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Influence of residual normal metaphases in acute myeloid leukemia patients with monosomal karyotype

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Key words: monosomal karyotype, acute myeloid leukemia, normal metaphases, overall survival, cytogenetics.
Cytogenetics is one of the most important prognostic factors in AML(1-4). Breems *et al* have distinguished a monosomal karyotype (MK) as associated with particularly poor survival (5). MK is defined by the presence of a clone containing two or more autosomal monosomies or a single autosomal monosomy with other structural abnormalities. MK patients had a 4-yr survival probability of 4%, contrasted with a 21% 4-yr survival probability in patients with other poor-risk cytogenetics but without MK. Although there was extensive overlap between MK and complex karyotypes (either 3 or 5 separate abnormalities) the prognostic effect of the latter was essentially due to its association with the former; specifically MK without a complex karyotype fared worse than a complex karyotype without MK. Medeiros *et al* for The Southwest Oncology Group (SWOG) confirmed this observation and extended it to patients age 60 or above (6).

Previous observations have suggested variability in outcome even within distinct cytogenetic groups. For example, M.D. Anderson Cancer Center data indicated that those patients with monosomy 7 but with some residual normal metaphases had better outcomes than patients with monosomy 7 but without normal metaphases (7). Here we investigated the impact of normal metaphases on MK patients treated in SWOG clinical trials.

We used the data of Medeiros *et al* (7), which included 1,344 patients enrolled between 1986 and 2009 in one of ten successive SWOG clinical trials (S8600, S9031, S9034, S9126, S9333, S9500, S9617, S9918, S0106, and S0112) for untreated AML. Induction therapies were grouped into those: (1) with “standard” doses of Ara-C (100 mg/m² daily X 7 days), (2) with higher than “standard” doses of Ara-C (typically at least 1 g/m² per dose), (3) without Ara-C. Cytogenetic results were reviewed centrally. Abnormalities were considered clonal if at least two metaphases had the same aberration in the case of a structural abnormality or an extra chromosome, or if at least 3 shared the same abnormality in the case of a monosomy. Criteria for MK were those of Breems *et al* (5). The total number of normal and abnormal (MK and other) cells was tallied. Per SWOG cytogenetics guidelines, a minimum of 20 metaphase cells were analyzed for each sample. An abnormal study with less than 20 cells was accepted only if the quality of the metaphases was such that interpretation is unequivocal. The SWOG laboratory approval process and the central review process require that at least two different cultures, for example unstimulated and mitogen-stimulated, are set up for each sample and that only AML-appropriate mitogens are used. Results based solely on the stimulated culture are rejected. Survival was calculated from the date from registration to the study until death from any cause and was censored at the date of last follow-up for patients last known to be alive. Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. Association of survival with treatment (grouped as above), age, gender, and number of normal or abnormal cells was examined using univariate and multivariate proportional hazards regression models.

As in Medeiros *et al* (7), 176 of the 1,344 patients (13%) were classified as MK. The 176 MK patients had a median age of 61 years; 94% had a complex karyotype (≥ 3 distinct clonal...
abnormalities); 68% received induction with standard dose of ara-C, 14% with higher Ara-C doses, and 18% without Ara-C. The median survival of the 176 patients was 4 months (95% confidence interval 3-5 months).

Among the 176 patients with MK we first considered the number of normal cells and, then separately, the number of abnormal cells. A univariate proportional hazards model indicated that survival improved as the number of normal cells increased (hazard ratio 0.95, 95% CI 0.9 - 0.99, p = 0.02). The presence of 5 or more normal cells was associated with an HR of 0.76. The number of normal cells remained prognostic after accounting for age, gender, and treatment. In the multivariate model, older age was the only other factor associated with shorter survival. In contrast, the number of abnormal cells was not associated with survival in either univariate or multivariate analyses.

To jointly examine the number of normal cells and the number of abnormal cells we calculated the percentage of normal cells (which equals 1- percentage of abnormal cells). A higher percent of normal cells was associated with longer survival (hazard ratio 0.99, 95% CI 0.98-1.0, p = 0.02) in both a univariate model and a multivariate model controlling for therapy, age, gender, WBC count, and blood blast percentage (Table 1).

How residual normal metaphases translate into longer survival is unclear. Despite the statistically significant findings the survival of even those MK patients with residual normal cells is very poor (Figure 1). While the medical significance of our findings in MK patients is thus limited, our observations suggest that it might be worthwhile to examine the prognostic effect of residual normal metaphases in patients with better prognosis karyotypes. More generally our results provide further evidence for the heterogeneity of even well defined cytogenetic groups.
References


Table 1. Multivariate model for percent of normal cells.

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Multivariate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>% cells with normal metaphases</td>
<td>0.99</td>
<td>0.03</td>
</tr>
<tr>
<td>Age (numerical)</td>
<td>1.03</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Gender (ref=female)</td>
<td>0.96</td>
<td>0.80</td>
</tr>
<tr>
<td>Standard Ara-C (ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-standard Ara-C</td>
<td>0.90</td>
<td>0.88</td>
</tr>
<tr>
<td>No Ara-C</td>
<td>0.79</td>
<td>0.31</td>
</tr>
<tr>
<td>WBC (numerical)</td>
<td>1.01</td>
<td>0.03</td>
</tr>
<tr>
<td>Peripheral blood blast percentage</td>
<td>0.99</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Figure 1. Overall survival curves estimated by the method of Kaplan-Meier with or without at least one normal metaphase.