Leukemia Research 83 (2019) 106174

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Letter to the Editor

Fibrinogen consumption and use of heparin are risk factors for delayed bleeding during acute promyelocytic leukemia induction

1. Introduction/methods

Acute promyelocytic leukemia (APL) is characterized by distinct treatment paradigms and coagulopathy-related complications during induction therapy. APL is classified by a translocation between chromosomes 15 and 17, resulting in clonal expansion of premature promyelocytes [1]. Long-term outcomes have improved with incorporation of all-trans retinoic acid (ATRA) into standard regimens [2]. ATRA and arsenic trioxide (ATO) alone have further improved outcomes in patients with baseline WBC ≤ 10 k/ul [3]. Unfortunately, despite improved long term survival, mortality in the first 30 days remains the most common cause of treatment failure [4,5]. Hemorrhagic complications, particularly intracerebral hemorrhage, are the most common cause of early death [4,5]. The prediction of early death in newly diagnosed APL patients remains a challenging barrier to improving outcomes. Both single institution and registry reports have indicated that while many hemorrhagic deaths occur between day 0–4, up to half of events occur during day 5–30 of induction treatment [6–8]. There is limited literature comparing the etiologies of early (days 0–4) and delayed (days 5–30) bleeding events [9].

This study aims to explore differences in early versus delayed hemorrhagic events. Hemorrhagic events on presentation and during the first 4 days of therapy are frequently unavoidable due to delays in presentation and preexisting profound coagulopathy. A greater understanding of bleeding events after day 4, when initial treatment protocols and supportive care paradigms have been initiated, may identify modifiable risk factors for these delayed events.

Adult patients (≥age 18 years) with a diagnosis of APL between January 2000 and September 2018 at the Johns Hopkins Hospital were included. Diagnosis was confirmed by florescence in situ hybridization or conventional karyotyping revealing translocation between chromosomes 15 and 17, or reverse transcriptase polymerase chain reaction (RT-PCR) for the PML-RARA fusion gene. Two patients with bleeding at an unknown time were excluded. Standard induction chemotherapy during the study period included ATRA combined with an anthracycline. ATO was included in consolidation for many patients [10]. After 2013, ATO has been substituted for anthracyclines in patients with initial WBC ≤ 10 k/ul [3]. Coagulopathy management included platelet transfusion to goal > 50 k/ul and cryoprecipitate or plasma to maintain fibrinogen > 100-150 mg/dl. Low-dose heparin infusions were occasionally used for refractory disseminated intravascular coagulation (DIC).

Data were obtained via retrospective chart review approved by the institutional review board. Bleeding was documented via clinical assessment and imaging reports. In patients with multiple bleeding events, the day of bleed was determined by the initial event. Epistaxis and bruising were not considered bleeding events. Percentage drop in fibrinogen was measured from the peak fibrinogen level day 1–6 to the fibrinogen nadir day 6–10. This was a planned metric to measure fibrinogen consumption in the days after patients receiving our standard protocols received their initial anthracycline.

Categorical variables are reported as proportions and compared using the chi-squared test with two-tailed p values (Fisher's exact test used where noted). Continuous variables without a normal distribution were compared using the Mann-Whitney U test for two groups, and one-way ANOVA for more than two groups. Multivariate logistic regression analysis was used to investigate associations with $p < 0.10$ in the univariate analysis. Comparisons between groups were completed using SAS version 9.4 (SAS Institute Inc, Cary, NC) and GraphPad Prism version 7.04 (GraphPad Software, La Jolla, CA).

