

Letter to the Editor**Is There a Better Therapeutic Time Window from Diagnosis to Treatment for Elderly Acute Myeloid Leukemia Patients Receiving Hypomethylating Agents?****Keywords:** Elderly patients; Acute myeloid leukemia; Hypomethylating agents.**Published:** July 01, 2024**Received:** March 03, 2024**Accepted:** June 14, 2024**Citation:** Molica M., Maurillo L., Rossi M., Breccia M., Mazzone C., de Fabritiis P., Perrone S. Is there a better therapeutic time window from diagnosis to treatment for elderly acute myeloid leukemia patients receiving hypomethylating agents? *Mediterr J Hematol Infect Dis* 2024, 16(1): e2024055, DOI: <http://dx.doi.org/10.4084/MJHID.2024.055>This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.**To the editor.**

In fit patients with newly diagnosed acute myeloid leukemia (ND-AML), immediate treatment is recommended due to the poor prognosis of untreated acute leukemia; however, this paradigm has been challenged by a German study.¹ The authors stratified patients into 4 groups for a time from diagnosis to treatment start (TDT), showing no difference in waiting before starting intensive chemotherapy. The actual clinical practice, therefore, considers it acceptable to delay ND-AML patients completing the laboratory work-up recommended by the European Leukemia Net (ELN2022)² and solve toxicities present at the time of diagnosis. Turnaround times for targeted gene panels performed with next-generation sequence (NGS) techniques are generally from 5 to 14 days,³ so several days can elapse before a definite clinical entity can be assigned, and some mutations have an impact on the choice of the first line therapy.⁴ On the contrary, AML patients unfit for intensive chemotherapy are candidates for agnostic therapy encompassing hypomethylating drugs (HMAs) ± venetoclax (VEN)⁵ or glasdegib + low-doses cytarabine;⁶ thus, laboratory work-up is not mandatory before choosing the frontline treatment, but molecular determinants of outcome are of prognostic significance.⁷ Because of the scant data published on TDT in the context of HMAs in ND-AML, we evaluated the prognostic value of TDT in 220 patients with AML older than 75 years, already reported in a multicentric retrospective study in a real-life setting of HMAs usage.⁸ Patients were treated with only HMAs due to comorbidities. The main reason for treatment delay was the presence of an infectious event at baseline.

In this study, data were collected from patients treated with azacitidine (AZA) (164) and decitabine (DEC) (56) between September 2010 and September 2023. We recorded baseline patient-related and disease characteristics, including age, ECOG, Charlson comorbidity index (CCI) scores, kidney function (eGFR

and CKD-EPI equation), molecular profiling, ELN 2017, cytogenetic risk, dates of regimen initiation, and survival (**Table 1**). Patients were divided into 4 cohorts: those that started therapy in <15 days (n= 85 patients), 15-30 days (n = 64 patients), 31-45 days (n= 33 patients), 46 days and beyond (n= 38 patients) from their initial diagnosis of AML (**Table 2**). These 4 cohorts received homogeneous treatment with HMAs. We analyzed survival using the Kaplan-Meier curves, with significance determined by the log-rank test. The event for calculating the overall survival (OS) was the date of death, and for event-free survival (EFS), was the time of progressive disease, relapse, or death. Patients were otherwise censored at the date of the last follow-up.

The median TDT of patients treated with AZA or DEC was 21 or 15 days, respectively; overall, it was 19 days. The median OS (**Figure 1**) was 7.5 months (95%CI 4.5-10.5 mts), 11 months (95%CI 4.5-17.4), 7.4 months (95%CI 4.7-10.1), and 7.6 months (95%CI 2.3-13) for the subgroups of TDT <15, 15-30, 31-45 and >46 days, respectively (p=0.224). The median EFS was 5.8 months (95%CI 2.4-9.1), 9.8 months (95%CI 7.9-11.7), 5.0 months (95%CI 0.9-9.1), and 5.7 months (95%CI 0.5-12.2), for the subgroups of TDT <15, 15-30, 31-45 and >45 days, respectively (p=0.187). No statistically significant difference was noted when considering patients receiving AZA or DEC in terms of OS (p=0.08) and EFS (p=0.083) considering the four different groups.

