Lessons learned from therapy-related acute myeloid leukemia

Sabine Kayser

NCT Trial Center, National Center of Tumor Diseases, German Cancer Research Center (DKFZ), Heidelberg and Institute of Transfusion Medicine and Immunology, Medical Faculty Mannheim, Heidelberg University, German Red Cross Blood Service Baden-Württemberg-Hessen, Mannheim, Germany

Correspondence: S. Kayser
s.kayser@dkfz-heidelberg.de

Received: August 10, 2022.
Accepted: August 19, 2022.
Early view: August 25, 2022.

https://doi.org/10.3324/haematol.2022.281742

In this issue of *Haematologica*, Nilsson and colleagues present the results of a large retrospective analysis of 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.[1] 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 datasets 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

Table 1. Outcomes of patients with therapy-related acute myeloid leukemia.

N of patients	Age in years, median (range)	Study period	MAC	TRM	CIR	OS	Reference
Allogeneic hematopoietic cell transplantation							
868 (545 t-AML, 323 t-MDS)	40 (4-72)	1990-2004	77%	41% at 1 year 48% at 5 years	27% at 1 year 31% at 5 years	37% at 1 year 22% at 5 years	Litzow MR, *et al.* Blood. 2010;115(9): 1850-1857
70 (39 t-AML, 31 t-MDS)	37 (16-55)	1980-1998	64%	49% at 2 years	CIR not given 2-year relapse risk: 42%	30% at 2 years	Yakoub-Agha I, *et al.* J Clin Oncol. 2000;18(5): 963-971
Intensively treated patients							
2853 (200 t-AML, 2653 *de novo* AML)	54.5 (16.2-85)	1993-2008	Data not given	at 4 years: in patients ≤ 60 years: t-AML: 22.9% *de novo* AML: 8.6% in patients > 60 years: t-AML: 6%* *de novo* AML: 10%*	at 4 years: in patients ≤ 60 years: t-AML: 45.1% *de novo* AML: 46.3% in patients > 60 years: t-AML: 85%* *de novo* AML: 75%*	at 4 years after allo-HCT in 1st CR: t-AML: 42.6% *de novo* AML: 58%	Kayser S, *et al.* Blood. 2011;117(7): 2137-2145
6779 (including 686 with t-AML)	70 (18-100)	1997-2015	47%**	at 3 years: in patients ≤ 60 years: t-AML: 49%** *de novo* AML: 28%** in patients > 60 years: t-AML: 59%** *de novo* AML: 46%**	at 3 years: in patients ≤ 60 years: t-AML: 21%** *de novo* AML: 22%** in patients > 60 years: t-AML: 28%** *de novo* AML: 32%**	at 5 years: t-AML: 48% *de novo* AML: 57%	Nilsson C, *et al.* Haematologica. 2023;108(4): 1015-1025

*Estimated from cumulative incidence curves; **personal communication. allo-HCT: allogeneic hematopoietic cell transplantation; CIR: cumulative incidence of relapse; CR: complete remission; MAC: myeloablative conditioning; OS: overall survival; t-AML; therapy-related acute myeloid leukemia; t-MDS: therapy-related myelodysplastic syndrome; TRM: treatment-related mortality.

with a yearly increase in t-AML of 4.5% (95% confidence interval: 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.[2,3] It also points to the increasing likelihood of encountering these patients in 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 regarding prognosis within AML risk groups.[4] Genetically, t-AML was underrepresented in patients with favorable risk, and overrepresented in patients with intermediate or adverse risk.[5] Despite a good performance status (Eastern Cooperative Oncology Group score ≤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 those with *de novo* AML. The reason for the worse outcome of patients with intermediate- and poor-risk t-AML compared to their *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.[6,7]

Allogeneic hematopoietic cell transplantation (HCT), regardless of disease state, was performed in 9% of the patients with t-AML as compared to 16% in those with *de novo* AML (*P*<0.001). Corresponding rates of allogeneic HCT in first remission were 7% in t-AML and 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 AML, but had no significant impact on outcome in favorable-risk AML, including core binding leukemias, acute promyelocytic leukemia and AML with mutated *NPM1* without *FLT3*-ITD. This suggests that t-AML patients with favorable-risk AML should be approached using the same treatment strategy as *de novo* favorable-risk patients and intensive chemotherapy including allogeneic HCT, if appropriate, should not be withheld from these patients. Biologically, this raises the question of whether t-AML with favorable risk (i.e., acute promyelocytic leukemia, *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 shed light on this issue.

Intermediate- and adverse-risk patients with t-AML have even poorer survival compared to their *de novo* counterparts. After allogeneic HCT, these patients suffer from high transplant-related mortality (Table 1), possibly reflecting cumulative toxicity of cancer treatment.[5] However, the data should be interpreted with caution since relapses might be underreported, and thus the transplant-related mortality might be overestimated. Nevertheless, novel treatment approaches for these patients are highly warranted.[8] 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.[9]

More recently, new therapeutic options, targeting *FLT3*, *IDH1/2* and *BCL2* have become available[10] and may have the potential to improve outcome in certain subtypes of t-AML.

Disclosures

No conflicts of interest to disclose.

References

1. Nilsson C, Linde F, Hulegardh E, et al. Characterization of therapy-related acute myeloid leukemia: increasing incidence and prognostic implications. Haematologica. 2023;108(4):1015-1025.
2. Arnold M, Rutherford MJ, Bardot A, et al. Progress in cancer survival, mortality, and incidence in seven high-income countries 1995-2014 (ICBP SURVMARK-2): a population based study. Lancet Oncol. 2019;20(11):1493-1505.
3. Jemal A, Ward EM, Johnson CJ, et al. Annual report to the nation on the status of cancer, 1975-2014, featuring survival. J Natl Cancer Inst. 2017;109(9):djx030.
4. Dohner H, Estey EH, Amadori S, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood. 2010;115(3):453-474.
5. Kayser S, Dohner K, Krauter J, et al. The impact of therapy-related acute myeloid leukemia (AML) on outcome in 2853 adult patients with newly diagnosed AML. Blood. 2011;117(7):2137-2145.
6. Lindsley RC, Mar BG, Mazzola E, et al. Acute myeloid leukemia ontogeny is defined by distinct somatic mutations. Blood. 2015;125(9):1367-1376.
7. Wong TN, Ramsingh G, Young AL, et al. Role of TP53 mutations in the origin and evolution of therapy-related acute myeloid leukaemia. Nature. 2015;518(7540):552-555.
8. Lancet JE, Uy GL, Cortes JE, et al. CPX-351 (cytarabine and daunorubicin) liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute myeloid leukemia. J Clin Oncol. 2018;36(26):2684-2692.
9. Yakoub-Agha I, de La Salmonière P, Ribaud P, et al. Allogeneic bone marrow transplantation for therapy-related myelodysplastic syndrome and acute myeloid leukemia: a long-term study of 70 patients-report of the French Society of Bone Marrow Transplantation. J Clin Oncol. 2000;18(5):963-971.
10. Kayser S, Levis MJ. The clinical impact of the molecular landscape of acute myeloid leukemia. Haematologica. 2023;108(4):956-957.