2. Results

A total of 149 patients with newly-diagnosed APL were included and have characteristics listed in Table 1. In this cohort, 46 (30.9%) patients had a bleeding event during the first 30 days of therapy (Fig. 1A). Bleeding events included 17 intracranial, 6 gastrointestinal, 10 retinal and orbital, 9 pulmonary, and 10 in other locations (patients with multiple sites included for each site). There were 28 early and 18 late bleeding events. The mean platelet count at time of delayed bleeding was significantly higher than platelet count at time of an early bleed (30.8 and 57.9 k/ul, respectively, $p = 0.006$, Fig. 1B). Median baseline WBC was 16.5 k/ul for patients with an early bleed, and 5.9 k/ul for those with a delayed bleed ($p = 0.259$). There was no significant difference in total delayed bleeds between patients treated with ATRA + anthracycline and ATRA + ATO. Eight patients developed an intracerebral hemorrhage (ICH) after day 4, all of whom had been treated with an anthracycline-including regimen; two were fatal, both on day 9.

Eight of 40 (20.0%) patients with a ≥50% decline in fibrinogen between peak value day 1–6 and nadir day 6–10 had a delayed bleed, compared with 9/104 (8.7%) without ≥50% fibrinogen decline ($p = 0.074$). There was a significant difference in the fibrinogen decline between patients with a delayed bleeding event and those without a

https://doi.org/10.1016/j.leukres.2019.106174
Received 22 March 2019
Available online 21 June 2019

Table 1
Patient characteristics and bleeding event outcomes.

	All Patients (%) (n = 149)	No Bleed (%) (n = 103)[a]	Early Bleed Day 0-4 (%) (n = 28)	Delayed Bleed Day 5-30 (%) (n = 18)	p value (Delayed Bleed vs No Bleed)
Age (years)					
< 50	75 (50.3)	53 (70.7)	15 (20.0)	7 (9.3)	0.32
≥50	74 (49.7)	50 (67.6)	13 (17.6)	11 (14.9)	
Sex					
Male	69 (46.3)	43 (62.3)	18 (26.1)	8 (11.6)	0.83
Female	80 (53.7)	60 (75.0)	10 (12.5)	10 (12.5)	
Baseline WBC (k/ul)					
< 3	78 (52.3)	65 (83.3)	7 (9.0)	6 (7.7)	0.59
3-10	27 (18.1)	17 (63.0)	5 (18.5)	5 (18.5)	
> 10	44 (29.5)	21 (47.7)	16 (36.4)	7 (15.9)	
Baseline PLT (k/ul)					
≤40	99 (66.4)	62 (62.6)	25 (25.3)	12 (12.1)	0.60
> 40	50 (33.6)	41 (82.0)	3 (6.0)	6 (12.0)	
Baseline Hb (g/dL)					
< 9	66 (44.3)	43 (65.2)	18 (27.3)	5 (7.6)	0.26
≥9	83 (55.7)	60 (72.3)	10 (12.0)	13 (15.7)	
Peripheral Blasts[b]					
None reported	75 (50.7)	60 (80.0)	6 (8.0)	9 (12.0)	0.61
1-49%	46 (31.1)	28 (60.9)	11 (23.9)	7 (15.2)	
≥50%	27 (18.2)	14 (51.9)	11 (40.7)	2 (7.4)	
Baseline LDH (U/L)[b]					
≤440	101 (68.2)	80 (79.2)	12 (11.9)	9 (8.9)	0.02[c]
> 440	47 (31.8)	23 (48.9)	15 (31.9)	9 (19.1)	
Sanz risk score:					
Low	43 (28.9)	36 (83.7)	2 (4.7)	5 (11.6)	0.22
Intermediate	62 (41.6)	46 (74.2)	10 (16.1)	6 (9.7)	
High	44 (29.5)	21 (47.7)	16 (36.4)	7 (15.9)	
Baseline FBG					
< 150	47 (31.8)	32 (68.1)	9 (19.1)	6 (12.8)	0.86
≥150	101 (68.2)	70 (69.3)	19 (18.8)	12 (11.9)	
Baseline Cr (mg/dL)					
≤1.3	134 (89.9)	97 (72.4)	21 (15.7)	16 (11.9)	0.33[c]
> 1.3	15 (10.1)	6 (40.0)	7 (46.7)	2 (13.3)	
FLT3-ITD Mutation					
Absent	41 (27.5)	33 (80.5)	3 (7.3)	5 (12.2)	0.09[d]
Present	36 (24.2)	21 (58.3)	7 (19.4)	8 (22.2)	
Not Tested	72 (48.3)	49 (68.1)	18 (25.0)	5 (6.9)	
PML-RARA Isoform					
bcr-1/L or 2/V	45 (30.2)	32 (71.1)	10 (22.2)	3 (6.7)	0.13[c]
bcr-3/S	31 (20.8)	18 (58.1)	7 (22.6)	6 (19.4)	
Not Tested	73 (49.0)	53 (72.6)	11 (15.1)	9 (12.3)	
Treatment					
ATRA + Anthra	114 (76.5)	79 (69.3)	21 (18.4)	14 (12.3)	1.0[c], [e]
ATRA + ATO	30 (20.1)	22 (73.3)	5 (16.7)	3 (10.0)	
TRA + ATO + GO	2 (1.3)	0 (0)	1 (50.0)	1 (50.0)	
ATRA	3 (2.0)	2 (66.7)	1 (33.3)	0 (0)	
Day 6-10 FBG					
Decline < 50%	104 (69.8)	76 (73.1)	19 (18.3)	9 (8.7)	0.074
Decline ≥50%	40 (26.8)	24 (60.0)	8 (20.0)	8 (20.0)	
Unknown	5 (3.4)	3 (60.0)	1 (20.0)	1 (20.0)	
Heparin Exposure					
No	108 (72.5)	86 (79.6)	19 (17.6)	3 (2.8)	< 0.001[c]
Yes	41 (27.5)	17 (41.5)	9 (22.0)	15 (36.6)	

