Published in final edited form as:

J Pediatr Hematol Oncol. 2019 January ; 41(1): 51–55. doi:10.1097/MPH.0000000000001280.

Risk Markers for Significant Bleeding and Thrombosis in Pediatric Acute Promyelocytic Leukemia; Report From the Children's Oncology Group Study AAML0631

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Summary:

Acute promyelocytic leukemia (APL) is characterized by a heightened risk of coagulopathy with significant morbidity and mortality. Here we report our evaluation of presenting white blood cell (WBC) and the International Society on Thrombosis and Haemostasis (ISTH) disseminated intravascular coagulation (DIC) scoring system as markers for early death and nonlethal coagulopathy in pediatric APL. We evaluated 79 pediatric patients treated on a Children's Oncology Group phase III clinical trial. There were 4 early deaths and 13 nonlethal, clinically significant (grade III to IV) coagulopathy events during induction. Elevated presenting WBC was significantly associated with early death but not with both lethal and nonlethal coagulopathy events. An ISTH DIC score of ≥ 5 (the original ISTH criteria for overt DIC) was not associated with either early deaths or coagulopathy events. An ISTH DIC score threshold of 6, however, was significantly associated with early death (12% score ≥ 6 vs. 0% score <6) and with both lethal and nonlethal coagulopathy events (35% score ≥ 6 vs. 11% score <6). In pediatric APL patients, the presenting WBC is a marker for risk of early death. Although the ISTH score using a cutoff of ≥ 6 showed improved correlation with adverse coagulation events during induction, the sensitivity was only 70.6% (95% confidence interval, 44.0%–89.7%) and the specificity was 64.5% (95%

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The authors declare no conflict of interest.

confidence interval, 51.3%–76.3%). Thus, there is a strong need to identify other biomarkers that can predict APL-associated coagulopathy.

Keywords

acute promyelocytic leukemia; pediatrics; coagulopathy; hemorrhage; thrombosis

Survival rates for acute promyelocytic leukemia (APL) have improved significantly with the use of targeted therapies including all-trans retinoic acid (ATRA) and arsenic trioxide. Although these therapies have greatly decreased relapse risk, a significant proportion of patients with APL suffer early death or morbidity due to coagulopathy. These events remain a major barrier to cure of all APL patients. This coagulopathy generally occurs early in the disease course before or within several weeks of initiation of antileukemic therapy.¹ Although the term disseminated intravascular coagulation (DIC) is sometimes used interchangeably with APL coagulopathy, unique characteristics of APL blasts distinguish the pathogenesis of APL coagulopathy.² APL blasts augment procoagulant activity due to an increased expression of tissue factor and a unique cysteine protease (a procoagulant). Microparticles from APL blasts further contribute to activation of the coagulation cascade. APL blasts stimulate fibrinolysis through increased expression of Annexin 2, tissue plasminogen activator and urokinase like plasminogen activator receptor.³ Increased elastase in APL cells cleaves fibrinogen which leads to increased primary fibrinolysis and secondary fibrinolysis. Depletion of α_2 antiplasmin and decreased expression of thrombin activatable fibrinolysis inhibitor also contribute to the hyperfibrinolytic state. Thus, APL coagulopathy is characterized by increased thrombin production with a prominent decrease in fibrinogen by a consumptive process and due to exaggerated fibrinolysis. In addition, production of cytokines by APL blasts causes downregulation of thrombomodulin (which results in an anticoagulant effects as thrombomodulin is a cell surface receptor for thrombin), activation of the coagulation cascade, an increase in vascular permeability, and diminished vascular integrity.

Two recent epidemiological studies suggest that early death rates have not fallen as much as expected following the introduction of ATRA. The Swedish registry reported 105 patients with APL presenting between 1997 and 2006. Thirty patients (29%) died within 30 days (median, 4 d) with the majority (28/30) dying within 14 days from diagnosis. In total, 41% of these deaths were reported to be due to hemorrhage.⁴ In addition, the USA Surveillance, Epidemiology and End Results program reported 1400 patients with APL between 1992 and 2007. In this study early death rate was reported to occur in 17.3% of patients reflecting only a modest change in early death rate over time.⁵

