Clinical Roundtable Monograph

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# Early Death in Patients With Acute Promyelocytic Leukemia

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### Abstract

With the introduction of all-trans retinoic acid (ATRA) and arsenic trioxide, acute promyelocytic leukemia (APL) has become a highly curable malignancy. Approximately 90% of patients achieve complete remission with induction, which generally includes ATRA and an anthracycline-based chemotherapy. Early death, either before treatment is initiated or during induction, has emerged as one of the most critical issues involved in the current care of patients with APL. The main cause of early death in APL is bleeding, often intracranial. It has become increasingly clear that induction therapy should be initiated in patients at the earliest time possible, even before confirmation of the diagnosis of APL has been made. In this roundtable, several experts discuss important insights into the high rate of early death observed in APL. In addition to the importance of rapid diagnosis, the pathophysiology of the coagulopathy associated with APL will be discussed, as will factors that may be predictive of early death and potential interventions to prevent this important limitation to the cure of many, if not most, patients.

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## Target Audience

This activity has been designed to meet the educational needs of oncologists and other healthcare professionals who treat patients with acute promyelocytic leukemia.

## Statement of Need/Program Overview

Acute promyelocytic leukemia (APL) is a highly curable malignancy, but these patients are at risk of early death either before treatment is initiated or during induction. The main cause of early death in APL is bleeding. At the time of presentation, the majority of APL patients already have some degree of coagulopathy, which is why this malignancy is often considered a medical emergency. Pretreatment patient characteristics that are significantly associated with an increased risk of fatal hemorrhage are thrombocytopenia, elevated absolute blast and promyelocyte counts, older age, and anemia. New guidelines call for immediate initiation of all-trans retinoic acid without waiting for genetic diagnostic confirmation, initiation of aggressive supportive care including blood transfusions, and submission of a biopsy sample to a reference laboratory for genetic confirmation of the disease. Current interventions to prevent early death (platelet transfusions and cryoprecipitation) are not adequate. Certain populations of APL patients may benefit from treatment with heparin or recombinant human soluble thrombomodulin.

## Educational Objectives

After completing this activity, the participant should be better able to:

- Describe the importance of rapid diagnosis and early induction therapy in APL
- Analyze the pathophysiology of the coagulopathy associated with APL
- Identify factors that are predictive of early death in APL patients
- Evaluate approaches to mitigate early death in APL

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# New Insights into the Molecular Pathogenesis of APL: The Importance of Rapid Diagnosis

Francesco Lo-Coco, MD

A distinct subtype of the larger class of acute myeloid leukemias, acute promyelocytic leukemia (APL) is characterized by a unique morphology and a clinical presentation with coagulopathy. The underlying pathogenesis of APL involves a translocation of the promyelocytic leukemia (*PML*) gene located on chromosome 15, causing it to become adjacent to the retinoic acid receptor (*RAR*) alpha gene located on chromosome 17.[1-3] This results in the production of a specific fusion protein that disrupts the function of the RAR protein and leads to an accumulation of promyelocytic blasts in both the bone marrow and peripheral blood.

With the introduction of specific therapies used to treat APL, including all-trans retinoic acid (ATRA) and arsenic trioxide (ATO), this leukemia is now considered to be highly curable, with rates of complete remission (CR) of approximately 90% among patients who do not die early.[4] As was recently noted by Sanz and Montesinos, primary leukemia resistance has virtually been eliminated as a cause of treatment failure.[4] However, in its place, coagulopathy-related death before or during induction therapy has remained a major cause of mortality among APL patients.