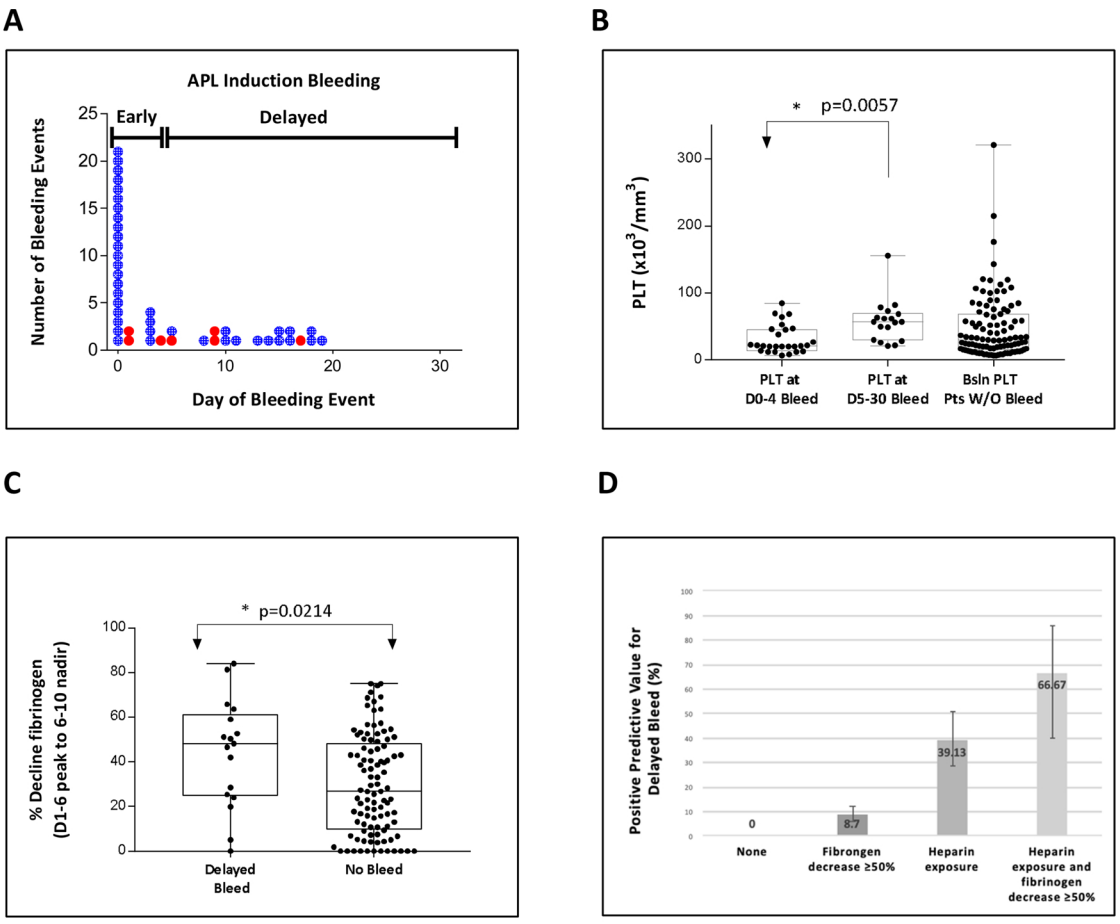
[a] Reference group for comparison with delayed bleeding group.
[b] 1 patient with missing data.
[c] Fisher's exact test.
[d] Comparison of patients with positive versus negative FLT3-ITD testing, excluding those without testing.
[e] Comparison of ATRA + Anthracycline with ATRA + ATO.

