Longer time from diagnosis to initiation of hypomethylating agents plus venetoclax for acute myeloid leukemia does not worsen survival: results from the Consortium on Myeloid Malignancies and Neoplastic Diseases (COMMAND)

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Abstract

A diagnosis of acute myeloid leukemia (AML) has been considered an oncologic emergency. However, the prevailing wisdom to quickly administer AML-directed therapy is often in conflict with the time needed to complete the evaluation of actionable AML disease biology. Previous studies in intensively treated patients reported that time from date of diagnosis to treatment start date (TDT) did not impact survival outcomes. We conducted a US-based, multi-center, retrospective cohort study assessing the impact of TDT on overall survival (OS) in patients with newly diagnosed AML treated with hypomethylating agents (HMA) + venetoclax at eight participating academic centers. Four hundred and eighty-eight patients were included with a median age of 76 years. Patients had favorable (47.6%), intermediate (22.8%), and adverse (29.6%) risk disease by the 2024 European LeukemiaNet (ELN) 2024 less-intensive risk classification. Median TDT for the cohort was 9 days (interquartile range [IQR], 5-17). Those with TDT <14 days (median OS, 8.2 months; 95% confidence interval [CI]: 6.8-9.9) *versus* ≥14 days (median OS, 11.3 months; 95% CI: 9.5-15.4) had worse OS (*P*=0.007). TDT ≥14 days was associated with improved OS in multivariable analysis (hazard ratio =0.73, 95% CI: 0.54-0.97; *P*=0.033) adjusting for age, performance status, use of cytoreductive therapy, white blood cell count at presentation, ELN 2024 less-intensive risk classification, and presence of *FLT3*-ITD, *TP53*, and *IDH1/2* mutations. These results suggest that stable patients with newly diagnosed AML eventually treated with HMA + venetoclax may await appraisal of disease biology and medical optimization before initiating induction therapy.

Introduction

Acute myeloid leukemia (AML) is an aggressive hematologic malignancy that has been considered by many oncologists to be an oncologic emergency often leading to immediate hospital admission for expeditious evaluation and treatment. However, the prevailing wisdom to quickly administer AML-directed therapy is commonly in conflict with the time needed to complete the evaluation of actionable AML disease biology. The past two decades have seen substantial

progress in the availability and use of molecular testing in the form of polymerase chain reaction (PCR) and next-generation sequencing (NGS) to better inform AML subtype, the utility in using one of the growing armamentarium of targeted agents including IDH and FLT3 inhibitors,[1-4] assessing prognosis, and defining the best consolidative strategy that may include allogeneic hematopoietic stem cell transplantation (alloHCT). These events can lengthen the time from diagnosis to treatment initiation as most commercial and academic center NGS panels average up to 2 weeks turn-around time depending on the number of genes assessed and the laboratory performing the test. Some centers have validated and perform "rapid" NGS panels that evaluate a limited number of genes with more immediate treatment implications and can shorten the turn-around time, which can still be up to 1 week.[5] The time currently required to ascertain PCR/NGS data for newly diagnosed AML is also used in parallel for pre-treatment activities such as baseline echocardiogram evaluation, central venous catheter placement, the arrangement of sub-specialist evaluation(s), optimization via nutritionists and physical therapists, and evaluation for clinical trials.[6]

A few studies over the past decade have evaluated whether time from diagnosis to treatment (TDT) impacts outcomes in patients with newly diagnosed AML.[7-9] Three key studies by Sekeres *et al*, Bertoli *et al.,* and Röllig *et al.* evaluated large cohorts of United States (US), French, and German patients, respectively, treated with intensive induction regimens. All three studies found no difference in survival with longer TDT in older adults (age ≥60 years), although there was discordance when evaluating younger, US patients who had inferior OS when treatment was initiated beyond 5 days from diagnosis.[7] These results have recently been challenged by large, population-based studies of Swedish and US intensively-treated patients who were shown to have worse OS with longer TDT.[10,11] However, the impact of TDT on outcomes amongst patients with AML receiving less-intensive regimens, including *de facto* standard of care hypomethylating agent (HMA) + venetoclax, is largely unknown.[12-14] A recent retrospective German study evaluated a combined cohort of patients treated with HMA/low-dose cytarabine + venetoclax for newly diagnosed AML as ascertained from registry (N=138) and electronic health record data (N=717) and found no difference in OS when using a dichotomous TDT cutoff of 10 days (i.e., <10 days *vs*. TDT ≥10 days).[15] To date, no study has assessed the impact of TDT exclusively in HMA + venetoclax-treated patients. This gap in knowledge is particularly relevant considering that most patients will receive less-intensive frontline therapy, these regimens are being investigated against intensive therapy for many subgroups, the proportion of patients having molecular testing will further improve, and, lastly, AML diagnosis and sub-classification will increasingly rely upon biological data.[4] We conducted a US-based, multi-center, retrospective cohort study from the Consortium on Myeloid Malignancies and Neoplastic Diseases (COMMAND) assessing the impact of TDT on outcomes in patients with newly diagnosed AML treated with HMA + venetoclax. We hypothesized that TDT would not impact OS, even after accounting for relevant clinicopathologic covariates, due to the importance of a thorough biologic evaluation and the predictive value of mutational and cytogenetic profiling preceding treatment initiation.

