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Prediction of Early Death in Adults with Relapsed or Refractory Acute Myeloid Leukemia

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LETTER TO THE EDITOR

Despite declining early death rates following intensive chemotherapy in acute myeloid leukemia (AML) [1,2], patients undergoing curative-intent therapies remain at risk for treatment-related mortality (TRM). Given the individual variation in TRM risk [3], there has been interest in identifying patients at highest risk to possibly assign them to lower-intensity treatments. Our initial studies on TRM prediction focused on patients undergoing intensive chemotherapy for newly diagnosed AML. These efforts led to the TRM score (“ND-TRM” score), a multivariable measure that includes age, performance status, disease type (primary vs. secondary AML), creatinine, white blood cell (WBC) count, peripheral blood blast percentage, platelet count, and albumin [4]. In 2,238 adults with newly diagnosed AML treated at MD Anderson Cancer Center from 1995 to 2008, this score predicted death within 28 days of treatment initiation (“TRM”) with good accuracy as indicated by an area under receiver operator characteristic curve (AUC) of 0.82 [4]. At our institution, this ND-TRM score has since served to assign patients to intensive or non-intensive AML therapies, and although derived from patients with newly diagnosed AML, has also been used for those with relapsed/refractory AML disease. Here, we tested the ability of the ND-TRM score to

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POTENTIAL CONFLICT OF INTEREST

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predict early death in adults with relapsed/refractory AML, and evaluated which covariates are associated with early death in this population.

Via electronic database, we identified adults aged ≥ 18 years with relapsed/refractory AML or high-grade MDS ($\geq 10\%$ blasts) treated at our institution with intensive chemotherapy (defined as treatment as intense or more intense than standard “7+3” chemotherapy, i.e. containing cytarabine at a daily dose ≥ 100 mg/m²) from January 2008 to May 2014. We also identified a comparison cohort of patients aged ≥ 18 years with newly diagnosed AML treated with intensive chemotherapy over the same time period. Demographic, clinical and laboratory data were obtained from medical records. This study was approved by the Institutional Review Board, and clinical data were de-identified in compliance with the Health Insurance Portability and Accountability Act (HIPAA) regulations.

TRM was defined as death with 28 days of treatment initiation [4]. In addition, we used “death within 60 days” and “death within 90 days” as alternative definitions of early death. The simplified ND-TRM score was calculated as previously reported [4]. For newly diagnosed patients, only covariates required for calculation of the ND-TRM score were collected. For relapsed/refractory patients, the following additional covariates were collected: race (Caucasian or non-Caucasian), gender, cytogenetic risk at diagnosis [5], oxygen requirement, number of therapeutic (i.e. non-prophylactic) antibiotics at baseline, receipt of therapeutic antifungals at baseline, number of prior allogeneic or autologous hematopoietic cell transplantations (HCTs), duration of first complete remission (CR1), duration of the most recent CR, number of prior intensive chemotherapy cycles, time since the most recent intensive chemotherapy regimen, bilirubin, absolute neutrophil count (ANC), and hemoglobin (Hgb). Laboratory values were used only if available from one week or less prior to beginning treatment, and the value closest to start of treatment was chosen.

We conducted logistic regression analyses to assess the relationship between individual covariates and TRM, and then used the AUC to quantify a model’s ability to predict early death [4,6,7]. Generalized estimating equation (GEE) regression models were used to account for correlation within patients, as some patients may have had several salvage regimens and be represented in the dataset with more than one patient encounter. To select covariates for a multivariable model, we built ridge regression models for each outcome including all possible covariates. For each outcome we fixed the maximum number of covariates included in a final model based on the number of outcome events (two, four, and six covariates for TRM, 60 day mortality, and 90 day mortality, respectively). The covariates with the smallest ridge regression *P*-values were then put in a GEE model to estimate a final model for each outcome. Reported AUCs were bootstrapped 100 times to account for the model selection procedure. With this method, AUCs of 0.6–0.7, 0.7–0.8, and 0.8–0.9 indicate poor, fair, and good predictive ability, respectively [8–10]. All analyses were performed using R (<http://www.r-project.org>).