## Incidence of Early Death in APL

The incidence of early death due to coagulopathy in APL is largely unreported. Studies rarely include patients who are not eligible for therapy, which in many cases is due to the coagulopathy and related poor clinical condition. For example, in studies from the North American Intergroup and the PETHEMA (Programa para el Estudio de la Terapéutica en Hemopatía Maligna) group, approximately 5% of APL patients were ineligible for induction therapy because of poor clinical condition.[5,6] In the PETHEMA study, 42 patients were considered ineligible for therapy, 19 because of coagulopathy (15 cases due to intracranial hemorrhage and 4 cases due to pulmonary hemorrhage).[7] In a 2010 study, 29% of patients with untreated APL were not enrolled in clinical trials.[8] This finding led to the conclusion that early mortality may be underestimated in multicenter clinical trials.

Further, early death is both poorly and heterogeneously defined in clinical trials. At the 2009 International Symposium on APL, held in Rome, Italy, a report from a Swedish registry of patients with APL diagnosed between 1997 and 2006 (n=105) reported an early death rate of 29%.[9] In this study, early death was defined as death within the first month of diagnosis; the median time from diagnosis to early death for these patients was only 4 days. At the 2010 American Society of Hematology annual meeting, Park and colleagues reported results from a population-based study in APL patients using data from the Surveillance, Epidemiology, and End Results (SEER) Program (n=1,400) and the New York State Cancer Registry (n=721), limiting the analysis to patients diagnosed between 1992 and 2007.[10] The rate of early death, which was defined as death reported within the first month of diagnosis, was found to have remained similar over time with little change (22.7% [1992–1996], 15.6% [1997 and 2001], and 18.1% [2002–2007] in the SEER registry, and 10.9% [1992–1996], 11.9% [1997–2001], and 11.2% [2002–2007] in the New York State Cancer registry). Again, these rates are higher than commonly reported in large multicenter clinical trials.

One way to improve the rate of early death in APL may be the very early introduction of definitive therapy with ATRA well before the diagnosis is genetically confirmed. Physician education will also be important, to ensure that the wide spectrum of health care professionals, including nurses, emergency room physicians, internists, and family physicians, who may see these patients first are aware of the disease and understand the risk of early death. This issue is made more difficult by the fact that due to the relative rarity of the disease, many centers may see just a few APL patients in a year.

To help prevent early death in APL, the European LeukemiaNet recently published guidelines for physicians

**Table 1.** Methods for Genetic Diagnosis of APL

| Assay | Target | Advantages | Disadvantages |
|---|---|---|---|
| Karyotype for t(15;17) | Chromosomes | Specific | Time-consuming<br>False negatives |
| FISH for *PML/RAR*α | DNA | Specific<br>Rapid | Poor sensitivity<br>No information on the specific *PML/RAR*α isoform |
| RT-PCR for *PML/RAR*α | RNA | Specific<br>Rapid | Artifacts<br>Contamination |
| Anti-PML monoclonal antibody | Protein | Rapid<br>Low cost | No information on the specific *PML/RAR*α isoform |

APL=acute promyelocytic leukemia; FISH=fluorescence in situ hybridization; PML=promyelocytic leukemia; RT-PCR=reverse transcription polymerase chain reaction.

who have patients with suspected APL.[11] These include the immediate initiation of ATRA without waiting for genetic diagnostic confirmation, the initiation of aggressive supportive care including blood transfusions, and the submission of a biopsy sample to a reference laboratory for genetic confirmation of the disease. These 3 actions should be performed simultaneously; neither treatment nor supportive care should be withheld pending a genetic diagnostic confirmation.

## Diagnostic Confirmation of Suspected APL

Treatment for APL should be initiated based on a morphologic diagnosis alone, a practice that is typically done in approximately 80% of cases. Morphologic diagnosis can be coupled with both immunocytochemistry—specifically, staining for strong expression of myeloperoxidase (MPO)—and immunophenotyping flow cytometry, with a typical expression profile of DR-negative, CD34-negative, CD13-positive, lightly CD15-positive, and strongly CD33-positive. However, this profile is not necessarily specific for APL, and thus it is not required for the diagnosis.

