosis of MK+ patients. None of the strategies has currently proved any efficacy on these MK+ unfavorable-risk AML, especially in elderly patients. The EBMT Group conducted a study in a cohort of 278 patients with AML or myelodysplastic syndromes with chromosome 7 abnormalities, showing that the 63 MK+ patients did not benefit from allo-SCT, unlike MK- patients with chromosome 7 abnormalities.\textsuperscript{27}
Up to now, there are no data supporting therapeutic recommendations for patients with MK+ AML. Considering the extremely poor prognosis of MK in older patients with a 7% 2-year OS as reported here, our opinion is to consider for these patients alternative treatment strategies. Rather than standard intensive treatment with a classical induction course, these patients should be offered, whenever possible, access to investigational drugs in the setting of prospective trials or less intensive, palliative chemotherapy combined with supportive care. AlloSCT might also be considered as an option for patients with the best ECOG performance status.

In conclusion, this study of a cohort of elderly patients with cytogenetically unfavorable AML shows that MK, according to the criteria proposed by Breems et al.,\textsuperscript{13} is also, as expected, an independent factor of very poor prognosis in older age. MK is more frequent in elderly patients and stands out as the major independent prognostic factor, distinguishing prognostic subgroups better than CK. It appears to be the most pertinent factor to stratify unfavorable cytogenetics in elderly AML patients and guide therapeutic decisions especially in future prospective trials.
Acknowledgements
The authors are grateful to all GOELAMS’ investigators for including patients and to Roselyne Delepine and all clinical research assistants of the GOELAMS for insuring the validity of clinical data.

Authorship

Contributions: AP performed the study, analyzed data and wrote the manuscript; FW conceived and designed the study, wrote and reviewed the manuscript; IL reviewed cytogenetic data and reviewed the manuscript; MCB wrote and reviewed the manuscript; PG reviewed statistical data; AP, FM, JD, JDH, CB, JYC, CH, CR, NV, BL, MOU, NF, CB and ER included patients, reviewed data and contributed to the manuscript; NI gave final approval of manuscript.

Conflict-of-interest Disclosure: The authors declare no competing financial interests.
References


Table 1: Distribution of unfavorable cytogenetic abnormalities among the 186 patients, CR rate and outcome.

<table>
<thead>
<tr>
<th>Cytogenetic abnormalities</th>
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<th>2-year OS [95% CI]</th>
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<td>3q abnormalities</td>
<td>15</td>
<td>53% [25-81]</td>
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<td>del(5q)</td>
<td>55</td>
<td>41% [28-54]</td>
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<td>48% [33-63]</td>
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<td>11q23/MLL except t(9;11)</td>
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<td>CK (≥ 3 abnormalities)</td>
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<td>CK5 (≥ 5 abnormalities)</td>
<td>91</td>
<td>38% [28-48]</td>
<td>6% [3.5-8.5]</td>
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Table 2: Incidence of autosomal monosomies and prognostic effect of combination with other chromosomal structural abnormalities (all monosomies -isolated or associated- are taken into account, explaining that the total number of monosomies exceeds the total number of patients) (CI: confidence interval).

<table>
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<tr>
<th>Type of monosomy</th>
<th>Number of patients with autosomal chromosomal monosomy</th>
<th>Number of patients with one monosomy without other structural abnormality</th>
<th>Number of patients with one monosomy and at least one structural abnormality</th>
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<td>0</td>
<td>1</td>
<td>9</td>
</tr>
</tbody>
</table>

Total number of patients (%): 119 (64%) 9 (5%) 26 (14%) 84 (45%)

CR rate [95% CI]: 39% [32-46] 77% [56-98] 40% [26-54] 37% [27-47]

2-year OS rate [95% CI]: 8% [5.5-10.5] 18% [13.5-22.5] 7% [3-11] 7% [4-10]
Table 3: Relationship between MK status and other prognostic factors (WBC: white blood count).

