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A Danish nationwide population-based cohort study on acute myeloid leukemia with *RUNX1::RUNX1T1* – Real-world outcomes and clinicopathological characteristics

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To the Editor,

Core-binding factor (CBF) acute myeloid leukemia (AML) with the *RUNX1::RUNX1T1* fusion oncogene resulting from the recurrent balanced translocation t(8;21)(q22;q22.1) was among the first acute leukemias to be defined based on cytogenetics [1]. It has been estimated to account for 7% of all AML cases [2, 3] and is associated with a favorable prognosis [4]. The addition of gemtuzumab ozagamicin (GO) to intensive chemotherapy was initially reported to improve both relapse-free survival (RFS) and overall survival (OS) in patients with favorable cytogenetic profiles [5–7]. However, multiple randomized clinical trials failed to demonstrate an OS benefit upon final analysis [8–12]. Additionally, relapse rates of up to 40% have been reported, significantly reducing survival [13, 14]. Data regarding the precise risk of relapse and long-term outcomes for patients with *RUNX1::RUNX1T1* CBF-AML remains warranted at a population level. We conducted a population-based characterization of clinical- and molecular features and analyzed long-term outcomes for *RUNX1::RUNX1T1* CBF-AML patients.

A total of 99 patients diagnosed with *RUNX1::RUNX1T1* CBF-AML from 2000 – 2022 were included in the cohort (Table 1; Supplementary Fig. S1), with a median follow-up of 7.6 years (IQR 1.6–13.2)(Supplementary Fig. S2). Patients with *RUNX1::RUNX1T1* CBF-AML comprised 2.3% (95% CI 1.9% – 2.8%) of all AML patients diagnosed within the study period. Intensively treated patients accounted for 87.9% (N = 87), and 11 patients (11.2%) were allocated for an allogeneic hematopoietic stem cell transplantation (HSCT) of which 2 (18.2%) were transplanted in the first complete remission (CR1) and 9 (81.8%) in CR2, respectively (Table 1; Supplementary Fig. S2).

Most patients were treated using DA-based induction therapy (88.3%) relative to FLAG-based (9.4%) and other (2.3%) regimens. Intensive treatment resulted in a CR proportion of 97.7% ($N = 85$). The estimated 5-year OS was 74.3% (95% CI 63.4–82.3%)(Fig. 1; Supplemental Table S1). Notably, there was no detectable improvement in crude OS observed during the study period (Supplementary Fig. S3). In a proportional hazards model, independent risk factors for death were increasing age with a 52% increase in risk of death per increasing decade of life (HR 1.52 (95% CI 1.13–2.07)) and chromosome 17 aberrations (HR 8.00 (95% CI 1.91–33.5); Supplementary Figs. S4 and S5).

Of patients achieving CR1, 21 were subsequently diagnosed with relapse, with an estimated 3-year cumulative incidence of relapse (CIR) of 23.6% (95% CI 15.2–33.0%)(Fig. 1). Among relapsed cases, 95% ($N = 20$) occurred within 2.6 years of follow-up. Relapses were diagnosed as: (i) molecular in 7 patients (33.3%); (ii) morphological in 11 patients (52.4%); and (iii) extramedullary in 3 patients (14.3%). The majority were salvaged with FLAG- or DA-based regimens accounting for 35% ($N = 7$) and 40% ($N = 8$), respectively (Supplementary Fig. S6). For relapsed patients, the 3-year OS dropped to an estimated 38.1% (95% CI 18.3–57.8%) (Supplementary Fig. S6).

We then interrogated the effect of intensive treatment with or without GO in patients with available data ($N = 75$). Patients treated with ($N = 48$) and without ($N = 27$) GO had similar baseline characteristics (Supplemental Table S2). No difference in crude 5-year OS was observed between the GO-treated (75.0% (95% CI 60.1–85.0%)) and non-GO-treated (70.4% (95% CI 49.4–83.9%)) patients (Fig. 1). Restricting the analysis to patients with minimum 5 years of follow-up suggested an OS benefit for the GO-treated ($p = 0.049$). Patients who received GO had a better 5-year RFS at 68.5% (95% CI 54.2–80.2%) as compared to 60.0% for non-GO-treated patients (95% CI 38.4–76.1%) (Fig. 1). In addition, the 3-year CIR of GO-treated patients (18.4% (95% CI 9.1–30.2%)) was lower than for the non-GO-treated patients (36.0% (95% CI 18.2–54.2%)) (Fig. 1) with a non-significant trend towards a decreased risk of relapse (sHR 0.42 (95% CI 0.16–1.07)).