The brain and the lungs are the most common site of lethal hemorrhage and the median times to intracranial and pulmonary hemorrhage are 6 and 9 days, respectively.⁶ In addition, the occurrence of intracranial hemorrhage has been associated with a higher risk of central nervous system (CNS) seeding and CNS relapse. CNS hemorrhage during induction chemotherapy was shown to be an independent risk factor for later CNS relapse in patients on the 2 consecutive PETHEMA trials (LPA96 and LPA 99).⁶ Also of note, the incidence of

thrombotic events is likely underestimated in patients with APL. Recent studies have shown that patients with APL are susceptible to both arterial and venous thrombotic events, and the incidence of thrombosis in APL is higher (up to 10%) than in any other form of leukemia including acute lymphoblastic leukemia (where prothrombotic medications such as asparaginase and steroids are used).⁷

Currently, clinicians attempt to manage the problem of APL coagulopathy through blood product support which is clearly inadequate in a subset of patients. Clinicians could benefit from a predictive model that identifies those patients most in need of prophylactic and/or therapeutic interventions. Further, such a model could help identify target populations for clinical trials of novel coagulation modifying treatments such as recombinant thrombomodulin.⁸

The International Society on Thrombosis and Haemostasis (ISTH) disseminated DIC scoring system was developed objective criteria for establishing the diagnosis and grading the severity of DIC with a score of 5 correlating with overt DIC.⁹ When applied to coagulopathy in APL, one retrospective study of 56 adult patients with APL showed that an ISTH DIC score of 6 independently correlated with early hemorrhagic death.¹⁰ It is important to examine coagulopathy in a purely pediatric population because both the risk of coagulopathy and the severity of events resulting from coagulopathy may differ between adults and children. Here, we report on an investigation of the predictive value of the ISTH DIC score and presenting white blood cell (WBC) for pediatric patients with newly diagnosed APL treated on Children's Oncology Group (COG) study AAML0631.

METHODS

The COG AAML0631 clinical trial was a phase III, nonrandomized, cooperative group trial open to patients age 2 to below 22 years with previously untreated APL confirmed by PML-RARA reverse transcription polymerase chain reaction. There were no exclusion criteria based on performance status or presence of active coagulopathy. High risk (HR) APL and standard risk (SR) APL were defined as presenting WBC count of $\geq 10,000$ and $<10,000$ cells/ μL , respectively. Induction therapy included ATRA 12.5 mg/ m^2 /dose twice daily on days 1 to 30 and idarubicin 12 mg/ m^2 /dose once daily on days 1, 3, 5 for HR APL or days 3, 5, 7 for SR APL. Survival results from the AAML0631 trial have previously been published.¹¹ Protocol guidelines regarding management of coagulopathy included maintenance of the platelet count $> 50,000/\mu\text{L}$ and the fibrinogen above 100 mg/dL during the first 10 days of induction therapy or until the coagulopathy has resolved. Routine use of heparin or antifibrinolytics was not recommended.

Coagulopathy adverse events (those related to bleeding or thrombosis) were to be reported if grade 3 or higher by the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4. The Fisher exact test was used to determine the significance of correlation between coagulopathy adverse events during induction therapy and risk grouping (including WBC count and ISTH DIC score). Coagulopathy adverse events were limited to clinically significant (grade 3 or higher) bleeding or thrombosis and did not include adverse event reports of just laboratory abnormalities such as "fibrinogen decreased." Early death

was defined as death due to any cause that occurred during induction therapy. Sensitivity and specificity of the ISTH DIC score ≥ 6 were calculated relative to the occurrence of at least 1 grade 3 or higher coagulopathy event occurring during induction. Exact 95% confidence intervals (CI) were calculated for sensitivity and specificity. The ISTH DIC score was calculated per the ISTH published guideline (Table 1) and specific D-dimer cutoffs were derived from a previously published APL DIC study.^{9,10} Coagulation parameter results from tests obtained at initial enrollment onto the trial were used to calculate the ISTH DIC score.

This study received approval from an institutional review board for the protection of human subjects. Also patients and their families provided informed consent or assent for the COG AAML0631 clinical trial. The trial was conducted in accordance with the Declaration of Helsinki. The trial was registered at <http://www.clinicaltrials.gov> as NCT00866918.