Methods

Study design, setting, and population

This retrospective cohort study was comprised of adult patients with newly diagnosed AML treated with HMA + venetoclax, either on trial or off-trial, identified by chart review at eight participating US academic centers. Data collection ended May of 2024. AML was defined as per 4th edition World Health Organization classification of myeloid neoplasms and acute leukemias.[16] Patients with AML progressed from MDS or MPN with prior exposure to HMA therapy were included in the analysis and prior HMA exposure was collected as a covariate. Patient demographics were collected including age at diagnosis, sex and self-reported race/ethnicity.

Variables

TDT was defined as the number of days between date of diagnosis and date of initiation of HMA + venetoclax. The dose, duration, number of cycles to first and best response, number of cycles in total, treatment setting (inpatient or outpatient) of venetoclax, and receipt of alloHCT in first remission were collected. Laboratory data at presentation including complete blood count and complete metabolic panel data inclusive of transaminases, baseline uric acid, lactate dehydrogenase and presence of tumor lysis syndrome (TLS) evaluation were collected. Cytogenetic profiling was done by fluorescence *in situ* hybridization (FISH) and conventional chromosome analysis/full karyotyping, while molecular analyses were completed by each institution's myeloid gene panel via NGS and PCR. A prognostic risk score was assigned using the 2024 European LeukemiaNet (ELN) less-intensive risk classification.[17] Key patient-specific variables of fitness for anti-leukemic therapy, hematopoietic stem cell transplant comorbidity index (HCT-CI) score and Eastern Cooperative Oncology Group performance status (ECOG PS), were collected in order to control for the impact of patient fitness on TDT.[18] HCT-CI score >3 and ECOG PS ≥3 defined high comorbidity burden and poor performance status, respectively.[19,20] To control for severity of presentation biasing early TDT toward worse OS, white blood cell (WBC) count at diagnosis was categorized as ≥25,000 or <25,000 and data on the use cytoreductive therapy inclusive of receipt of hydroxyurea and use of leukocytapheresis were collected. Cause of death was documented for all patients.

Outcomes

Response to HMA + venetoclax was assessed using the 2022 ELN AML response criteria.[6] Measurable residual disease (MRD) status at time of remission was defined by multiparameter flow cytometric analysis as per each institution's standard. OS was defined as days from initiation with HMA + venetoclax to date of death. Early death, defined as death within 30 or 60 days, was assessed from date of treatment initiation.

Statistical methods

The primary objective was to evaluate the association between TDT and OS. We explored the hazards ratio (HR) of OS against restricted cubic splines of TDT, and decided to use TDT ≥14 in multivariable Cox model given this time point's alignment with most commercial and academic center NGS panels average turn-around times. Description of continuous baseline variables of the entire cohort were summarized using medians and interquartile ranges (IQR). Methods for time-to-event data, such as the Kaplan-Meier method and Cox proportional hazards model, were applied to OS. Multivariable Cox model was conducted controlling for the following: HMA used, ECOG PS, age at diagnosis, AML type, WBC at diagnosis ≥25,000, receipt of cytoreduction, alloHCT in CR1, ELN 2024 less-intensive risk classification;[17] the backward elimination method (based on *P* values between nested models) was applied to mutations detected by NGS other than *FLT3*-internal tandem duplication (ITD) which we mandated be included given the proliferative nature of that AML subtype. *FLT3*-ITD, *TP53*, and *IDH1/2* were included in the final model while RAS pathway and *NPM1* mutations were not selected by the backward elimination method. All analyses were performed using R (The R Foundation for Statistical Computing).

Each institution received approval from the institutional review board to conduct this retrospective project. All investigators ensured the planning, conduct, and reporting of this human research was in accordance with the Declaration of Helsinki. The manuscript was written in accordance with The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies.[21]

Results

Description of patients

Four hundred and eighty-eight patients were included in the analysis. Median age was 76 years (IQR, 70-80), 57% were male, 78.5% were White/Caucasian (Table 1). An ECOG PS <2 and HCT-CI score of ≤2 was assigned to 91.2% and 52.8% of patients, respectively. Patients had favorable (47.6%), intermediate (22.8%), and adverse (29.6%) risk disease by ELN 2024 less-intensive risk, respectively. The most common mutations identified were *TP53* (27.5%), *IDH1/2* (19.3%), *NPM1* (16.4%), *DNMT3A* (16.8%), *ASXL1* (15.4%), and *FLT3*-ITD (13.7%). AML progressed from myelodysplastic syndrome (MDS) or myeloproliferative neoplasm (MPN) occurred in 30% of patients, 21% of whom had prior HMA exposure prior to transformation to sAML.

