Special Blood Product Requirements Of Acute Promyelocytic Leukemia

BY NICOLE L. DRAPER

cute promyelocytic leukemia (APL) is a distinct clinical subtype of acute myelogenous leukemia (AML) with unique pathologic and clinical characteristics. APL is considered a medical emergency because it is characterized by sudden onset and a significant risk of death due to hemorrhage. The risk of death within 30 days of diagnosis is estimated at 5-10 percent in clinical trials and 17-29 percent in general, with the difference likely attributable to an inherent selection bias due to inclusion criteria for clinical trials. There is a risk of hemorrhage with all leukemias due to the common finding of thrombocytopenia, but APL has a higher risk directly attributed to unique properties of malignant promyelocytes and their interaction with other cells. Two recent review articles have assessed the pathogenesis of coagulopathy and optimal treatment strategies in APL (Curr Opin Hematol 2016;23(2):127-36); Curr Opin Hematol 2016;23(2):121-6).

The vast majority of cases of APL have a t(15;17) balanced translocation that creates an abnormal promyelocytic leukemia/retinoic acid receptor α (PML-RARA α) fusion gene leading to abnormal function of retinoic acid receptor α . This in turn leads to disruption of differentiation of myeloid progenitors after the promyelocyte stage. Thus, promyelocytes and blasts increase in number in the bone marrow and peripheral blood. Many research studies have found characteristics of these malignant cells that make disseminated intravascular coagulation (DIC) and hyperfibrinolysis more likely to occur in patients with

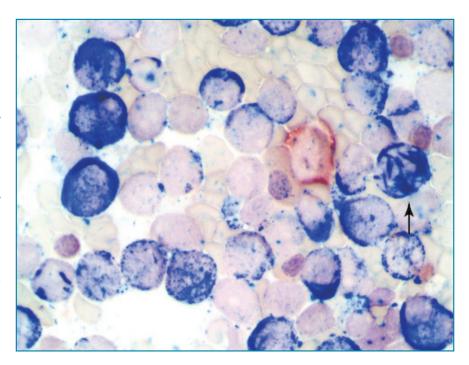
Pathogenesis of Coagulopathy

Tissue factor (TF) is one of the primary mediators of normal and pathologic clot formation. In APL, the abnormal PML/RARAα protein causes activation of the TF promoter leading to increased expression of TF in the leukemic cells. Additionally, high peripheral blood levels of microparticles derived from APL cells that express TF on their surface have also been identified and exhibit procoagulant activity. The enhanced procoagulant effect of the increased TF produces a consumptive coagulopathy in many patients. An incidence of overt DIC as high as 88 percent has been reported. This would typically lead to significant clot formation with signs/symptoms of thrombosis followed by, or in conjunction with, bleeding.

In the case of APL, fibrinolysis is also enhanced, leading to quick clot breakdown, and an increased propensity for bleeding. Evidence for hyperfibrinolysis includes high expression of factors that potentiate fibrinolysis such as annexin II, tissue plasminogen activator (tPA) and urokinase plasminogen activator (u-PA) with a deficiency of inhibitors of fibrinolysis including alpha-2 antiplasmin and plasminogen activator inhibitor.

Bleeding Risk Stratification

Several studies have attempted to identify factors in patients with APL that could accurately predict high versus low risk of severe bleeding. Elevated WBC count, peripheral blast count or creatinine; low platelet count, fibrinogen, or performance status; and prolonged activated partial thromboplastin time (aPTT) or prothrombin time (PT) have



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Learning Objectives for This Month's CME Activity: After participating in this CME activity, readers should be better able to recognize measures recommended to counteract the coagulopathy often found in patients with APL.

all been identified as predictors of severe bleeding or hemorrhagic death in different studies. The most consistently identified predictor of bleeding in APL, found in 6/9 studies, is an elevated WBC count. Many classification schemes use a WBC count >10,000/mcL to identify patients with high-risk disease who have a greater risk of death during induction therapy.

Treatment

Prompt initiation of treatment with all-trans retinoic acid (ATRA) is the mainstay of treatment for APL. ATRA causes degradation of the PML/RARA α protein with maturation of the APL cells and a subsequent rapid decrease in procoagulant activity. The improvement in Continued on page 6

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clinical status is so pronounced that ATRA should be started in any patient suspected of having APL before the diagnosis is confirmed by cytogenetics or other molecular testing.