RESULTS

Of 108 patients enrolled on AAML0631, 101 were deemed eligible and 7 patients were ineligible due to negative PML-RARA reverse transcription polymerase chain reaction testing at diagnosis. Complete data on coagulation parameters at diagnosis (for ISTH DIC score calculation) were available for 79 patients, and no patients were lost to follow-up. Thirteen patients had grade III to IV coagulopathy events, and 4 patients died during induction with each having coagulopathy as a contributing factor (Table 2). There was no significant difference in the prevalence of early deaths (grade V events) or early deaths plus grade III to IV coagulopathy adverse events comparing the 79 patients with complete coagulation parameter data for ISTH DIC scoring versus the 22 patients with incomplete data (Table 3). Thus, there is no indication that our outcome analysis would be biased by excluding the minority of patients with missing coagulation data. The subsequent analyses include only those patients with complete data for scoring.

WBC at diagnosis is a known risk factor for poor outcomes, including early deaths, in APL. We evaluated the rates of early death and coagulopathy adverse events comparing patients with HR APL (WBC $\geq 10,000$ cells/ μ L; N = 27) to those with SR APL (WBC $< 10,000$ cells/ μ L; N = 52). Early death rate was significantly different between SR and HR APL with all deaths occurring in HR APL patients (SR APL 0% vs. HR APL 15%; $P = 0.012$). Next we evaluated the prognostic value of risk group in predicting the combined prevalence of early death events and nonlethal grade III and IV bleeding and thrombosis adverse events. Risk grouping by WBC was not significantly associated with these events (SR APL 17% and HR APL 30%; $P = 0.253$).

We calculated ISTH DIC score (Table 1) and correlated score with coagulopathy outcome to determine whether this might be a better predictor of these events than diagnostic WBC-risk grouping. We evaluated score cutoffs of both 5 (as proposed in the original publication as suggestive of DIC) and 6 (as published in a series of adult APL patients). Comparing patients with score of ≥ 5 (N = 69, 87%) versus score of < 5 (N = 10, 13%), there was no significant difference in the prevalence of early deaths (6% vs. 0%, respectively; $P = 1.0$) or prevalence of early deaths and coagulopathy adverse events (23% vs. 10%, respectively; $P = 0.681$; Table 3). However, when comparing patients with ISTH DIC score of ≥ 6 (N = 34,

43%) versus score of ≤ 6 ($N = 45$, 57%) there was a difference in early death rate. ISTH DIC score ≥ 6 was significantly associated with a higher rate of grade V events (deaths) during induction compared with score ≤ 6 (12% vs. 0%; $P = 0.031$; Table 3). The 4 patients who died in induction had ISTH DIC scores of 6 ($N = 1$), 7 ($N = 2$), and 8 ($N = 1$). Next we analyzed clinically significant coagulopathy events by combining early death events and nonlethal grade III and IV bleeding and thrombosis adverse events. Patients with ISTH DIC score ≥ 6 also had a significantly increased rate of these events compared with those with score ≤ 6 (35% vs. 11%, respectively; $P = 0.013$; Table 3). The sensitivity of the ISTH DIC score ≥ 6 in predicting patients experiencing at least 1 lethal or nonlethal coagulopathy event during induction was 70.6% (95% CI, 44.0%–89.7%) and the specificity was 64.5% (95% CI, 51.3%–76.3%). For the HR Group, sensitivity was 87.5% (95% CI, 47.4%–99.7%) and the specificity was 42.1% (95% CI, 20.3%–66.5%). For the SR group, the sensitivity was 55.6% (95% CI, 21.2%–86.3%) and the specificity was 74.4% (95% CI, 58.8%–86.5%).

DISCUSSION

Early death during induction and morbidity due to coagulopathy remain significant concerns for children diagnosed with APL. On the COG AAML0631 clinical trial, which was the study cohort of this analysis, the early death rate (4%) was similar to the relapse rate at 3 years (4%).¹¹ This highlights the need to prevent early death to further improve cure of this disease. Furthermore, clinically significant bleeding in the CNS may be associated with a higher risk of late CNS relapse. Predictive models are important to identify the patients at highest risk for these complications who require more aggressive supportive care and may be candidates for testing novel preventive strategies. WBC at presentation is a well-validated marker for poor outcome in APL and is one of the best prognostic markers for overall survival and relapse risk. Our results further support WBC at presentation as a prognostic marker for early death, but as a single measure it failed to predict significant coagulopathy events that contribute to the morbidity of this disease. A recent retrospective study of several international pediatric study groups evaluated multiple clinical criteria as risk factors for early death due to coagulopathy in pediatric APL. In multivariate analysis, they identified presenting WBC and body mass index (obesity) as independent risk factors.¹² Their analysis, however, differed significantly from our study as they analyzed individual clinical features and several lab values (WBC, blast count, platelet count, and hemoglobin) without utilizing a scoring system to combine multiple coagulation results. We investigated use of the ISTH DIC scoring system as a predictive model that might allow specific supportive care to favorably impact the course of these serious and lethal disease complications.