Description of treatment

Twenty-seven percent of patients received cytoreduction with either hydroxyurea (24%) or leukapheresis (3%) prior to initiation of HMA + venetoclax (Table 2). Azacitidine + venetoclax was the most common regimen utilized (59.7%). Median number of cycles of HMA + venetoclax received was 3 (IQR, 1-6) and 7.4% of the cohort proceeded to alloHCT in first remission.

Responses and survival of the cohort

Median follow-up for the entire cohort was 7.3 months. MRD-negative CR, MRD-positive CR, and CRi was achieved in 21.5%, 10.5%, and 16.4% of patients while recieving HMA + venetoclax. There were 114 patients (23.4%) who relapsed after date of first remission with a median of 7.75 months to relapse from first remission. Median OS for the cohort was 9.5 months (95% CI: 8.2-10.5) (Figure 1). Early death, occurred in 6.0% and 15.2% of patients at 30 and 60 days, respectively.

Time from diagnosis to treatment

Median TDT for the cohort was 9 days (IQR, 5-17). Differences in TDT by baseline patient characteristics and treatments are shown in Tables 1 and 2, respectively. TDT did not differ by treatment regimen, HCT-CI score, receipt of alloHCT in CR1, response to induction therapy. However, TDT did differ by *IDH1/2* status, ECOG PS, WBC at presentation, requirement of cytoreduction, and ELN 2024 less-intensive risk category. Patients with *IDH1/2*-mutated disease compared to those with IDH1/2 wild-type disease (median, 7.0 [IQR, 4.0-14.3] *vs*. 9.0 [IQR, 5.0-18.0] days; *P*=0.031), ECOG of 3-4 compared to those of ECOG of 0 (8.5 [IQR, 4.0-13.0] *vs*. 11.0 [IQR, 6.5-23.0]; *P*=0.022), WBC >25,000 compared to those with WBC <25,000 (median, 6 [IQR, 4-11] *vs*. 10 [IQR, 5-19]; *P*<0.0001), and those who received cytoreduction, compared to those who did not (median, 7 [IQR, 4-11] *vs*. 10 [IQR, 5-19]; *P*=0.0004), all had shorter TDT. Longer TDT was associated with improved OS in univariate analysis (HR=0.99; 95% CI: 0.98-0.999; *P*=0.026), and TDT ≥14 days was associated with improved OS in multivariable analysis (HR: 0.73, 95% CI: 0.54 to 0.97; *P*=0.033) adjusting for age, ECOG PS, AML type (*de novo vs*. progressed from MDS or MPN or therapy-related), use of cytoreductive therapy, WBC at presentation, prior HMA exposure, ELN 2024 less-intensive risk classification, and mutational status of *FLT3*-ITD, *TP53*, and *IDH1/2*. When comparing TDT <14 days (median OS, 8.2 months; 95% CI: 6.8-9.9) and ≥14 days (median OS, 11.3 months; 95% CI: 9.5-15.4) a difference in OS was

Table 1. Characteristics of 488 patients with newly diagnosed acute myeloid leukemia with comparison of time from diagnosis to treatment according to these characteristics.