Additional immediate supportive measures also are endorsed to counteract the coagulopathy often found in patients with APL. The table summarizes recommendations from the National Comprehensive Cancer Network (NCCN) and the European LeukemiaNet (ELN) for goal parameters for prophylactic transfusions in AML in general and how they differ in APL. They both advocate for transfusion of platelets, cryoprecipitate, and/or plasma to maintain platelet and fibrinogen levels higher in APL than in other types of AML. These higher thresholds for transfusion should be maintained until coagulopathy has resolved with normalization of laboratory values (PT, aPTT, D-dimer). The recommendations indicate laboratory values to monitor coagulopathy should be checked at least daily, but some studies and reviews recommend checking laboratory values every six hours. The NCCN and ELN both recommend invasive procedures, such as central venous cath-

Recommendations From the NCCN and FLN

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Parameter	NCCN and ELN AML	NCCN APL	ELN APL
Platelet count (x10 ⁹ /L)	>10	>50	>30-50
Fibrinogen level (mg/dL)		>150	>100-150
PT (sec)		Close to normal	
PTT (sec)		Close to normal	
Hemoglobin (g/dL)	>8	>8	>8
Monitor lab values		Daily	At least once a day
A blank table cell indicates that no specific recommendation was given			



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eterization and lumbar puncture, be avoided until completion of induction chemotherapy for APL. Leukapheresis for elevated WBC counts is also not recommended. Of note, these recommendations are based on evidence classified as IIb according to the "General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine," which means it is largely expert opinion with well-designed quasi-experimental studies as support.

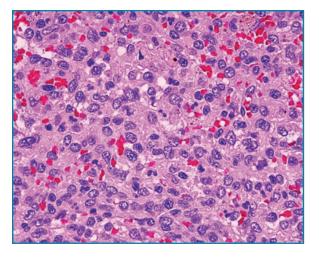
Severe DIC can make it difficult to achieve a higher platelet count and goal fibrinogen level. A study by Yanada et al in 2007 (*Eur J Haematol* 2007;78:213–219.) reported that 18 patients (6.5%) experienced severe hemorrhage, which was associated with lower levels of fibrinogen and higher fibrin degradation product ratios at presentation, consistent with DIC. On the day of severe hemorrhage, 71 percent achieved the goal platelet count of 30×10^9 /L and only 40 percent achieved the goal fibrinogen of 150 mg/dL despite receiving frequent transfusions.

Leukocyte reduction of cellular blood products is almost universally recommended to reduce the risk of CMV transmission, decrease the incidence of febrile nonhemolytic transfusion reactions, and prevent HLA alloimmunization. Platelet refractoriness due to HLA alloimmunization can be especially difficult to manage in patients with APL. The higher platelet goal requires more frequent transfusions, and obtaining adequate units of HLA-matched or crossmatch compatible platelets to meet this need can be problematic to impossible.

Additionally, the most common sites for severe hemorrhage in patients with APL are intracranial then pulmonary. Intracranial hemorrhage would typically raise the goal platelet count to $>100 \times 10^9/L$, which would be even more difficult to maintain. Patients with significant platelet refractoriness or severe DIC can be put on a platelet or plasma drip if goal levels cannot be achieved. $\boxed{\textbf{OI}}$

AML TREATMENT

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experiencing first leukemia relapse who were 60 years of age and older and not considered candidates for other cytotoxic chemotherapy.

But in 2010, the FDA announced that Pfizer had voluntarily agreed to discontinue commercial marketing of GO.

The decision was based on interim results of the Southwest Oncology Group (SWOG) S0106 trial, which showed no improvement for GO in relative response compared with standard chemotherapy and a higher incidence of serious adverse events (*Blood* 2013;121:4854-60).

Bring It Back?

Alex Mejia-Garcia, MD, Assistant Professor, Division of Hematology/ Oncology and Director of Early Phase Experimental Therapeutics for Hematological Malignancies at the University of Texas Health Science Center at San Antonio, thought the trial's results were enough for the FDA to re-examine GO for this patient population.

"I think the company should bring this agent back to the Food and Drug Administration for re-evaluation for this specific population," said Mejia-Garcia, who was not associated with the AML17 study. "They may decide not to move forward because of the limited improvement in overall survival, but it may be worth a longer follow-up for this trial to see whether the clinical benefit increases without added toxicity."

When toxicities were seen earlier, they were in regimens with other chemotherapies, he noted.

In the meantime, the data are very compelling for this very select population, he said.

"I do hope we get some other form of therapy for these patients," Mejia-Garcia said, but he emphasized he would use this drug only for this specific population.

Garcia-Mejia said the additional 1.3 months improvement in overall survival in this trial, while not great, is something to be discussed with the patient.

"This is a population for which the traditional agents have a much lower response rate, and the best survival is probably with the hypomethylating agents, decitabine or azacitidine, perhaps reaching eight to 10 months in general," he told *OT*. "In this trial of frail, elderly patients, survival with GO was approximately five months, which is still better than the standard of low-dose ara-C with best supportive care." OI

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