Alternatively, there are several genetic assays that provide specific confirmation of APL.[12] One of these is a karyotype to confirm the t(15;17) chromosomal translocation pathognomonic of this disease. Fluorescent in situ hybridization (FISH) is an alternative assay that can also be used to detect the *PML/RAR*α gene fusion, as is reverse-transcription polymerase chain reaction (RT-PCR), which uses DNA amplification to detect the *PML/RAR*α gene fusion (Figure 1).[13] Recently, an anti-PML monoclonal antibody was found to provide rapid and accurate confirmation of APL, providing an alternative approach to diagnosis in settings in which genetic testing is not readily available.[14]

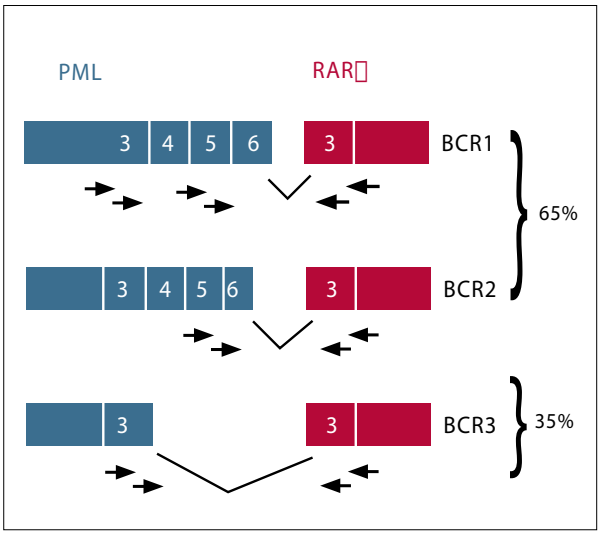


**Figure 1.** Reverse-transcription polymerase chain reaction uses DNA amplification to detect the *PML/RAR*α gene fusion.

Although they all revolve around the *PML/RAR*α gene fusion, each of these assays differs in their specific targets (Table 1). Thus, they have unique advantages and disadvantages to their use and in the extent of information that they can provide. For example, RT-PCR for the *PML/RAR*α fusion gene is a specific and rapid test, but it is associated with the potential for artifacts and contamination. Although both FISH and the anti-PML monoclonal antibody can rapidly identify APL, they offer no specific information on the type of *PML/RAR*α isoform present in the individual case.

## Clinical Relevance of the PML/RARα Genetic Fusion

The *PML/RARα* gene fusion, a characteristic hallmark of APL, is clinically relevant for a number of reasons. It offers the availability of a unique diagnostic marker for genetic confirmation of the disease, and it is a determinant of the pathogenesis of APL. Because it involves the RARα protein, this fusion protein can be targeted with specific therapies, including ATRA and ATO, and in fact the expression of PML/RARα is predictive of the response to these agents. Finally, because of its ability to be measured genetically, the *PML/RARα* gene fusion is an ideal marker for determining the presence of minimal residual disease.

The t(15;17) chromosomal translocation results in a number of possible fusions, each of which has the potential to exhibit a unique sensitivity to targeted therapy. The vast majority (approximately 98%) of APL cases exhibit the classic *PML/RARα* fusion, which is sensitive to treatment with both ATRA and ATO. However, in contrast, a small minority of APL patients (approximately 0.5%) exhibit the *PLZF/RARα* fusion, which is not sensitive to either of these agents. The remaining fusions that have been identified in APL have been shown to have varying sensitivity to ATRA and ATO.[15]

## Discussion

**Martin S. Tallman, MD** In the 2010 ASH abstract that you discussed, in which data from the SEER and New York cancer registries were analyzed, no significant differences in the rate of early death were observed between urban and rural areas in either registry.[10] Do you believe that despite these data, there is a center effect that impacts the early death rate in APL?