Characteristic	N (%), total 488	TDT, days, median (IQR)	*P**
Age at diagnosis, years, median (IQR) <75, N ≥75, N	76 (70-80) 209 279	 8 (5-15) 10 (5-19)	 Ref 0.076
Sex Male Female	 278/488 (57.0) 210/488 (43.0)	 9 (5-17) 9 (5-17)	 Ref 0.789
ECOG PS 0 1 2 3-4	 51/431 (11.8) 223/431 (51.7) 119/431 (27.6) 38/431 (8.8)	 11.0 (6.5-23.0) 10.0 (5.0-19.0) 8.0 (5.0-15.0) 8.5 (4.0-13.0)	 Ref 0.130 0.077 0.022
HCT-CI score 0-2 ≥3	 159/301 (52.8) 142/301 (47.2)	 9.0 (4.0-16.0) 7.0 (4.0-13.8)	 Ref 0.259
Received cytoreduction *vs.* not	135/478 (28.2)	6 (4-11) *vs.*11 (5-19)	<0.0001
Cytoreduction: hydroxyurea alone Received hydroxyurea No cytoreduction	89 *vs.* 377 89/466 (19.1) 377/466 (80.9)	 7 (4-12) 10 (5-19)	 Ref <0.001
Cytoreduction: leukapheresis and hydroxyurea Received leukapheresis and hydroxyurea No cytoreduction	 101/377 266/377	 7 (4-11) 10 (5-19)	 Ref <0.001
WBC at diagnosis ≥25,000 <25,000	 118/483 (24.4) 365/483 (75.6)	 6 (4-11) 10 (5-19)	 Ref <0.0001
ELN 2022 risk category Favorable Intermediate Adverse	 46/467 (9.9) 91/467 (19.5) 330/467 (70.7)	 6.5 (4.0-14.0) 9.0 (4.0-17.0) 9.0 (5.0-17.0)	 Ref 0.375 0.171
ELN 2024 less-intensive category risk Favorable Intermediate Adverse	 215/452 (47.6) 103/452 (22.8) 134/452 (29.6)	 11.0 (5.0-19.5) 7.0 (4.0-13.0) 8.0 (4.0-14.0)	 Ref 0.003 0.004
Molecular testing, Ref: wt *FLT3*-ITD mutated *vs.* not *FLT3*-ITD or *FLT3*-TKD mutated *vs.* not *IDH1/2* mutated *vs.* not TP53 mutated *vs.* not *NPM1* mutated *vs.* not *DNMT3A* mutated *vs.* not	 67/461 (14.5) 78/461 (16.9) 92/462 (19.9) 134/451 (29.7) 80/447 (17.9) 82/438 (18.7)	 7.0 (3.5-11.5) *vs.* 9.0 (5.0-17.0) 7.0 (3.3-12.8) *vs.* 9.0 (5.0-17.0) 7.0 (4.0-14.3) *vs.* 9.0 (5.0-18.0) 8 (4-14) *vs.* 9 (5-19) 7 (4-14) *vs.* 9 (5-17) 8.5 (4.0-15.0) *vs.* 9.0 (5.0-17.0)	 0.052 0.063 0.031 0.060 0.105 0.625
De novo AML	256/486 (52.7)	8.0 (4.0-16.0)	Ref
Therapy-related AML	78/486 (16.0)	9.5 (6.0-14.0)	0.228
AML progressed from MDS or MPN	146/486 (30.0)	10.0 (4.3-22.8)	0.150
Prior HMA exposure Prior HMA exposure: yes Prior HMA exposure: no	 31/347 (8.9) 316/347 (91.9)	 13.0 (7.0-23.5) 8.0 (5.0-15.3)	 Ref 0.045

*Wilcoxon rank sum test for the comparison of time from diagnosis to treatmen (TDT) between 2 groups. AML: acute myeloid leukemia; DNMT3A: DNA methyltransferase 3 α; ELN: European LeukemiaNet; *FLT3*-ITD: FMS-like tyrosine kinase 3 internal tandem duplication; *FLT3*-TKD: FMS-like tyrosine kinase 3 tyrosine kinase domain; HCT-CI: hematopoietic stem cell transplant comorbidity index; HMA: hypomethylating agent; IDH: isocitrate dehydrogenase; IQR: interquartile range; MDS: myelodysplastic syndrome; MPN: myeloproliferative neoplasm; NMP1: nucleophosmin 1; Ref.: reference; TP53: tumor protein 53; WBC: white blood cell; wt: wild-type.

noted (*P*=0.007, log-rank test). In the final multivariable Cox model (Table 3), TDT ≥14 days (*P*=0.033), ECOG PS 3-4 (*P*=0.002), AML progressed from MDS or MPN (*P*=0.008) or therapy-related (*P*=0.013), *IDH1/2* (*P*=0.025), *TP53* (*P*=0.026), and receipt of alloHCT in CR1 (*P*=0.0003) were significant after having adjusted for other factors. Simililarly, in the multivariable logistic regression model for 60-day mortality (Table 4) those with TDT >14 days had lower 60-day mor-

