White Blood Cell Count Nadir Following Intensive Chemotherapy is a Negative Predictive Factor for Treatment Outcomes in Patients with Acute Myeloid Leukemia

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Introduction

Acute Myeloid Leukemia (AML) is a common type of acute leukemia in older adults. The incidence of AML is 3-5 cases per 100,000 and median age of diagnosis is approximately 68 years. The 5-year survival rate for AML is 28.7%. Standard of care for patients with AML is intensive chemotherapy (induction), followed by some form of consolidation therapy An estimated 20% of adult patients with AML fail to achieve remission with initial induction therapy, and 50% experience relapse after achieving full remission. Identifying predictive factors for response to therapy can be clinically useful in risk stratifying patients. It is assumed that treatment efficacy depends on elimination of leukemic blasts, and thus the kinetics of white blood cell (WBC) elimination and nadir may serve as a predictive factor for response to therapy. We hypothesized that a low WBC nadir would be a positive predictive factor for response to intensive induction chemotherapy.

Methods and Statistical Analysis

- We performed a retrospective analysis of 162 newly-diagnosed AML patients treated with ≥1 round of intensive chemotherapy at University of Colorado Health and followed to initial response assessment or death.
- Mean patient age at initial treatment was 49.7 years, and initial treatment dates ranged from 2007-2020.
- WBC count was monitored for 28 days after initial treatment.
- WBC count <0.1*10^9/L was defined as a WBC nadir=0.
- Using Generalized Linear Model techniques and a logit link function, we performed a multivariate logistic regression analysis examining the relationship between WBC nadir, age (≥50 years), percent blasts in marrow, secondary AML, treatment-related AML, and ELN group with response.
- Response was examined via two definitions: complete response (CR) and CR with incomplete hematopoietic recovery (CRi).
- Overall survival (OS) and progression free survival (PFS) were compared using Kaplan-Meyer curve analysis
- Statistical analysis was performed in R 4.1.0.

Table 1. Patient Baseline Characteristics (N=162)

	WBC Nadir		Test	P-value
	No (n=125)	Yes (n=37)		
Age at Initial Treatment (yrs)				
Mean (SD)	48.4 (14.4)	54.1 (12.7)	T-test	0.022
Median (Min, Max)	52.2 (15.1, 73.5)	56.0 (24.2, 74.9)		
Age (Binary), n (%)				
<50 yrs old	57 (45.6%)	11 (29.7%)	Fisher's exact	0.126
≥50 yrs old	68 (54.4%)	26 (70.3%)		
Percent Blasts in Marrow (%)				
Mean (SD)	55.6 (24.3)	52.5 (24.7)	T-test	0.512
Median (Min, Max)	57.8 (5.0, 95.5)	53.5 (10.5, 95.5)		
Percent Blasts in Marrow (Binary), n (%)				
<50%	54 (43.2%)	13 (35.1%)	Fisher's exact	0.628
≥50%	70 (56.0%)	22 (59.5%)		
ELN Group, n (%)				
Adverse	38 (30.4%)	12 (32.4%)	Fisher's exact	0.442
Favorable	45 (36.0%)	9 (24.3%)		
Intermediate	18 (14.4%)	5 (13.5%)		
Unable to assess	24 (19.2%)	11 (29.7%)		
Secondary AML, n (%)				
No	98 (78.4%)	29 (78.4%)	Fisher's exact	1
Yes	27 (21.6%)	8 (21.6%)		
Treatment-Related AML, n (%)				
No	114 (91.2%)	33 (89.2%)	Chi-squared	0.749
Yes	11 (8.8%)	4 (10.8%)		