Original guidelines for use of the ISTH DIC score included a score of ≥ 5 as suggestive of overt DIC.⁹ The distribution of DIC scores in our cohort was as follows: score 0 ($N = 0$), score 1 ($N = 0$), score 2 ($N = 2$), score 3 ($N = 4$), score 4 ($N = 4$), score 5 ($N = 35$), score 6 ($N = 19$), score 7 ($N = 10$), and score 8 ($N = 5$). Therefore most patients (87%) with APL on our trial had an ISTH DIC score ≥ 5 , and thus this score threshold is too low to effectively identify those patients at most risk for clinically significant bleeding and thrombosis. Indeed our analysis showed that an ISTH DIC score cutoff of 5 could not predict early death or significant coagulopathy events. There could be several reasons for this. First, the original ISTH DIC score was developed to primarily identify DIC associated with infections, trauma,

and other nonmalignant conditions. In patients with leukemia, the platelet count is low due to bone marrow infiltration thus increasing the total score while not reflecting the true nature of the coagulopathy. Second, this scoring system and the associated laboratory cutoffs were developed for an adult population. Pediatric-specific investigations, such as our analysis, are important to validate or revise the scoring system. Third, the physiology of coagulopathy in APL is distinct from infection-related DIC. Thus, APL may require a cutoff score that is different from other nonmalignant conditions to provide a better predictor of coagulopathy. Previously reported data in adult APL, suggested that an ISTH DIC score ≥ 6 may better predict coagulopathy-related events in APL.¹⁰ Our analysis supported a similar conclusion for pediatric patients with APL. An ISTH DIC score ≥ 6 was predictive of both early death and significant coagulopathy events.

Several scoring systems have been developed to predict the adverse outcomes after DIC: the Japanese Ministry of Health and Welfare's DIC diagnostic criteria (JMHW criteria), the ISTH's DIC diagnostic criteria (ISTH DIC score), and the Japanese Association for Acute Medicine's DIC diagnostic criteria (JAAM criteria).¹³ The JMWH score allocates 1 point each to bleeding and organ failure, whereas the JAAM criteria incorporate a systemic inflammatory response syndrome (SIRS) score. As our primary intention was to utilize a score that could be used in future trials to predict clinical events, we did not choose the JMWH criteria where the score was calculated after an adverse event (bleeding and organ failure). Also, most patients with APL do not present with typical SIRS symptoms and therefore we believed that the JAAM criterion would not be of utility for this study, the ISTH DIC scoring system utilizes easy to measure coagulation parameters. Such predictive tools are critical to helping clinicians appropriately prevent and treat the devastating coagulopathy events that characterize APL.

Our study had limitations in the availability of data for the study population. Coagulation testing was recommended for all patients; however, 3 patients did not have data on activated partial thromboplastin time value, 1 patient did not have data on fibrinogen levels, and 18 patients had missing data on D-Dimer values. Thus, the ISTH DIC score could be calculated for 79 patients for use in the risk score analysis. However, we believe that these missing data do not cause a bias. In this trial, no patients were excluded based on performance status or presence of active coagulopathy. Further, as presented in Table 3, there was no difference in the adverse events rate in patients who had missing data compared with those with complete data, and thus these seem to be similar populations without selection bias.

This study shows that aggressive supportive care should be advocated for patients with high WBC at presentation and for those with an ISTH DIC score ≥ 6 . Neither of these markers, however, provide a perfect predictive model. We found that ISTH DIC score ≥ 6 had sensitivities and specificities of $<90\%$ for the entire cohort and for both WBC-based risk groups. Traditional coagulation tests (such as those used to calculate the ISTH DIC score) cannot measure the unique contribution of fibrinolysis or the balance between coagulation and fibrinolysis that underlies APL coagulopathy. Thus, until better models are available, it may be best to utilize aggressive coagulation supportive care in all pediatric APL patients. Testing of other biomarkers and coagulation assays, including thrombomodulin levels and thrombin generation, ought to be studied for their predictive value and to inform potential

intervention strategies. Such prospective studies are underway in the current Children's Oncology Group clinical trial for APL.