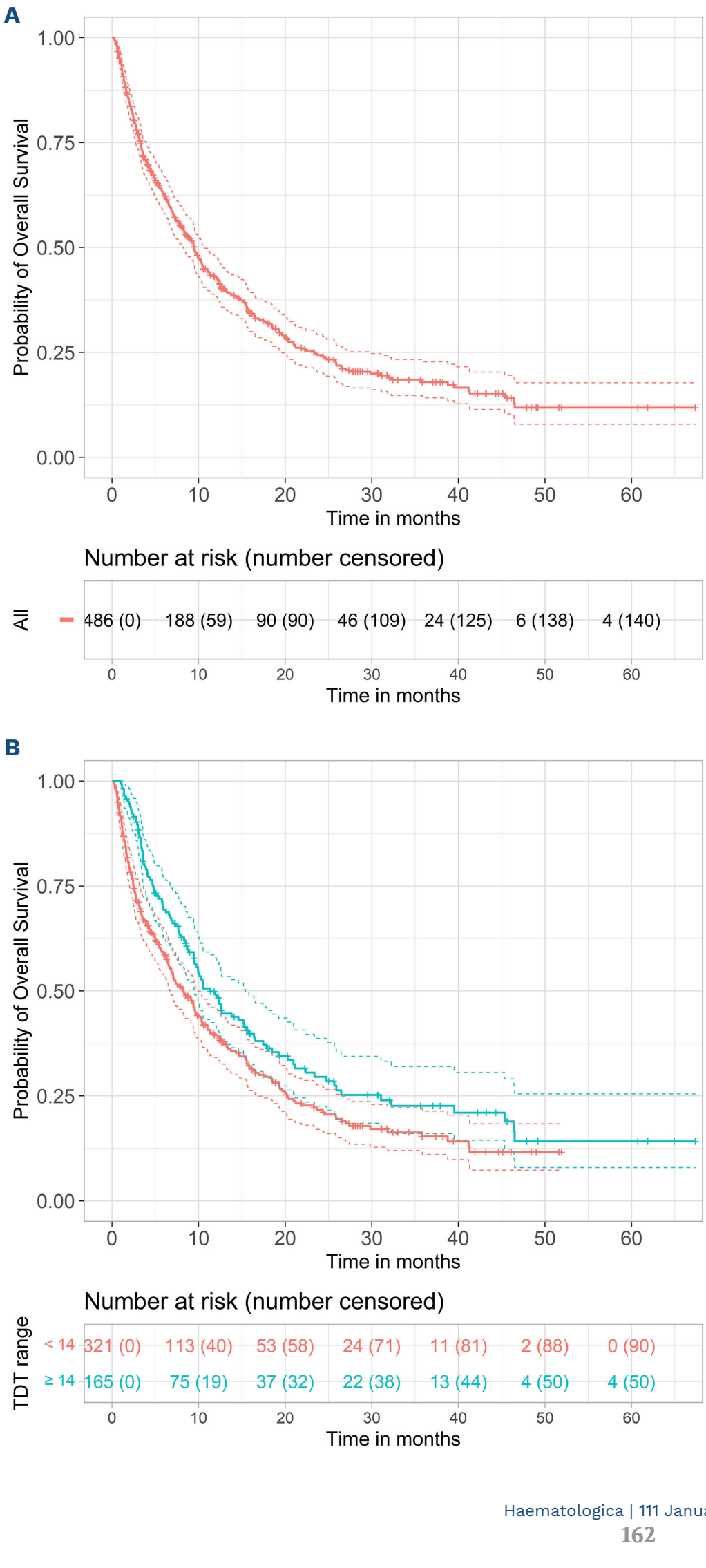

Figure 1. Survival curves for 488 adults with acute myeloid leukemia treated with hypomethylating agents + venetoclax within the United States-based Consortium on Myeloid Malignancies and Neoplastic Diseases. Median overall survival (OS) for the entire cohort (A) was 9.5 months (95% confidence interval [CI]: 8.2-10.5). When comparing time from diagnosis to treatment (TDT) <14 days (median OS, 8.2 months; 95% CI: 6.8-9.9) and ≥14 days (median OS, 11.3 months; 95% CI: 9.5-15.4) (B) a difference in OS was noted (*P*=0.007, log-rank test).

Table 2. Differences in time from diagnosis to treatment by treatment received, receipt of transplant, and response to frontline therapy.

Characteristic	N (%)	TDT days, median (IQR)	*P*
Treatment regimen			
Azacitidine + venetoclax	263/440 (59.7)	9 (5-17)	Ref
Decitabine + venetoclax	177/440 (40.3)	8 (4-15)	0.057
Receipt of alloHCT			
Yes	36/486 (7.4)	9.5 (7.0-15.5)	0.510
No	450/486 (92.6)	9.0 (4.3-18.0)	Ref
Response to frontline therapy			
MRD-negative CR	105/426 (24.6)	9.0 (5.0-15.0)	
MRD-positive CR	51/426 (11.9)	9.0 (6.0-21.5)	
CRi	80/426 (18.8)	11.5 (4.0-19.0)	
MLFS	36/426	11.0 (5.0-17.3)	0.460*
Partial response	33/426	7.0 (4.0-13.0)	
Progressive disease	71/426	13.0 (6.0-19.0)	
Stable disease	50/426	8.0 (4.0-13.0)	

*Compares time from diagnosis to treatment (TDT) of those measurable residual disease (MRD)-negative complete remission (CR), MRD-positive CR and CR with incomplete hematologic recovery (CRi) with partial response/progressive disease/stable disease. alloHCT: allogeneic hematopoietic stem cell transplant; IQR: interquartile range; MLFS: morphologic leukemia-free state; Ref: reference.

tality rates compared to <14 days (OR=0.45; 95% CI: 0.21-0.93; *P*=0.04). No variables were statistically significant in predicting 30-day mortality.