Targeted NGS data from time of diagnosis were available for 38.3% ($N = 38$) of the cohort. An estimated 89.5% (95% CI 75.2–97.0%) harbored pathogenic variants at the time of diagnosis, of which 78.9% harbored variants in signaling pathways (Supplementary Fig. S7). Neither variants related to signaling pathways, myelodysplasia, nor the combination of signaling and cohesin complex variants conferred an impact on crude OS (Supplementary Fig. S8). In seven patients with paired data from the time of diagnosis and the time of relapse, 85.7% ($N = 6$) had longitudinally persisting clones (Supplementary Fig. S9).

In this nationwide population-based cohort study, our findings reveal that the main risk factor for mortality in patients eligible for intensive treatment is patient age at the time of diagnosis. We were unable to demonstrate a significant improvement in OS and CIR with the addition of GO to standard treatment. Furthermore, 1 in 4 patients who achieve a CR subsequently relapse, leading to a worsening of the survival probability.

We found that *RUNX1::RUNX1T1* CBF-AML accounts for less than 3% of patients diagnosed with AML, which is less than half of the commonly cited 7–10%. Given the high coverage of the Danish National Leukemia Registry, we believe our findings provide an accurate estimate of the true incidence of *RUNX1::RUNX1T1* CBF-AML. Most patients harbored pathogenic variants in addition to the fusion oncogene. We could not demonstrate any effect on OS from interrogating the most commonly affected pathways, including the high-risk combination of variants in kinase signaling and the cohesin complex as identified by Duployez N et al. [15].

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Table 1. Cohort characteristics.

	Total cohort (*N* = 99)	Intensively treated (N = 87)	Non-intensively treated (*N* = 12)
Age, y			
Median	53.0	51.0	75.5
IQR	40.0–67.0	37.0–64.0	60.0–78.5
Range	19–80	19–79	43–80
Sex, n (%)			
Male	61 (61.6%)	54 (62.8%)	6 (50%)
Female	38 (38.4%)	32 (37.2%)	6 (50%)
WHO Performance Score, n (%)			
0-1	92 (93.8%)	84 (96.7%)	8 (66.7%)
2-4	6 (6.1%)	2 (2.0%)	4 (33.3%)
nd	1 (1%)	1 (1.0%)	0 (0%)
Prior cytotoxic treatment, n (%)			
Yes	11 (11.1%)	9 (10.3%)	2 (16.7%)
No	88 (88.9%)	78 (89.7%)	10 (83.3%)
Extramedullary disease, n (%)			
Yes	3 (3.0%)	3 (3.4%)	0 (0%)
No	96 (97.0%)	84 (96.6%)	12 (100%)
Hemoglobin, mmol/L			
Mean	5.5	5.5	6.0
IQR	4.9–6.5	4.8–6.3	4.9–7.5
Platelets, 10^9/L			
Median	33.0	32.0	35.5
IQR	17.5–69.0	17.5–59.5	14.0–96.5
Leukocytes, 10^9/L			
Median	9.1	9.9	3.5
IQR	3.7–18.8	4.4–19.7	1.9–15.2
LDH at diagnosis, U/l			
Median	501	539	408
IQR	314 – 998	330–1028	213–871
Peripheral blood blasts, %			
Mean	36.3	38.3	23.9
IQR	11.5 – 56.0	18.5–56.5	4.8–34.5
Bone marrow blasts, %			
Mean	50.0	49.5	53.3
IQR	32.0 – 69.0	35.0–67.0	30.0–77.0
Allogeneic stem cell transplantation, n (%)			
Yes	11 (11.2%)	11 (12.8%)	0 (0%)
CR1	*2 (18.2%)*	*2 (18.2%)*	*0 (0%)*
CR2	*9 (81.8%)*	*9 (81.8%)*	*0 (0%)*
No	87 (88.8%)	75 (87.2%)	12 (100%)

Values given for time of diagnosis. *CI* confidence interval, *CR* complete remission, *IQR* inter quartile range, *nd* no data, *y* years.

In Denmark, DA-based regimens have for decades been the recommended standard induction, and our data demonstrate that these are highly effective and associated with long-term OS and RFS comparable to that of the FLAG-based regimens for which Borthakur G. et al. [12] reported a 5-year OS of 72% and 5-year RFS of 63%. Thus, the high remission-inducing potential of FLAG-based regimens must be weighed against the inherent toxicity, as DA-based treatment represents a highly efficient alternative.