We identified 312 patients with relapsed or refractory AML or high-risk MDS treated with intensive chemotherapy at our institution between January 2008 to May 2014; all patients had sufficient data available for calculation of the ND-TRM score [4]. Of these, 83 had

refractory disease after 1–2 cycles of chemotherapy, and 229 had relapsed disease (Table 1). Among the 312 patients, 20 (6.4%) died within 28 days. Because of the low number of early deaths, patients with relapsed or refractory AML were analyzed as one cohort. Still the ND-TRM model [4] performed poorly, yielding an AUC of 0.68. One concern was that this poor performance was related to treatment era rather than relapsed/refractory disease status, as the model was developed in patients treated from 1995–2008 compared to our cohort of patients treated from 2008–2014. Therefore, we identified 285 patients with newly diagnosed AML treated with intensive induction chemotherapy from 2008–2014. Among these 285 patients, 17 (6.0%) died within 28 days, with the AUC of the ND-TRM score being 0.76. Since it might be hypothesized that pre-treated patients are less fit, we then examined whether relapsed/refractory disease status was an independent predictor of TRM. Combining the above 312 relapsed/refractory patients and 285 newly diagnosed patients yielded a cohort of 597 patients, with an AUC of the ND-TRM score of 0.72 for this combined group. Including disease status did not change the AUC, with an odds ratio (OR)=0.79 (95% CI: 0.39–1.60, $P=0.50$) for this covariate within multivariable analysis.

We then addressed whether TRM modeling could be improved for relapsed/refractory patients with additional clinical and laboratory covariates. For 273 of the 312 patients (88%), we had complete data for both the covariates required for calculation of the ND-TRM score and the additional covariates detailed above. Within this subset of 273 patients, 15 (5.5%) died within 28 days of treatment initiation, with AUC of 0.60 for the ND-TRM score. Univariate analyses identified several factors that were statistically significantly associated with day 28 mortality, including gender (female more likely), performance status, albumin, creatinine, peripheral blood blast percentage, oxygen requirement, and duration of first CR, with univariate AUCs for these covariates ranging from 0.59–0.74 (Supplemental Table 1). Several of these covariates overlapped with those found important for newly diagnosed AML (performance status, albumin, creatinine, and peripheral blood blast percentage) [4], further supporting the relevance of these covariates in predicting TRM following intensive therapy. We also identified factors specific to patients with relapsed/refractory AML (e.g. duration of first CR). Because of the relatively low TRM rate in our patient cohort (a rate comparable to that reported in recent clinical trials [11,12]), we were limited in our ability to build complex multivariable model that included all covariates that were statistically significant in univariate analyses. Nonetheless, a model with 2 covariates, performance status and creatinine, was able to predict TRM (“RR-TRM” score) with an AUC of 0.81 (Table 2). These two covariates were in the ND-TRM model, and the change in relative weighting of these covariates accounted for the AUC improvement compared to the original TRM model.

In addition to 28-day mortality, we also investigated the variables’ ability to predict 60- and 90-day mortality as alternative definitions of early death. In our subset of 273 patients with complete data, 268 and 266 had sufficient follow-up data at 60 and 90 days, respectively, for inclusion in multivariable models. Forty one patients (15.3%) died by day 60, and 67 (25.2%) died by day 90 after treatment initiation. Univariate analyses again identified several covariates that were statistically significantly associated with 60-day mortality (gender, disease type, performance status, albumin, oxygen requirement, with AUCs ranging from 0.54–0.68) or 90-day mortality (disease type, performance status, albumin, creatinine,

peripheral blood blast percentage, oxygen requirement, and duration of first and most recent CR, with AUCs ranging from 0.53–0.62) (Supplemental Table 1). Multivariable RR-TRM models for prediction of death at 60 and 90 days included a number of the above covariates and had predictive power similar to the day 28 model (AUCs of 0.81 and 0.78 respectively; Table 2). Notably, some covariates were consistently associated with early death regardless of time point chosen: performance status, albumin, and oxygen requirement. The similarity of these covariates to those in the ND-TRM model underscores their importance in predicting TRM.

Together, our studies identify covariates associated with early death in contemporary AML patients undergoing treatment for relapsed/refractory disease and suggest that accurate prediction of TRM with multivariable models is possible. Despite examining a relatively large patient cohort, our analyses are limited by the uncommon occurrence of TRM among contemporary patients. Analysis of additional very large patient cohorts treated with intensive chemotherapy will therefore be required for development of robust prediction models. Such cohorts will need to be well characterized for many covariates that are not typically available in AML patient databases. If confirmed, findings such as those described in our studies could improve the conduct of clinical trials in relapsed/refractory AML by providing quantitative “medical fitness” criteria for patient selection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Baseline patient characteristics of study cohort.