Discussion

In this US-based, multi-center, retrospective cohort study in patients with newly diagnosed AML treated with HMA + venetoclax we found longer TDT did not associate with worsening in patient outcomes, even when controlling for key patient- and disease-related variables known to impact survival in newly diagnosed patients with AML treated with less-intensive regimens. We speculate the association of marginal improvement in OS among those with longer TDT is due to two factors. First, more unfit patients (defined by ECOG PS, HCT-CI score) were treated earlier, potentially due to being excluded at diagnosis for clinical trials and thus providers initiating the *de facto* standard of care regimen. Additionally, patients who had a longer TDT may have benefited from thorough treatment planning and medical optimization, including comorbidities, infectious complications, dietician intervention, and physical therapy evaluation and optimization, prior to starting treatment.

Table 3. Multivariable analysis of time from diagnosis to treatment effect on overall survival in the entire cohort based on disease biology, hypomethylating agent used, age, and receipt of allogeneic stem cell transplant in first complete remission.

Variable in Cox proportional hazards model	Hazard ratio (95% CI)	*P*
Time from diagnosis to treatment ≥14 days, Ref: <14 days	0.73 (0.54-0.97)	0.033
Treatment regimen, Ref: AZA + venetoclax		
Decitabine + venetoclax	1.17 (0.90-1.53)	0.246
Age at diagnosis	1.00 (0.98-1.01)	0.617
ECOG PS, Ref: 0		
1	1.07 (0.72-1.60)	0.724
2	1.39 (0.91-2.11)	0.128
3-4	2.23 (1.34-3.71)	0.002
AML type, Ref: *de novo*		
Progressed from MDS or MPN	1.46 (1.08-1.96)	0.013
Therapy-related	1.58 (1.09-2.31)	0.016
WBC at diagnosis ≥25,000, Ref: <25,000	1.27 (0.77-2.09)	0.355
Receipt of cytoreduction, Ref: no	1.01 (0.61-1.67)	0.979
Mutation status, Ref: wt		
FLT3-ITD mutated	1.00 (0.56-1.77)	0.987
IDH1/2 mutated	0.65 (0.44-0.95)	0.025
TP53 mutated	1.79 (1.07-2.98)	0.026
ELN 2024 less-intensive category risk, Ref: adverse	0.99 (0.60-1.63)	0.955
AlloHCT in CR1, Ref: no	0.32 (0.17-0.59)	0.0003

*Multivariable analysis was conducted controlling for the following: acute myeloid leukemia (AML) type, Eastern Cooperative Oncology Group performance status (ECOG PS), age, white blood cell (WBC) at diagnosis, receipt of cytoreduction, European LeukemiaNet (ELN) 2024 less intensive risk classification. AlloHCT: allogeneic hematopoietic stem cell transplant; AZA: azacitidine; CI: confidence interval; *FLT3*-ITD: FMS-like tyrosine kinase 3 internal tandem duplication; HMA: hypomethylating agent; IDH: isocitrate dehydrogenase; MDS: myelodysplastic syndrome; MPN: myeloproliferative neoplasm; TP53: tumor protein 53; wt: wild-type.

Notably, even in patients requiring cytoreduction there was no detriment noted with longer TDT in our multivariable analysis for OS, suggesting that treating physicians can allow for medical optimization and molecular testing to return before administering HMA+venetoclax in most clinically stable patients.

Our findings add to the body of literature on TDT in newly diagnosed AML as the first to describe the impact of TDT in the ever-expanding population of patients treated with frontline HMA + venetoclax in the US. Baden *et al*. described TDT amongst German patients treated with venetoclax-based regimens inclusive of HMA + venetoclax and low-dose cytarabine + venetoclax (with an unknown distribution between the regimens) using registry (N=138) and electronic medical record (EMR) (N=718) data. This analysis found that treatment before or after 10 days from diagnosis had no impact on survival or 30- or 60-day mortality when controlling for comorbidity status, age, and disease severity as assessed via WBC count at presentation.[15] Wolach *et al.* recently found no differences in OS when assessing TDT at cutoffs of 7 and 14 days in a prospective, real-world cohort of patients with AML treated with venetoclax-containing regimens.[22] The bulk of literature, namely derived from three large European cohorts and two large US cohorts, describing the impact of TDT on outcomes, has focused on intensively treated patients and has offered divergent findings. Sekeres *et al*. evaluated 1,317 US patients diagnosed at MD Anderson Cancer Center and the Cleveland Clinic and found that patients age ≤60 years, but not older adults, had worse overall survival when TDT was >5 days.[7] Similar findings were shown from real-world academic and community practice data in the National Cancer Database from 55,985 incident cases of AML diagnosed and treated intensively during 2004-2018 where patients age ≤60 years, but not age >60 years had worse OS at a TDT of 5-9 or >9 days when compared with 1-4 days.[10] Limitations of these data include the lack of accounting for cytogenetic or molecular data, receipt of cytoreduction, patient frailty as measured by accepted surrogates like performance status, and a small effect size with relatively higher 5-year number needed to treat. Analyses of European cohorts such as those from France,[9] Germany,[8] and Sweden[11] all show no difference on outcomes by TDT, regardless of age group, in multivariable analyses when comparing TDT categorically by <5 days or <1 day *versus* a number of other strata (e.g., 0-5, 6-10, >15 days or 2-3, 4-6, >6 days, respectively).[8,9,11] Differences in findings from European and US-based cohorts of intensively treated patients may potentially be explained by differences in treatment regimens, specifically that European groups often employ double induction strategies and higher doses of cytarabine.