Despite the effective treatment, relapse constituted the main cause of mortality for patients in accordance with data from Hospital MA. et al. [13]. Interestingly, we found that 95% of relapses occurred within 3 years of the initial diagnosis. These data align with the results of the AML19 trial data reported by Russell NH. et al. [7] who present a plateau in the event-free survival at ≈24 months from randomization. As such, the 3-year post-diagnosis timepoint could be considered a relevant milestone during the follow-up of patients.

We furthermore analyzed the real-world effect of GO in *RUNX1::RUNX1T1* CBF-AML by comparing patients treated before and after GO was approved and incorporated into Danish AML treatment guidelines. We did not detect an improvement in OS from the addition of GO to intensive regimens, with OS of the non-GO-treated (70.4%) being comparable to that of the GO-treated patients in the landmark publication by Hills R. et al. [6]. The data did indicate improvements in RFS and CIR, favoring the GO-treated. While these observed improvements did not reach statistical significance, they are in accordance with the results of the randomized clinical trials ALFA-0701 [9] and MRC AML-15 [5]. It is plausible that the lack of an OS benefit from the addition of GO may be attributed to highly effective salvage regimens which negate the RFS and CIR benefits observed, rendering them undetectable when analyzing OS. Additionally, the cohort with available data regarding treatment with GO may have been underpowered to detect an improvement in OS with statistical significance.

The population-based design of this study allowed for robust estimates of clinically relevant outcomes; however, it was not without limitations. While we identified aberrations related to chromosome 17 to be associated with a high risk of death, this association was based on outcomes of 3 patients; thus, the finding may only be considered hypothesis-generating. The cohort consisted of 87 intensively treated *RUNX1::RUNX1T1* CBF-AML patients, and while this represents a sizeable cohort as compared to the available literature, subtle differences in the investigated outcomes may be missed in the statistical analysis. As treatment with GO was analyzed as a categorical variable, the impact of the various dosing regimens that have been utilized during the study period could not be evaluated. Furthermore, patients treated with intensive regimens prior to the introduction of GO served as a comparator. We believe this control group to be a relevant and robust comparator as the treatment of AML has been consistent and uniform in the study period across the AML-treating centers in Denmark, reflecting the highly centralized AML-treatment. Nevertheless, it is plausible to expect that advancements in supportive care and overall management of AML may have influenced outcomes during the study period, such as the observed benefit of GO with regard to survival beyond 5 years of follow-up. Here, the improved treatment of co-morbidities during the study period, e.g., cardiac diseases, has likely contributed to the observed improvement in OS.

In conclusion, we provide population-based data on *RUNX1::RUNX1T1* CBF-AML showing that, despite the upfront favorable prognosis, relapse is an important driver of mortality for these patients. Furthermore, we report that GO may reduce the risk of relapse; however, the clinical benefit did not reach statistical significance in this study. Collectively, our data highlight an unmet need for improved care for patients with AML with *RUNX1::RUNX1T1*, emphasizing the need for novel agents for the treatment of this patient population, particularly for those who relapse.