**Francesco Lo-Coco, MD** In my experience, I have seen important differences in the rate of early death in APL depending on the center. It is a difficult issue, because often the case is a medical emergency that should be treated without causing the patient to travel to another center or region. However, the potential for treatment errors is higher in peripheral centers that have little or no experience with APL.

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# The Pathophysiology of Coagulopathy in APL

Hau C. Kwaan, MD, PhD

At the time of presentation, the majority of APL patients have a significant degree of coagulopathy. This is why this malignancy should be considered a medical emergency. Before the introduction of differentiation therapies, including ATRA and ATO, bleeding occurred in more than half of patients. Currently, coagulopathy is still responsible for more than 60% of early deaths in APL. Among the presenting bleeding complications in APL, intracranial hemorrhage is the most common (65–80%), followed by gastrointestinal hemorrhage and diffuse intra-alveolar hemorrhage in the lung.[1-3] Adding to the complexity is the presence of thrombosis in up to one-quarter of patients. Approximately one-third of these thrombotic complications occur after induction treatment.

## Typical Coagulation Profile in APL

Most patients with APL have varying degrees of abnormalities in their coagulation profiles. Overall, almost all patients present with signs of disseminated intravascular coagulation (DIC) and exhibit increased prothrombin time (PT), partial thromboplastin time (PTT), and thrombin time (Figure 1). Both fibrinogen and platelet counts are decreased, along with an increase in fibrin degradation products (measured as D-dimer).[4-6]

In addition to coagulopathy, abnormalities in the fibrinolytic system are also present, as evidenced by increased levels of tissue plasminogen activator (tPA), urokinase plasminogen activator (uPA), the uPA receptor, and the fibrinolytic receptor annexin A2.[6-8] However, the picture is confounded by a simultaneous increase in the expression of plasminogen activator inhibitor (PAI)-1 and PAI-2, both of which are antifibrinolytic.[6] Thus, the resultant picture represents a balance between the profibrinolytic and antifibrinolytic factors, and this varies from one patient to the other.

As the result of these hemostatic abnormalities, bleeding is the dominant clinical feature. Several risk factors for bleeding have been identified. These include a high white blood cell count (WBC), thrombocytopenia, low fibrinogen levels, and the presence of infection.

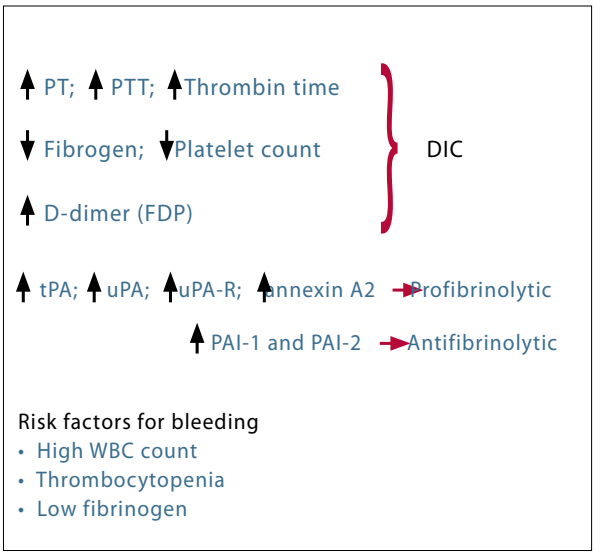


**Figure 1.** Coagulation profile in acute promyelocytic leukemia.

DIC=disseminated intravascular coagulation; FDP=fibrin degradation products; PAI=plasminogen activator inhibitor; PT=prothrombin time; PTT=partial thromboplastin time; tPA=tissue plasminogen activator; uPA=urokinase-type plasminogen activator; uPA-R=urokinase plasminogen activator receptor; WBC=white blood count.