A demonstration of lack of detrimental effect of increasing

Table 4. Multivariable logistic regression of death within 60 days from initiation of treatment with hypomethylating agents + venetoclax.

Variables in logistic regression model	Odds ratio (95% CI)	*P*
Time from diagnosis to treatment ≥14 days, Ref: <14 days	0.45 (0.21-0.93)	0.039
Treatment regimen, Ref: AZA + venetoclax Decitabine + venetoclax	 1.02 (0.54-1.91)	 0.938
Age at diagnosis	1.00 (0.96-1.04)	0.980
ECOG PS, Ref: 0 1 2 3-4	 2.03 (0.63-9.13) 3.84 (1.18-17.33) 5.75 (1.54-28.22)	 0.285 0.043 0.015
AML type, Ref: *de novo* Progressed from MDS or MPN Therapy-related	 1.21 (0.60-2.40) 1.40 (0.60-3.18)	 0.595 0.420
WBC at diagnosis ≥25,000, Ref: <25,000	0.44 (0.14-1.43)	0.164
Receipt of cytoreduction, Ref: no	1.49 (0.47-4.37)	0.475
Mutation status, Ref: wt *FLT3*-ITD present *IDH1/2* mutated *TP53* mutated	 1.58 (0.45-6.06) 0.70 (0.28-1.61) 1.63 (0.56-5.57)	 0.480 0.419 0.397
ELN 2024 less-intensive category risk, Ref: adverse	0.95 (0.32-3.26)	0.934

*Multivariable analysis was conducted controlling for the following: acute myeloid leukemia (AML) type, Eastern Cooperative Oncology Group Performance status (ECOG PS), age, white blood cell (WBC) at diagnosis, receipt of cytoreduction, European LeukemiaNet (ELN) 2024 less intensive risk classification. AZA: azacitidine; CI: confidence interval; *FLT3*-ITD: FMS-like tyrosine kinase 3 internal tandem duplication; HMA: hypomethylating agent; IDH: isocitrate dehydrogenase; MDS: myelodysplastic syndrome; MPN: myeloproliferative neoplasm; TP53: tumor protein 53; wt: wild-type.

TDT with outcomes amongst patients who initiate treatment with HMA + venetoclax has immediate clinical relevance. Our findings suggest that AML providers can defer immediate induction for most, stable patients and await a comprehensive patient and disease evaluation, including NGS results, with most attention to the ascertainment of disease biology that can strongly influence induction regimen preference and clinical trial eligibility. This finding is in line with the recommendation from the recent expert panel from the ELN providing recommendations on fitness assessment in AML. Specifically, there was high (96%) level of agreement for the statement, "Because the time to treatment start does not seem to affect short- and long-term outcomes, comprehensive fitness and biological assessment should be conducted before starting therapy."[18] Our finding is particularly relevant for an older adult population that is more likely to present with increased comorbidity burden, higher ECOG PS, higher risk disease biology, and are less likely to be offered potentially curative therapies such as alloHCT in comparison to their younger counterparts.[23-27] This population is highly likely to be treated with HMA + venetoclax, a regimen that may soon extend as a standard for younger patients with adverse disease risk, depending on the results of ongoing randomized clinical trials (*clinicaltrials gov. Identifier: NCT04801797, NCT03573024, NCT05554393, NCT05554406*).[28] The absence of longer TDT having no adverse impact on outcomes as shown in our cohort provides potential opportunities to optimize care for this vulnerable patient population and reduce healthcare utilization with unnecessary hospital admission and pre-mature, sub-optimal treatment selection. This afforded time allows for the addressing of AML-attributable complications at presentation, either with cytoreduction, anti-microbial therapy or other supportive measures, and the possibility of abrogating initially assigned barriers to intensive induction. Furthermore, providers may be provided an appropriate window to perform a comprehensive assessment of fitness and frailty. Multiple studies have shown the feasibility and prognostic significance of fitness and frailty evaluation via a comprehensive geriatric assessment (CGA) in older adults with AML receiving both intensive induction and less-intensive regimens.[29-32] Yet, incorporation of CGA into standard clinical practice is lacking due in part to concerns of lack of time to perform the assessment.[33] "Pre-habilitation" optimization programs guided by a CGA have shown to improve outcomes in patient's undergoing alloHCT and chimeric antigen receptor (CAR) T therapy and could potentially be explored in these patients.[34-36] Future work to identify disease biology defining "clinically stable AML", a subset behaving more like high-risk MDS, and thus the true beneficiaries of prolonged TDT and prehabilitation, is warranted.[37,38]