<table>
<thead>
<tr>
<th></th>
<th>Absence of MK (MK- group)</th>
<th>Presence of MK (MK+ group)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patients</td>
<td>CR rate [95% CI]</td>
</tr>
<tr>
<td>Total cohort</td>
<td>76</td>
<td>64% [53-75]</td>
</tr>
<tr>
<td>Age groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-79</td>
<td>30</td>
<td>73% [56-90]</td>
</tr>
<tr>
<td>Type of leukaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary AML</td>
<td>5</td>
<td>/</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex karyotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 3 abnormalities</td>
<td>29</td>
<td>44% [24-64]</td>
</tr>
<tr>
<td>Other unfavorable abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-5</td>
<td>0</td>
<td>/</td>
</tr>
<tr>
<td>del(5q)</td>
<td>22</td>
<td>59% [36-82]</td>
</tr>
<tr>
<td>-7</td>
<td>6</td>
<td>83% [43-100]</td>
</tr>
<tr>
<td>del(7q)</td>
<td>14</td>
<td>57% [27-87]</td>
</tr>
<tr>
<td>3q21q26</td>
<td>7</td>
<td>71% [23-100]</td>
</tr>
<tr>
<td>11q23/MLL</td>
<td>4</td>
<td>/</td>
</tr>
<tr>
<td>t(6;9)</td>
<td>3</td>
<td>/</td>
</tr>
</tbody>
</table>
Table 4: Multivariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>Confidence Interval [95% CI]</th>
<th>Significativity (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete response rate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex karyotype</td>
<td>1.9</td>
<td>[0.8 - 5]</td>
<td>.14</td>
</tr>
<tr>
<td>Monosomal karyotype</td>
<td>2.3</td>
<td>[1 - 5.4]</td>
<td>.05</td>
</tr>
<tr>
<td><strong>Overall survival</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex karyotype</td>
<td>1.1</td>
<td>[0.7 - 1.7]</td>
<td>.65</td>
</tr>
<tr>
<td>Monosomal karyotype</td>
<td>1.7</td>
<td>[1.1 - 2.5]</td>
<td>.008</td>
</tr>
</tbody>
</table>
Figures legends

Figure 1: Treatment schedules of the three trials SA4, SA2002 and R04.

Figure 2: Overall survival of patients with unfavorable cytogenetics AML in relation to the number and type of autosomal chromosomal monosomies.

Figure 3: Overall survival of patients with unfavorable cytogenetics AML according to MK status.

Figure 4: Overall survival of patients with unfavorable cytogenetics AML according to CK status discriminated upon 3 or more abnormalities.
Figure 1

**Phase 3 SA4 trial**

- N = 294

**Phase 3 SA2002 trial**

- N = 330

**Phase 2 RO4 trial**

- N = 43

Number of patients with unfavorable cytogenetics

- Fludarabine arm: n = 30
- Control arm: n = 33

- Androgen arm: n = 41
- Control arm: n = 39

- Gemtuzumab ozogamicin group: n = 43

**INDUCTION**

- **Idarubicin 8 mg/m² d1-d5** / **Ara-C 100 mg/m² d1-d7**

  - +/- Fludarabine
    - 20 mg/m² d2-d7

  - + Lomustine
    - 200 mg/m² d1

  - + Gemtuzumab ozogamicin
    - 6 mg/m² d3

**Response assessment: CR or PR**

**CONSOLIDATION**

- Intermediate dose ara-C and carmustine
  - +/- Fludarabine

  - No consolidation

**MAINTENANCE**

During one year:

- 6-thioguanine
- ara-C

- 2 months every 15 months:
  - - d1-d15: 6-thioguanine
  - - d15-d30: methotrexate

  - +/- norethandrolone

**REINDUCTION COURSES every 3 months**

3 induction courses:

- Lomustine
- ara-C
- mitoxantrone
  - +/- Fludarabine

6 induction courses:

- **Idarubicin - ara-C**

  - +/- norethandrolone
Figure 2

- No autosomal monosomy (n=67)
- 1 monosomy without structural abnormality (n=9)
- 1 monosomy with structural abnormality (n=26)
- 2 or more autosomal monosomies (n=84)

P < .003
Figure 3:
Figure 4:
Dismal prognostic value of monosomal karyotype in elderly patients with acute myeloid leukemia: a GOELAMS study of 186 patients with unfavorable cytogenetic abnormalities

Aurore Perrot, Isabelle Luquet, Arnaud Pigneux, Francine Mugneret, Jacques Delaunay, Jean-Luc Harousseau, Carole Barin, Jean-Yves Cahn, Philippe Guardiola, Chantal Himberlin, Christian Recher, Norbert Vey, Bruno Lioure, Mario Ojeda-Uribe, Nathalie Fegueux, Christian Berthou, Edouard Randriamalala, Marie C Béné, Norbert Ifrah and Francis Witz

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