In conclusion, TDT did not show prognostic significance in our patients with AML treated with HMAs. However, a trend for better outcomes can be seen in the subgroup that started treatment 15-30 days after initial diagnosis. These results confirm the lack of difference found in the German study¹ but, at the same time, do not contrast with the results from Bouligny et al., who considered the impact of TDT on patients treated with VEN + HMAs.⁹ Indeed, in this study, OS was 5.8 months for patients included in the 0-7 day

Table 1. Patients' characteristics.

Characteristics	No. of Patients = 220
Male, <i>n</i> (%)	119 (54)
Female, <i>n</i> (%)	101 (46)
Median age at diagnosis (IQR)	78.2 (75–86.2)
Hb g/dL (median, IQR)	8.8 (7.9–10.0)
WBC × 10 ⁹ /L (median, IQR)	3.24 (1.6–9.8)
Platelet count × 10 ⁹ /L (median, range)	56 (32–92.5)
BMI, <i>n</i> (%)	
<25	97 (44.1)
≥25	123 (55.9)
ECOG PS, <i>n</i> (%)	
<2	132 (60)
≥2	88 (40)
eGFR, <i>n</i> (%)	
<60 mL/min	37 (16.8)
≥60 mL/min	183 (83.2)
CCI, <i>n</i> (%)	
<3	44 (20)
≥3	176 (80)
AML type, <i>n</i> (%)	
De novo-AML	135 (61.4)
s-AML	85 (38.6)
ELN risk stratification, data available <i>n</i> (%)	205 (93.1)
Favorable	17 (8.3)
Intermediate	100 (48.8)
Poor/adverse	88 (42.9)
Infection at diagnosis, <i>n</i> (%)	
No	171 (77.7)
Yes	49 (22.3)
Transfusion requirement, <i>n</i> (%)	
No	83 (37.7)
Yes	137 (62.3)
Median No of cycles (IQR)	5. (2–12)
TDT, <i>n</i> (%)	
<15 days	85 (38.6)
15–30 days	64 (29.1)
31–45 days	33 (15.1)
>45 days	38 (17.2)

Table 2. Patients' subgroups characteristics according to TDT.

	Time from diagnosis to treatment start (TDT)			
	<15 days	15–30 days	31–45 days	>45 days
Patients, <i>n</i>	85	64	33	38
Median age at diagnosis (IQR)	77.2 (75–82.3)	78.6 (75–84.4)	79.1 (76–86.2)	78.7 (75–84.8)
s-AML	35	20	14	16
Poor/adverse risk (ELN classification), <i>n</i>	37	24	12	15
Transfusion dependence, <i>n</i>	56	35	20	26
Infection at diagnosis, <i>n</i>	7	10	14	18
ECOG PS ≥2, <i>n</i>	35	24	13	16
CCI ≥3, <i>n</i>	68	50	26	32
eGFR <60 mL/min, <i>n</i>	15	10	4	7