Our study has several limitations, most notably the retrospective design limiting our ability to collect several relevant data points. First, we are unable to report on those who died before receiving HMA + venetoclax. However, in the BEAT AML master trial, a US-based, multicenter, precision medicine trial in AML that aimed to prospectively assess the feasibility of assigning treatment based on cytogenetic and molecular results for older patients with AML in ≤7 days, only six of 395 (1.5%) of patients enrolled on protocol died prior to beginning treatment.[39] Thus, we feel capturing similar patients within our cohort and the associated Immortal Time Bias would not have significantly altered our results. Due to the retrospective nature of this work we also were unable to systematically collect reasons for longer TDT, the degree to which NGS results informed treatment decision making given the entire cohort received HMA+venetoclax, and the degree of optimization of patient fitness that occurred during the time from diagnosis to treatment. We also did not systematically collect severity and duration of neutropenia, time from diagnosis to receiving the NGS/cytogenetic data and its association with TDT and outcome. Given the lack of data on neutropenia duration and severity in our analysis, caution ought to be utilized by clinicians applying our findings to those neutropenic at diagnosis. Finally, the survival in our cohort was inferior to those reported from VIALE-A[12] and the UK NHS real-world cohort (median OS, 13.6 months (95% CI: 11.7-15.1),[40] but similar to previous single-center[41,42] and community-based[43,44] studies which reported a median OS of 8 to 11 months. The lower OS observed in comparison to VIALE-A and UK NHS cohort may be, in part, explained by the higher rate of patients with AML progressed from MDS or MPN and therapy-related AML included in this study (46%) compared to that of the VIALE-A population (25%) and UK NHS (31%). Amongst those with AML progressed from MPN or MDS, 21% (31) patients had prior HMA exposure in our cohort compared to 8% in UK NHS. We also included those with ECOG PS >2 (8.8% of our cohort), a subgroup who did particularly poorly and was excluded from VIALE-A.

In conclusion, utilizing a large, multi-centre, retrospective, US-based cohort we demonstrate that a longer TDT was not associated with worse survival for patients with newly diagnosed AML treated with HMA + venetoclax even when controlling for severity of presentation and patient fitness. Our findings suggest that in clinically stable patients, time is available to conduct a thorough assessment inclusive of diagnostic/prognostic/predictive disease biology, patient fitness, AML sub-specialist evaluation, and clinical trial eligibility prior to therapy initiation.

Disclosures

GSM serves on the advisory board for BeiGene, Gilead Sciences/Kite, Pfizer, BMS, Autolus, and Syndax, receives research funding from LOXO/Lilly, Zentalis, Schrodinger, and Merck, and serves on the speakers bureau for Amgen and Rigel, and Stemline. TB is on the advisory board for Pfizer, Takeda, and Morphosys. ELA has received honoraria from Novartis Pharmaceuticals. CL is on the advisory board of Autolus

and ADC Therapeutics. YA serves on the scientific advisory boards or consults for Astellas, Bristol Myers Squibb, Daiichi Sankyo, Geron, KiTE, Pfizer, Rigel, and Servier and receives institutional trial support from AbbVie, ALX Oncology, Biomea, Biosight, Curis, and Novartis. AAP reports research funding (to institution) from Pfizer, Sumitomo, Incyte, Servier; honoraria from Jazz and AbbVie. RMS has served in a consulting/advisory role and/or received honoraria from Bristol Myers Squibb, Geron, Gilead Sciences Inc, Kura Oncology, Rigel, Servier, Syndax Pharmaceuticals and TScan Therapeutics and has participated in a Steering Committee for Servier. The remaining authors have no conflicts of interest to disclose.

Contributions

SJY designed the study, wrote the manuscript, and aided in data collection. WC performed analyses and assisted in manuscript writing. JJW, AS, EG, GSGM, TB, AI, CL, ESW, YA, MRL, ELA, and AS collected data and edited the manuscript. AAP and RMS designed the study, assisted in data collection, and assisted in manuscript writing.

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Data-sharing statement

All data reported within the manuscript and further may be available upon reasonable request to the corresponding author.

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