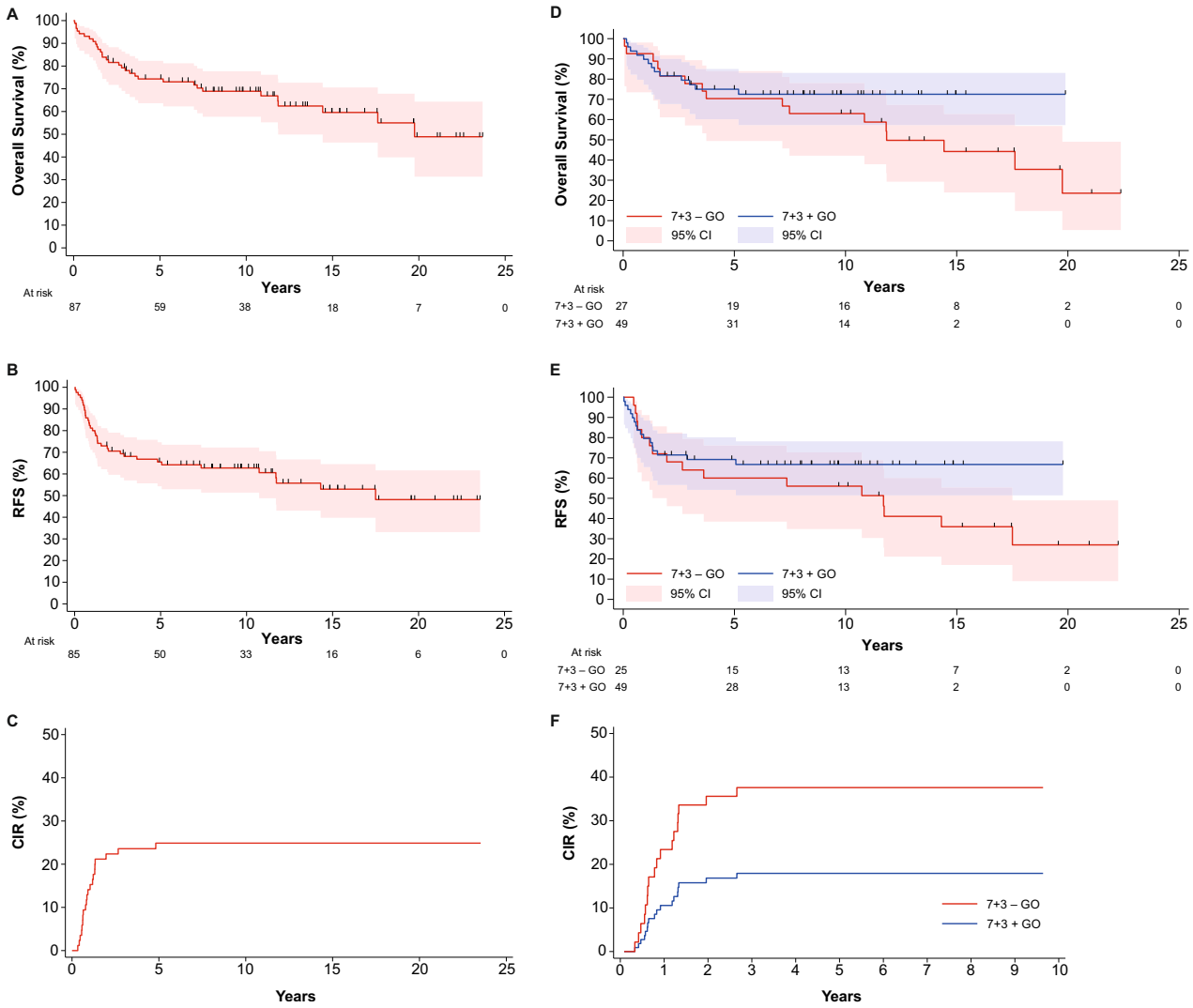

Fig. 1 Outcomes for patients with AML with *RUNX1::RUNX1T1* treated with curative intent. A–C The total cohort. **D–F** Patients stratified by treatment with gemtuzumab ozagamicin (GO). Hashed marks denote censoring. Filled area denote 95% confidence intervals.

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DATA AVAILABILITY

Requests regarding data availability can be made to M.L. at majlud@rm.dk.

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AUTHOR CONTRIBUTIONS

JFS, DTK, ASR, and ML designed the study. JFS, DTK, KG, ADØ and DLH collected the data. ML and JFS collected biobanked samples. AA and JFS performed variant calling. JFS created and managed the patient database, analyzed the data, made the figures, and wrote the first-drafted manuscript. The final manuscript was approved by all authors.

COMPETING INTERESTS

J.F.S.; A.D.R.; M.L.: No conflicts of interest to declare. D.T.K.: Consulting/advisory board: AbbVie, Astellas Pharma, Immedica pharma AB, Sevier; travel grants: Swedish Orphan Biovitrum; Research funding: unrestricted grant from Incyte Biosciences Nordic AB. A.S.R.: Jazz Pharmaceuticals: Travel grant, Daichii Sankyo: Consultancy fee, Immedica, Consultancy fee, unrestricted research grant, AbbVie: Consultancy fee. Servier: Consultancy fee. D.L.H.: Has served as Advisory Board member for Janssen and Takeda, Travel grants: EUSA Pharma, Alexion and SoBI outside this work. K.G.: Unrestricted research grants from Janssen Pharma and Medac. Not related to the current project.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Central Denmark Region Committees on Health Research Ethics (record no. 1-10-72-123-22) and conducted in accordance with Danish law. There was given exemption from informed consent in accordance with the Danish Health Care Act and the Decree on Information and Consent to Participation in Health Research Projects and on Reporting Supervision of Health Research Projects.

ADDITIONAL INFORMATION

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