bleeding event (median fibrinogen decline 48.2% versus 26.8%, respectively; p = 0.021; Fig. 1C). Median fibrinogen level at the time of delayed bleeding was 371 mg/dL.

Fifteen of 41 (36.6%) patients exposed to intravenous heparin during induction experienced a delayed bleeding event, while 3/108 (2.8%) not exposed to heparin experienced a delayed bleeding event (p < 0.001). Eight of 15 patients exposed to heparin who developed a delayed bleed had been treated with a low-dose heparin infusion for disseminated intravascular coagulation. Five of 7 patients exposed to full-strength heparin were being treated for pulmonary emboli. Fig. 1D depicts a delayed bleeding risk score based upon fibrinogen decrease ≥50% and use of heparin. Fig. 1E shows a multivariate analysis of factors associated with delayed bleeding.

3. Discussion

While more recent advances in APL therapy as well as supportive care have improved outcomes for APL patients, death in the initial 30



E

Multivariate Analysis of Risk for Delayed Bleed

	Adjusted Odds Ratio (95% Confidence Interval)	p value
Fibrinogen Decline ≥50%	8.71 (1.27-59.72)	0.027
FLT3-ITD Present	0.62 (0.107-3.606)	0.59
Baseline LDH >2x ULN (440 U/L)	2.16 (0.39-11.90)	0.37
Heparin Exposure	25.22 (3.22-197.21)	<0.001

Fig. 1. A. Bleeding events by day of induction therapy. Bleeding events prior to admission were considered to have occurred on day 0. Blue markers indicate a nonfatal bleeding event, red icons indicate fatal bleeding events. B. Plot representing platelet count at time of early bleed, delayed bleed, and baseline in patients without bleeding event. * represents a statistically significant difference between groups in 1-way ANOVA with Dunn's multiple comparisons test. C. Plot representing the percentage decrease from peak fibrinogen day 1–6 to nadir fibrinogen day 6–10. * represents a statistically significant difference between groups in Mann Whitney test. D. Positive predictive value with 95% confidence intervals for a delayed bleed based upon fibrinogen decrease ≥50% day 6–10 and exposure to heparin. Absolute values for delayed bleeding events for patients with available data: none (0/62), fibrinogen decrease ≥50% (2/23), heparin exposure (9/23), and both heparin exposure and fibrinogen decrease ≥50% (6/9). E. Multivariate logistic regression of associations with $p < 0.10$ on univariate analysis (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).
Abbreviations: Bsln, baseline; D, day; LDH, lactate dehydrogenase; PLT, platelet count; ULN, upper limit of normal; W/O, without.