## Pathogenesis of Thrombosis

In APL, bleeding and thrombosis are triggered by a number of events, including thrombocytopenia, increased tissue factor expression in the promyelocyte, abnormalities in fibrinolytic factors, apoptosis (induced by chemotherapy), comorbidities such as infection, and treatment with ATRA.[9-12] APL promyelocytes typically display a high expression of tissue factor. In vitro, the extent of this upregulation varies across different APL cell lines, with up to a 300-fold increased expression in the NB4 cell line.[11] Such increased expression of tissue factor is further escalated by inflammatory cytokines, such as tumor necrosis factor alpha (TNF) and interleukin (IL)-1b, and tumor-derived cytokines, such as IL-6. Tissue

factor is the primary factor that triggers the coagulation activation cascade. Normally encrypted and dormant on the surface of the intact cell, tissue factor is activated by phospholipids. During apoptosis, the phospholipids present in the cell membrane are exteriorized, enabling them to activate the dormant tissue factor. In addition, another activating process is by lipid peroxidation. Both apoptosis and lipid peroxidation occur during chemotherapy. Thus, the highest risk for coagulopathy occurs during treatment with chemotherapy, especially anthracyclines.

Other components that play a role in the pathogenesis of thrombosis include cancer procoagulant and fibrinolytic inhibitors (such as PAI-1 and PAI-2). Recent studies of microparticles in the plasma of APL patients revealed that high levels of activated tissue factor are present in those microparticles derived from myeloid cells.[12] The tissue factor level returns to normal on CR of the disease. These findings support the concept of the hypercoagulability of this disorder.

A number of risk factors for thrombosis in APL have also been defined. One factor is an elevated median WBC (>17,000). APL featuring the molecular characteristics of the bcr3 isoform (expressing CD2, CD15, and the internal tandem duplication [ITD] in the Fms-like tyrosine kinase [*FLT3*] gene) is associated with a higher risk of thrombosis.[13] There is a high risk of portal vein thrombosis, especially in the microgranular variant of APL that expresses CD2.[14,15] Other factors include the differentiation syndrome (previously referred to as the retinoic acid syndrome), the use of chemotherapy, and thrombophilia (either hereditary or acquired).

## Management

With treatment using ATRA and/or ATO, coagulopathy often resolves within 4–6 days after initiation of therapy.[5,6,16] However, during this time, the patient may experience extensive and life-threatening bleeding. Unfortunately, this coagulopathy is not well controlled with heparin, as was shown in a retrospective study that compared heparin with antifibrinolytic agents in the pre–ATRA era.[17] Even when antifibrinolytic agents are given prophylactically, they have not been shown to prevent intracranial hemorrhage.[18] Thus, ATRA should be initiated at the earliest point possible, particularly in patients at high risk for bleeding.

## Discussion

**Martin S. Tallman, MD** There is a movement in the field to combine ATRA with ATO as initial therapy for APL patients. Is there reason to believe that this combination will result in a faster resolution of the coagulopathy?

**Hau C. Kwaan, MD, PhD** To my knowledge, there is no evidence for an improved or more rapid resolution with the combination of these 2 agents. In addition, ATO induces apoptosis, which itself is a trigger for bleeding.

**Martin S. Tallman, MD** Are there any new agents that may warrant investigation as a combination therapy with ATRA in order to induce a faster resolution of coagulopathy?

**Hau C. Kwaan, MD, PhD** Agents that inhibit the coagulation pathway, such as those that block the action of tissue factor, may be effective in this setting. However, as of yet, none have been developed in clinical trials. Recombinant activated factor VII has been investigated to a limited extent, but because of its high cost and short half-life, it would be hard to administer over 4 days. In a randomized trial, heparin was shown to not improve survival.

**Steven D. Gore, MD** Heparin did not work in a randomized trial, but it works in individual patients if administered correctly. We still use heparin for patients with coagulopathy, and their fibrinogen goes right up.

**Martin S. Tallman, MD** Is there a risk of promoting thrombosis when too much cryoprecipitate is administered?

**Hau C. Kwaan, MD, PhD** No, I do not believe there is a significant risk, because we can safely adjust the dose of cryofibrinogen to normalize the plasma fibrinogen level.