Parameter	All patients (n = 312)	Complete case cohort (n = 273)	P-value
Age [years], median (range)	54 (19–83)	52 (19–79)	<0.001
Male gender, n (%)	182 (58)	160 (59)	0.86
Race, n (%)			0.4
Caucasian	238 (77)	208 (76)	
Non-Caucasian	71 (23)	65 (24)	
Missing	3		
Disease type, n (%)			<0.001
De novo AML	209 (67)	196 (72)	
Secondary AML	103 (33)	77 (28)	
ECOG performance status, n (%)			0.35
0–1	220 (71)	195 (72)	
2–4	92 (29)	78 (28)	
Platelets [$\times 10^3/\mu\text{L}$], median (range)	41 (3–437)	39 (3–437)	0.093
Albumin [g/dL], median (range)	3 (1–5)	3 (1–5)	0.096
Creatinine [mg/dL], median (range)	1 (0–2)	1 (0–2)	0.92
Peripheral blood blast percentage (range)	3 (0–99)	3 (0–99)	0.055
ANC [cells/ μL], median (range)	725 (0–34080)	720 (0–34080)	0.4
Hgb [g/dL], median (range)	10 (6–14.9)	10 (6–14.9)	0.93
Cytogenetic risk at diagnosis ^a , n (%)			0.0074
Favorable	20 (7)	19 (7)	
Intermediate	194 (63)	180 (66)	
Adverse	92 (30)	74 (27)	
Missing	6		
Antibiotic treatments, n (%)			0.56
No	215 (70)	188 (69)	
Yes	94 (30)	85 (31)	

Parameter	All patients (n = 312)	Complete case cohort (n = 273)	P-value
Missing	3		
Antifungal treatments, n (%)			1
No	248 (80)	219 (80)	
Yes	61 (20)	54 (20)	
Missing	3		
Oxygen requirement, n (%)			0.37
No	298 (96)	264 (97)	
Yes	11 (4)	9 (3)	
Missing	3		
History of hematopoietic cell transplants, n (%)			0.38
No	251 (81)	218 (80)	
Yes	60 (19)	55 (20)	
Missing	1		
Duration of CR1, n (%)			<0.001
0 months (i.e. primary refractory AML)	83 (27)	62 (23)	
<6 months	111 (36)	100 (37)	
6 months	118 (38)	111 (41)	
Duration of most recent CR, n (%)			<0.001
0 months (i.e. refractory AML)	83 (27)	62 (23)	
<6 months	118 (38)	106 (39)	
6 months	111 (36)	115 (38)	
Number of prior intensive chemotherapy cycles, median (range)	3 (0–10)	3 (1–10)	<0.001
Time since last intensive treatment, n (%)			0.43
<3 months	148 (51)	142 (52)	
3 months	140 (49)	131 (48)	
Missing	24		
TRM score **, median (range)	5 (0–72)	4 (0–57)	0.0016

Abbreviations: AML, acute myeloid leukemia; ANC, absolute neutrophil count; CR, complete remission; CR1, first complete remission; ECOG, Eastern Cooperative Oncology Group; Hgb, hemoglobin; TRM, treatment-related mortality.

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* Risk based on modified MRC criteria [5].

** As calculated per the simplified model including age [4].

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TABLE 2

Multivariate models for prediction of mortality at 28 (TRM), 60 and 90 days after treatment initiation.

Day 28 model, AUC = 0.81, n = 273**			Day 60 model, AUC = 0.81, n = 268			Day 90 model, AUC = 0.78, n = 266		
Covariates	OR (95% CI)	P-value	Covariates	OR (95% CI)	P-value	Covariates	OR (95% CI)	P-value
ECOG performance status (2-4)	6.34 (1.88-21.78)	0.0029	ECOG performance status (2-4)	3.68 (1.67-8.0)	0.0012	ECOG performance status (2-4)	2.69 (1.43-5.26)	0.0021
Creatinine	4.4 (0.93-21.61)	0.061	Male gender	0.42 (0.20-0.88)	0.019	Creatinine	1.98 (0.69-5.80)	0.21
			Albumin	0.56 (0.33-1.02)	0.032	Albumin	0.53 (0.31-0.93)	0.026
			Secondary AML	0.35 (0.12-0.97)	0.048	Secondary AML	0.48 (0.22-1.03)	0.063
						Peripheral blood blast percentage	1.01 (1.00-1.02)	0.15
						Prior CR < 6 months*	4.36 (1.66-11.25)	0.0029
						Prior CR > 6 months*	1.71 (0.63-4.57)	0.29

Abbreviations: AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group; CR, complete remission.

* Compared to refractory AML (i.e. CR=0 months).

** For this model, the probability of early death is equal to $e^x / (1 + e^x)$, where for performance status of 0-1, $x = \log(4.4)$ * creatinine, and for performance status of 2-4, $x = \log(6.34) + \log(4.4)$ * creatinine.