days of treatment remains a persistent problem. A review of the SEER database comparing APL patients diagnosed from 1992-95 and 2002-07, three-year overall survival improved from 54.6% to 70.1%; however, rates of early death only decreased from 22.1% to 17.5% [4]. Multiple groups have sought to understand predictors of this mortality in hopes that modifications to monitoring or treatment algorithms can decrease adverse outcomes. In two separate manuscripts, elevated baseline WBC count was more associated with early hemorrhage or death compared with late events [5,9]. In our patient cohort, baseline WBC count and platelet concentrations were better predictors of early rather than delayed bleeding. While our study population is too small to comment definitively on the question of delayed bleeds in ATRA + ATO patients with proliferation of WBC counts, we did note common leukocytosis without a trend towards increased bleeding events.

Additionally, in the multivariate analysis here, two factors were significantly associated with delayed hemorrhagic events: a ≥50%

drop in fibrinogen from day 1–6 peak to day 6–10 nadir, and the use of any dose of intravenous heparin. Absolute fibrinogen at time of bleed was not decreased in delayed bleeds, though patients with ≥50% decreases in fibrinogen were at greater risk of delayed bleeding. While fibrinogen decline during induction is not a standard metric, we used a ≥50% decline day 6–10 as a marker of significant fibrinogen consumption in the days after initial cytotoxic chemotherapy in our standard regimens. Delayed bleeding remains out of proportion to the degree of hypofibrinogenemia and thrombocytopenia, and thus we hypothesize the decline in fibrinogen represents only one lab manifestation of a consumptive coagulopathy.

The association of heparin use and delayed bleeding extended to both therapeutic and low-dose heparin infusions. A previous report noted free tissue factor pathway inhibitor levels are elevated through the first two weeks of APL induction therapy [11]. Previous studies have shown that heparin causes a rapid increase in tissue factor pathway inhibitor levels [12]. This mechanism could provide a biologic rationale for the increased susceptibility of APL patients to bleeding complications from heparin. Intriguingly, a trial of recombinant tissue factor pathway inhibitor administration in sepsis failed in part due to CNS bleeding events [13]. Alternatively, patients with evidence of refractory DIC may be selected for clinical exposure to heparin, and at a higher risk for coagulopathy complications, irrespective of heparin exposure.

Future studies could monitor fibrinolysis-specific coagulation labs to further characterize dynamic changes in fibrinolysis during APL induction. Wang et al have reported fibrinolysis assessments for patients treated without an anthracycline [14]. Measuring free levels of tissue factor pathway inhibitor could evaluate the mechanistic role it plays in the coagulopathy of APL.

Currently, the mainstay of prevention and treatment of severe hemorrhage during APL induction involves frequent laboratory monitoring and supportive transfusions with cryoprecipitate, platelets, and plasma [9,15]. Past treatment efforts have included small reports of antifibrinolytics, mostly in the pre-ATRA era [16–18]. A large prospective trial of antifibrinolytics in APL has not been conducted, in part due to concerns of increased rates of thromboembolic events [19]. Prophylactic heparin use has been described in multiple reports, with no large prospective trial indicating efficacy in improving coagulopathy-associated complications [15,20].

Early bleeding events in APL often occur prior to arrival on a designated leukemia unit, making dedicated interventions to improve outcomes challenging. Alternatively, patients with delayed bleeding events have received several days of induction therapy and supportive care pathways. Despite these advantages, delayed hemorrhagic events continue to account for a significant portion of complications in APL. This study highlights two key interventions which may decrease delayed bleeding events. First, early identification and correction of consumptive coagulopathy is vital into the second week of induction therapy. Second, any use of anticoagulation for events other than life-threatening thrombosis should be avoided. Additional studies, both retrospective and prospective, could address this further.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations of Interest

None.

Contributions

BH and AD drafted the manuscript. KN, BH, and JZ completed the data collection. JJ conducted the statistical analysis. ES, JW, MS, LG, WD, GP, DG, MS, KP, IG, GG, ML, and BS contributed to the study design and reviewed drafts of the manuscript. All authors reviewed the manuscript and agreed to submit for publication.

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