Acknowledgments

Supported by NIH grants to the Children's Oncology Group including U10-CA98543 (Chair's Grant), U10-CA98413 (Statistics and Data Center Grant), U10CA180886 (NCTN Operations Center Grant), and U10CA180899 (NCTN Statistics and Data Center). Generous funding was also provided by The St Baldrick's foundation to support the AAML0631 trial and by The Andrew McDonough B+ Foundation for statistical support.

The contents of this report are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

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TABLE 1.

ISTH DIC Scoring System

Score	Platelet Count (cells/ μ L)	Fibrinogen Level (mg/dL)	Prothrombin Time (Seconds Above Upper Limit of Normal)	D-dimer (Times the Upper Limit of Normal)
0	100,000	100	<3	<2
1	50,000-99,999	<100	3–6	NA
2	<50,000	NA	>6	2-4
3	NA	NA	NA	>4

DIC indicates disseminated intravascular coagulation; ISTH, International Society on Thrombosis and Haemostasis; NA, not available.

TABLE 2.

Description of Significant Coagulopathy Events and Deaths During Induction

Patients With Nonlethal Grade 3 or 4 Coagulopathy Events	Patient	Risk Group	ISTH DIC Score	DIC	Vitreous Hemorrhage	Oral Hemorrhage	Rectal Hemorrhage	Intracranial Hemorrhage	Hematuria	Thromboembolic Event
Patients with death during induction	1	SR	8	No	No	No	No	No	No	Yes
	2	HR	7	No	No	No	No	No	No	Yes
	3	SR	6	Yes	No	No	No	No	No	No
	4	SR	6	No	No	Yes	No	No	No	No
	5	HR	6	Yes	No	No	No	No	No	No
	6	SR	6	No	No	No	Yes	No	No	No
	7	SR	6	Yes	No	No	No	No	No	No
	8	HR	6	Yes	No	No	No	No	No	No
	9	HR	5	Yes	No	No	No	No	No	No
	10	SR	5	No	Yes	No	No	No	No	No
	11	SR	5	No	No	No	No	No	Yes	No
	12	SR	5	Yes	No	No	No	No	No	No
	13	SR	4	No	No	No	No	No	No	Yes
Description of death										
14	HR	8	Cerebral edema from likely ischemic event and death from respiratory failure on day 2 of induction							
15	HR	7	Intracranial hemorrhage and respiratory failure on day 2 of induction and death with DIC and Acinetobacter baumannii sepsis on day 14 of induction							
16	HR	7	Acidosis, DIC, and multiorgan failure and died on day 1 of induction							
17	HR	6	Coagulopathy and respiratory distress before starting therapy requiring intubation and then died with multiorgan failure on day 1 of induction							

DIC indicates disseminated intravascular coagulation; HR, high risk; ISTH, International Society on Thrombosis and Haemostasis; SR, standard risk.

TABLE 3.

Evaluation of Coagulopathy Adverse Event Prevalence by Availability of Scoring Data, WBC at Diagnosis, and 2 ISTH DIC Score Thresholds

	Grade III-V Coagulopathy Adverse Events		Grade V Adverse Events	
	n (%)	P	n (%)	P
Complete scoring data (N = 79)	17 (22)	0.552	4 (5)	0.574
Incomplete data (N = 22)	3 (14)	—	0 (0)	—
WBC 10,000 cells/ μ L (N = 27)	8 (30)	0.253	4 (15)	0.012
WBC < 10,000 cells/ μ L (N = 52)	9 (17)	—	0 (0)	—
ISTH DIC Score 5 (N = 69)	16 (23)	0.681	4 (6)	1.000
ISTH DIC Score <5 (N = 10)	1 (10)	—	0 (0)	—
ISTH DIC Score 6 (N = 34)	12 (35)	0.013	4 (12)	0.031
ISTH DIC Score <6 (N = 45)	5 (11)	—	0 (0)	—

Bold type indicates statistically significant result with $P < 0.05$.

DIC indicates disseminated intravascular coagulation; ISTH, International Society on Thrombosis and Haemostasis; WBC, white blood cell.