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Predictive factors of fatal bleeding in acute promyelocytic leukemia

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ABSTRACT

Acute promyelocytic leukemia (APL) is associated with a profound coagulopathy. Based on retrospective assessments, several potential risk factors for hemorrhagic morbidity and mortality have emerged. Several studies have shown elevated white blood cell (WBC) count at presentation to be a robust predictor of bleeding events. Other clinical and laboratory parameters have been evaluated with variable association with hemorrhagic morbidity or mortality. These include ECOG performance status, age, morphological subtype, platelet count, peripheral blood blast count, ethnicity, body mass index, prothrombin time, activated partial thromboplastin time, lactate dehydrogenase, D-dimers, creatinine and fibrinogen levels. Unfortunately, most of those assessments were based on a small patient sample and the results have been at times contradictory in terms of which parameters are independent predictors. More recently, two large retrospective studies have reported on the issue. They included data from several international trials of chemotherapy for APL, one on adults and the other focused on the pediatric population. Importantly, both analyses found that WBC count at presentation is the main predictor of early hemorrhagic death and early thrombo-hemorrhagic death, respectively.

Much remains to be done if the rate of induction mortality in APL is going to be reduced significantly. One approach would be to incorporate the known risk factors for early hemorrhagic death into a risk stratification system and devise personalized transfusion interventions to meet an individual patient's risk, which could be evaluated in future randomized trials.

1. Introduction

Acute promyelocytic leukemia (APL) is an aggressive hematological neoplasm characterized by the defining translocation t(15;17), resulting in the PML:RAR-alpha re-arrangement [1,2]. It constitutes about 13% of cases of newly diagnosed acute myeloid leukemia (AML) [3]. First described in 1949, it was noted very early on that patients with APL often suffered from a severe bleeding diathesis, commonly presenting with hemorrhagic complications [4,5]. This coagulopathy is multifactorial and still incompletely understood, however hyperfibrinolysis is thought to be a major component [6].

Over the last three decades, great strides have been made in the treatment of APL thanks to the development of all-trans retinoic acid (ATRA) and arsenic trioxide, both of which induce terminal differentiation of the malignant cells [7,8]. Complete response rates in first line are in excess of 90% [9], and some patients can be treated without cytotoxic chemotherapy. Treatment has become so that most deaths occurring early in the course of disease are secondary to bleeding. In multicenter trials, 5–10% of randomized patients die from hemorrhage [10,11]. Even higher early mortality estimates have been noted in population-based studies [12,13]. These figures have not improved since the advent of ATRA, and the standard approach for managing the coagulation disturbances remains empirically derived, based on blood product administration to maintain a fibrinogen above 100–150 mg/dL and a platelet count above 30,000–50,000/mcL [14]. Transfusion therapy is not founded on evidence-based risk stratification, as randomized trials have not been conducted to address this question. However, at this juncture substantial data have accumulated about potential risk factors for early hemorrhagic death in APL.

2. Mechanism of the coagulopathy of APL

Understanding the potential underpinnings of the coagulopathy seen in APL is crucial to identify and validate predictors of bleeding events. Patients with APL often have some form of bleeding manifestation at presentation, including hematoma formation, bruising, epistaxis and hematuria [11]. Laboratory tests of hemostasis are usually abnormal at least in part, including a prolonged prothrombin time (PT),

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activated partial thromboplastin time (aPTT) and decreased fibrinogen level [15]. The platelet count is almost always decreased. The total white blood cell (WBC) count can be variably decreased, normal or increased [15].

Disseminated intravascular coagulation (DIC) has long been thought to be an important driver of the coagulopathy of APL [5]. The APL blasts contain large amounts of tissue factor (TF) inside their cytoplasmic granules, as shown by studies of the NB4 cell line [16,17]. TF is also expressed at the surface of tissue factor microparticles, which have been identified in the blood of individuals with APL [18]. TF forms a complex with coagulation factor VII and activates it to factor VIIa. The complex of TF and FVIIa activates coagulation factors IX and X, leading to generation of thrombin and conversion of fibrinogen to fibrin. Moreover, nascent factor Xa in the TF-VIIa-Xa complex was recently shown to initiate factor VIII activation, thereby propagating thrombin generation *via* the intrinsic pathway of coagulation [19]. Thrombin generation and fibrin formation eventually culminate in secondary fibrinolysis. The TF:VII complex is the principal trigger for physiological hemostasis and is also central to the development of DIC in the setting of sepsis.

If classic, TF-mediated DIC, similar to that seen in sepsis, were the major cause of the coagulopathy in APL, one would expect to see universally decreased fibrinogen levels. However, many patients have normal fibrinogen levels despite bleeding. The aPTT also is often normal at presentation in APL [15], while in severe DIC this parameter is almost always elevated.

It appears another process accounts for the bleeding diathesis encountered in APL, and recent evidence indicates this is primary hyperfibrinolysis mediated by Annexin II. Annexin II is widely expressed on the surface of APL blasts [20,21]. It binds tissue plasminogen activator (tPA) and increases the enzyme's activity in converting plasminogen to plasmin [22]. The large amounts of plasmin generated lead to the depletion of fibrinogen and, more importantly, premature destruction of fibrin clots at bleeding sites.

