Lesions learned from therapy-related acute myeloid leukemia

by Sabine Kayser

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Lesions learned from therapy-related acute myeloid leukemia

Sabine Kayser

NCT Trial Center, National Center of Tumor Diseases, German Cancer Research Center (DKFZ), Heidelberg, Germany

Correspondence:
Sabine Kayser, MD
NCT Trial Center, National Center of Tumor Diseases, German Cancer Research Center (DKFZ), Heidelberg, Germany
Phone: +49 6221/ 566228, Fax: +49 6221/565863
E-mail: s.kayser@dkfz-heidelberg.de

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In this issue of *Haematologica*, Nilsson and colleagues present the results of a large retrospective analysis on real-world data regarding the incidence and prognostic implications of therapy-related acute myeloid leukemia (t-AML, n=686) based on three Swedish nationwide population-based registries. This methodology allows an unbiased view on prognostic implications and reliable observations of time trends in incidence. At the same time, this is one of the largest data sets investigating the clinical behavior of t-AML in comparison to de novo AML.

The authors report that during the study period, ranging from 1997-2015, the incidence of t-AML almost doubled with a yearly increase in t-AML of 4.5% (CI, 2.8% - 6.2%), most frequently due to t-AML after breast and prostate cancer. This is in part due to improvement of cancer treatments with decreased mortality during the same period, leading to better long-term survival after mutagenic cancer treatments. This also points to the fact of the increasing likelihood to encounter these patients in the clinical practice. Thus, a better knowledge of, as well as better treatment approaches for these patients is needed.

Secondly, the authors described the role of t-AML for the prognosis within AML risk groups. Genetically, t-AML was underrepresented in patients with favorable risk, and overrepresented in patients with intermediate or adverse risk. Despite a good performance status (ECOG ≤ 2) patients with t-AML were less likely to receive intensive induction treatment (60% vs. 71%, p < 0.001) and intensively treated patients were less likely to achieve complete remission (58% vs. 75%, p < 0.001) as compared to de novo AML. The reason for the worse outcome in intermediate and poor risk t-AML compared to the de novo counterparts, also when adjusting for other factors such as cytogenetics, age and performance status, is likely multifactorial. A higher frequency of unfavorable mutations and/or an enrichment of mutations originating from clonal hematopoiesis in patients with t-AML may contribute.
Allogeneic hematopoietic cell transplantation (allo-HCT), regardless of disease state, was performed in 9% of the patients with t-AML as compared to 16% in de novo AML (p < 0.001). Corresponding rates of allo-HCT in first remission were 7% in t-AML as compared to 12% in de novo AML (p = 0.002), with no increase or decrease of transplantation rates over time. In multivariable analysis, t-AML was associated with poorer outcome in cytogenetically intermediate and adverse risk but had no significant impact on outcome in favorable risk AML, including core binding leukemias, APL and AML with mutated NPM1 without FLT3-ITD. This suggests that t-AML patients with favorable risk AML should be approached by the same treatment strategy as de novo favorable risk patients and intensive chemotherapy including allo-HCT, if appropriate, should not be withheld for these patients. Biologically, this raises the question, whether t-AML with favorable risk (i.e. APL, NPM1 without FLT3-ITD and core-binding factor leukemias) are really therapy-related or more likely de novo AML. Comparative next generation sequencing analysis may further shed light on this issue.

On the contrary, intermediate and adverse risk patients with t-AML have even poorer survival compared to their de novo counterpart. After allo-HCT, patients suffer from high transplant-related mortality (Table 1), possibly reflecting cumulative toxicity of cancer treatment. However, the data might be interpreted with caution since relapses might be underreported, and thus the transplant-related mortality might be over-estimated. Nevertheless, novel treatment approaches for these patients are highly warranted. In addition, since intensifying the conditioning regimen was identified as a risk factor for worse outcome the most appropriate conditioning regimen remains to be established.

More recently, new therapeutic options, targeting FLT3, IDH1/2 and BCL2 have become available and may have the potential to improve outcome in certain subtypes of t-AML.
References


<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Median age (years, range)</th>
<th>Study period</th>
<th>Myeloablative conditioning</th>
<th>TRM</th>
<th>CIR</th>
<th>OS</th>
<th>Reference</th>
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<tbody>
<tr>
<td><strong>Allo-HCT</strong></td>
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<td>868 (545 t-AML, 323 t-MDS)</td>
<td>40 (4-72)</td>
<td>1990-2004</td>
<td>77%</td>
<td>41% at 1 year 48% at 5 years</td>
<td>27% at 1 year 31% at 5 years</td>
<td>37% at 1 year 22% at 5 years</td>
<td>Litzow M.R., et al. Blood. 2010; 115 (9):1850-1857</td>
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<td><strong>Intensively treated patients</strong></td>
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<td>2853 (200 t-AML, 2653 de novo AML)</td>
<td>54.5 (16.2-85)</td>
<td>1993-2008</td>
<td>Data not given</td>
<td>At 4 years: in patients ≤ 60 years: t-AML: 22.9% de novo AML: 8.6% in patients &gt; 60 years: t-AML: 6%* de novo AML: 10%*</td>
<td>At 4 years: in patients ≤ 60 years: t-AML: 45.1% de novo AML: 46.3% in patients &gt; 60 years: t-AML: 85%* de novo AML: 75%*</td>
<td>At 4 years after allo-HCT in 1st CR: t-AML: 42.6% de novo AML: 58%</td>
<td>Kayser S., et al. Blood. 2011; 117 (7):2137-2145</td>
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</table>

**Abbreviations:** CIR: cumulative incidence of relapse; DFS: disease-free survival; OS: overall survival; RFS: relapse-free survival; t-AML: therapy-related acute myeloid leukemia; t-MDS: therapy-related myelodysplastic syndrome; TRM: transplant-related mortality.

*Estimated from cumulative incidence curves; **Personal communication