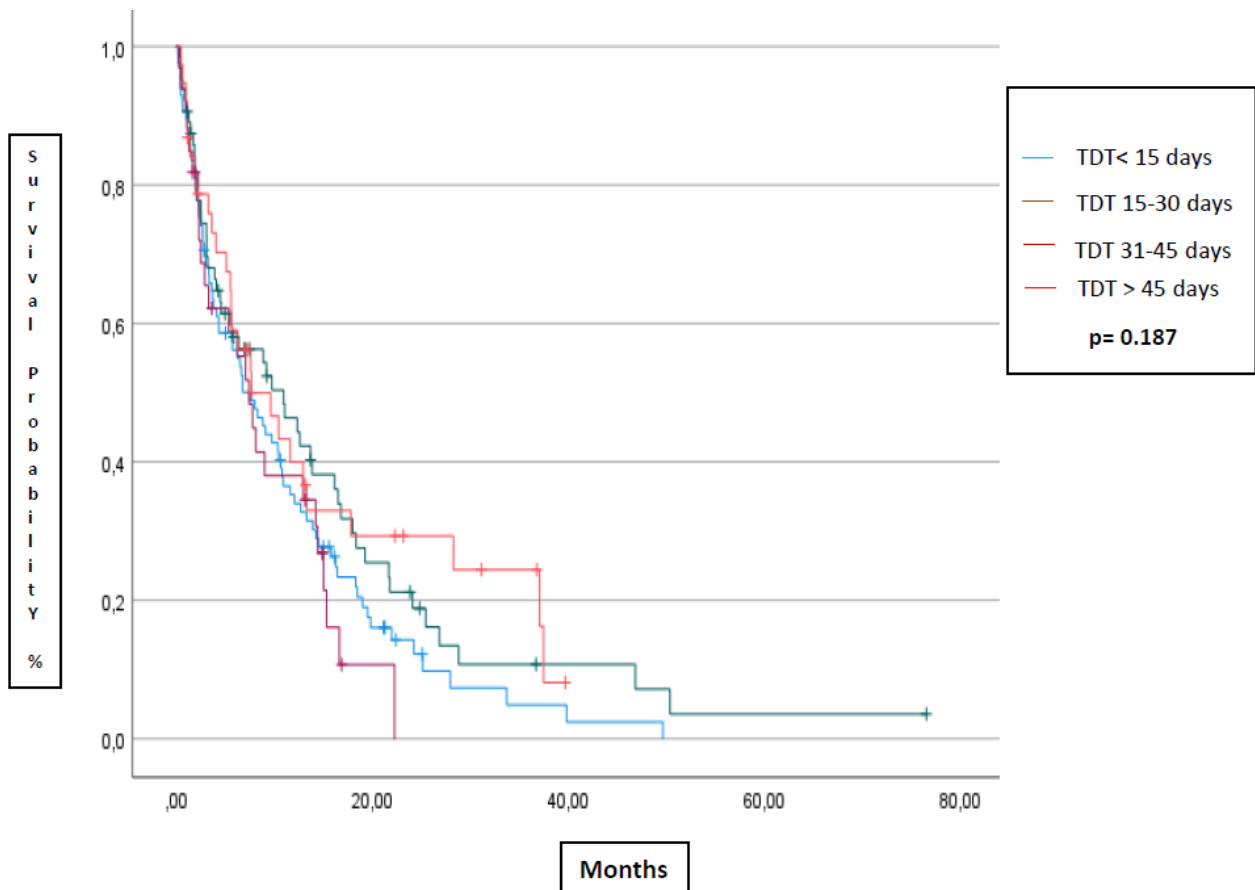


Figure 1. Median overall survival according to time from diagnosis to treatment initiation (<15 days, 15–30 days, 31-45 days, >45 days).

cohort of VEN+HMA initiation, significantly worse than 8.9 months for the 8-14 day cohort and the 12.7 months for 15 days and beyond ($p = 0.023$). Our study also found that the earliest TDT and the two delayed groups had worse results than the intermediate 15-30 days TDT group. This result can be explained by the time used to treat disease-related complications and mitigate existent comorbidities that can reduce toxicities related to HMA treatment.

On the other hand, waiting too long to start HMAs

worsens the prognosis of AML patients, therefore suggesting a possible temporal window to optimize results. Our study has several limitations, given its retrospective nature and the fact that time-passing bias can be present, considering that HMAs are actually rarely given without venetoclax. Therefore, more studies have to be developed to find the best temporal window in TDT when starting HMA + VEN, which could help to improve the results of patients with AML.

Matteo Molica¹, Luca Maurillo², Marco Rossi¹, Massimo Breccia³, Carla Mazzone⁴, Paolo de Fabritiis^{2,4} and Salvatore Perrone⁵.

¹ Department of Hematology-Oncology, Azienda Universitaria Ospedaliera Renato Dulbecco, 88100 Catanzaro, Italy.

² Department of Biomedicina e Prevenzione, Tor Vergata University, 00133 Rome, Italy.

³ Hematology, Department of Translational and Precision Medicine, Az. Policlinico Umberto I-Sapienza University, 00185 Rome, Italy.

⁴ Hematology, St. Eugenio Hospital, ASL Roma2, 00144 Rome, Italy.

⁵ Department of Hematology, Polo Universitario Pontino, S.M. Goretti Hospital, 04100 Latina, Italy.

Competing interests: The authors declare no conflict of Interest.

Correspondence to: Salvatore Perrone, MD. Department of Hematology, Polo Universitario Pontino, S.M. Goretti Hospital, 04100 Latina, Italy. E-mail: sperrone@hotmail.it

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