3. Predictors or hemorrhagic morbidity and mortality

Prior retrospective studies of hemorrhagic morbidity and mortality in the setting of induction chemotherapy for APL are presented in Table 1 [10,15,23–29]. Endpoints in the studies varied between severe bleeding and/or hemorrhagic death. Severe bleeding was defined differently between studies. Only one study evaluated the pediatric population [23], and the main endpoint was thrombo-hemorrhagic death. However, in this study only 2 of 25 thrombo-hemorrhagic mortality events were thrombotic in nature, so the predictors identified pertain largely to bleeding events.

Parameters reported to predict severe hemorrhage or hemorrhagic death include elevated WBC count, ECOG performance status (PS), age, morphological subtype (M3 *vs* M3v), platelet count, peripheral blood (PB) blast count, ethnicity, body mass index (BMI), PT, aPTT along with lactate dehydrogenase (LDH), D-dimers, creatinine and fibrinogen levels.

3.1. White blood cell (WBC) count and peripheral blood blast count

A total WBC count greater than 10,000/mcL has been demonstrated to predict lower relapse-free survival in APL [30]. Several studies have shown that the WBC count and PB blast count are also predictors of bleeding events, including bleeding mortality [10,15,23–25,27,28]. Total WBC count and PB blast count are strongly correlated, so typically only one parameter is retained in the final multivariate model [24]. The threshold chosen for WBC count has variably been 10,000/mcL and 20,000/mcL, however the relationship appears linear and the choice of cutoff value is arbitrary. WBC count seems to be the most robust parameter, identified as being an independent predictor in multivariate modeling of severe bleeding in 4 studies [23,24,27,28], while being significant in univariate analysis for 3 other studies [10,15,25]. It is not clear exactly why malignant APL blasts would be better predictors than coagulation parameters, but one possible explanation is that those cells mediate primary fibrinolysis at their surface, leading to removal of hemostatic thrombi in small vessels like those of the brain, with ensuing hemorrhagic episodes. This local process of fibrin cleavage would not be well measured by commonly performed coagulation laboratory tests like the PT, aPTT or fibrinogen level.

3.2. Platelet count

The platelet count is decreased in most patients presenting with acute myeloid leukemia, due largely to bone marrow replacement by malignant blasts. In APL, thrombocytopenia results both from marrow infiltration and DIC. Interestingly, thrombocytopenia has not emerged as a useful predictor of hemorrhagic events in APL. Only one study found the platelet count as being significant in univariate or multivariate analysis [26]. One reason why the platelet count would not be a strong driver of hemorrhagic complications of APL is that in general spontaneous bleeding rarely occurs solely due to thrombocytopenia unless this value is below 10,000/mcL, a situation not encountered in most patients presenting with APL before chemotherapy nadir occurs, and even then prevented to a large extent by platelet transfusions. This is also well illustrated by the fact that death from intracranial or pulmonary hemorrhage is far less frequent in non-APL AML subtypes, while thrombocytopenia is as much of a problem. Hence, thrombocytopenia is clearly not the main reason why bleeding is such a problem with *de novo* APL, even though it could conceivably contribute.

Table 1
Studies assessing predictors of hemorrhagic morbidity and mortality in APL. WBC, white blood cell; PB, peripheral blood; BMI, body mass index; PS, performance status; PT, prothrombin time; DIC, disseminated intravascular coagulation; PTT, activated partial thromboplastin time; LDH, lactate dehydrogenase.

Author	Number of patients	Endpoint	Significant predictors of bleeding risk
Abla et al. [23]	683	Thrombo-hemorrhagic early death	WBC count[b], PB blast count[a], morphological subtype[a], ethnicity[a], BMI[b]
Mantha et al. [24]	995	Hemorrhagic early death	WBC count[b], PB blast count[a], ECOG PS[a]
Mitrovic et al. [15]	56	Hemorrhagic early death	WBC count[a], ECOG PS[a], fibrinogen[a], PT[a], ISTH DIC score[b]
Chang et al. [25]	116	WHO grade 3 or 4 bleeding	WBC count[a], PT[a], PTT[a]
		WHO grade 4 bleeding	WBC count[a], PT[a], PTT[a]
Kim et al. [26]	90	Significant bleeding (defined by the authors)	Platelet count[a], LDH[b], fibrinogen[b], D-dimers[a]
		Hemorrhagic death	Platelet count[b], LDH[a], fibrinogen[a]
de la Serna et al. [10]	732	Hemorrhagic induction death	Age[a], creatinine[b], WBC count[a], PB blast count[b], coagulopathy[b]
Yanada et al. [27]	279	Severe hemorrhage (defined by the authors)	Fibrinogen[b], WBC count[b], ECOG PS[b]
Dally et al. [28]	34	Severe bleeding (defined by the authors)	PT[a], WBC count[b]
Higuchi et al. [29]	19	Hemorrhagic early death	Fibrinogen[a]

[a] Univariate analysis.
[b] Multivariate analysis.