Results: Response to Therapy

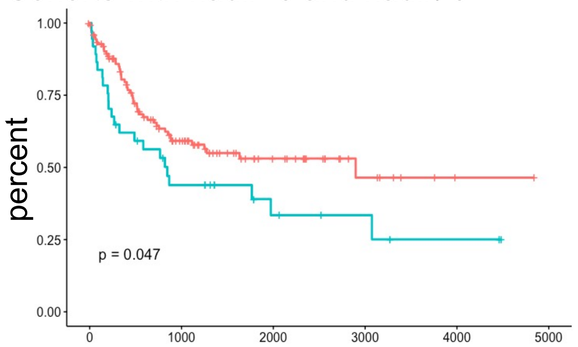
- Multivariate logistic regression analysis showed that WBC nadir=0, when controlling for the variables stated in methods, was significantly associated with reduced odds of response by both definitions.
- For complete response: OR: 0.295, 95% CI: 0.110-0.762, p=0.013.
- For complete response with incomplete hematopoietic recovery: OR: 0.298, 95% CI: 0.110-0.781, p=0.015.

Table 2. Multivariate Analysis of Odds Ratios For Response to Therapy by Both Definitions (N=162)

	1st Definition			2nd Definition		
	Odds Ratio	95% CI	P-value	Odds Ratio	95% CI	P-value
Intercept	1.620	(0.576, 4.860)	0.366	2.590	(0.890, 8.370)	0.092
WBC Nadir=0 (Yes)	0.295	(0.110, 0.762)	0.013	0.298	(0.110, 0.781)	0.015
Age (≥50 yrs)	0.900	(0.353, 2.280)	0.823	0.716	(0.268, 1.870)	0.496
Percent Blasts in Marrow (≥50%)	0.976	(0.365, 2.520)	0.960	1.050	(0.379, 2.810)	0.917
ELN Group (Favorable)	26.00	(6.530, 177.0)	<0.001	18.30	(4.550, 125.0)	<0.001
ELN Group (Intermediate)	4.900	(1.460, 20.00)	0.015	4.870	(1.320, 24.00)	0.028
ELN Group (Unable to Assess)	3.170	(1.130, 9.540)	0.033	2.440	(0.854, 7.420)	0.103
Secondary AML (Yes)	0.647	(0.183, 2.270)	0.493	0.497	(0.137, 1.770)	0.279
Treatment-Related AML (Yes)	0.485	(0.095, 2.330)	0.370	0.518	(0.102, 2.480)	0.414

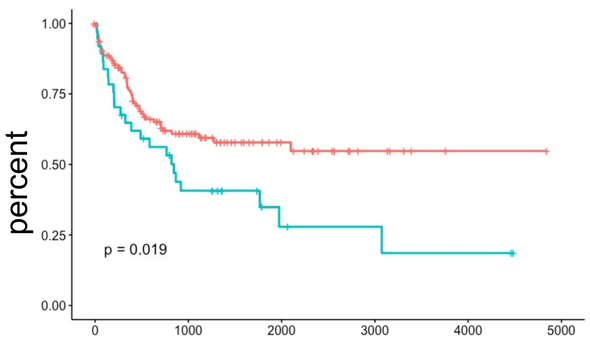
Overall Survival and Progression Free Survival

Figure 1. Overall Survival Between Cohorts with nadir=0 and nadir≠0



Time from initial treatment (days)

Figure 2. Progression Free Survival Between Cohorts with nadir=0 and nadir≠0



Time from initial treatment (days)

- In both figures above, red indicates patients with WBC nadir≠0 and blue indicates patients with WBC=0
- Patients with WBC nadir=0 had significantly reduced OS (p=0.047), and PFS (p=0.019)

Key Findings

- In patients with AML treated with initial intensive therapy, WBC nadir=0 is a negative predictive factor for response to therapy.
- In patients with AML treated with initial intensive therapy, WBC nadir=0 is associated with reduced OS and PFS.

Summary and Conclusions

- In patients with AML treated with initial intensive therapy, WBC nadir=0 is a negative predictive factor for response to therapy.
- Contrary to our clinical assumptions, a low absolute WBC is correlated to poor treatment outcomes.
- A low absolute WBC is also correlated with reduced overall survival and progression free survival.