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# Predictive Factors for Early Death in APL

Miguel A. Sanz, MD, PhD

Over the years, a number of definitions for early death in APL have been considered. One definition restricts early death to patients who die within the first 10 days of induction therapy. Other studies use a looser definition, restricting it to patients who die within the first 30 days of induction therapy. Arbitrarily, some reports define early death as death occurring at any time during induction therapy. However, one important set of patients left out of all of these definitions is those patients who died before even initiating induction therapy.

Most studies do not provide information about deaths before initiation of therapy, and when this information is provided, it may be unclear. For example, in a recently published study of the North American Leukemia Intergroup Study C9710, a total of 518 patients were assessed for study eligibility.[1] However, although 37 patients were considered ineligible due to lack of diagnostic confirmation by RT-PCR, no exclusions were made for performance status or protocol compliance. This is particularly confusing, given that over the 6-year period that this study was open, it is likely that patients normally considered ineligible for treatment (eg, those older than 85 years, those with an emergency room admission with a massive cerebral hemorrhage) would have been encountered. However, no mention is made of this type of patient. Instead, a comparison is made to a study from the PETHEMA group, which excluded up to 6% of patients due to poor clinical condition.[2,3] The discrepancy between these 2 studies has not been addressed. However, what is clear is that these APL patients with poor clinical condition are particularly difficult to treat. The best intervention is to initiate therapy with either ATRA or ATO at the earliest point that is feasible.

## Causes of Early Death

During induction therapy, the vast majority of APL patients (91%) achieve a CR. In the absence of resistance, the remaining 9% of patients die during induction therapy. As was demonstrated in an analysis of 2 PETHEMA Group studies, each of which treated APL patients with ATRA and idarubicin induction therapy, the main cause of early death during induction therapy was hemorrhage (5%), followed by infection (2.3%), differentiation syndrome (1.3%), and other causes (0.3%).[2] Most of these deaths occurred during the first week of induction therapy (57%), followed by 19% in the second week, 19% in the third week, and 5% in the fourth week of treatment. Throughout, the lethal bleeding event occurred most often as an intracranial hemorrhage (65%), although less frequently as a pulmonary hemorrhage (32%) or gastrointestinal hemorrhage.

The incidence of differentiation syndrome, previously referred to as the retinoic acid syndrome, also peaked in the first week of induction therapy, affecting nearly half (47%) of patients.[2] Although the incidence dropped in the second week (8%), it increased again in the third week (28%), finally lowering again in the fourth week (14%) and after (3%).

## Background of Prognostic Factors for Early Death

There is little background regarding the identification of factors that have been shown to be prognostic for early death. In one study of 60 APL patients morphologically diagnosed between 1973 and 1984, early fatal hemorrhage during induction therapy occurred in 16 patients (26%).[4] A multivariate analysis demonstrated 4 pretreatment patient characteristics that were significantly associated with an increased risk of fatal hemorrhage: thrombocytopenia, elevated absolute blast and promyelocyte counts, old age, and anemia. Patients with more than 2 of these factors had a significantly higher risk of fatal hemorrhage compared with patients having 2 or fewer of these factors (58% vs 5%; $P<.0001$).

Two studies of the Gruppo Italiano Malattie e Matologiche dell'Adulto (GIMEMA) group (one from the era prior to the introduction of ATRA treatment) also have investigated the prognostic factors for early death in APL. In the first, which analyzed 622 consecutive patients treated during 1989–1997, prognostic factors of early death found to be significant in multivariate analysis included blast count exceeding $30 \times 10^9$/L at diagnosis ($P<.001$) and a hemorrhagic score of 3 ($P<.001$).[5] In the second GIMEMA study of 268 consecutive APL patients, high blast cell counts on the day of admission were also found to be significantly associated with hemorrhagic death within the first 10 days.[6]

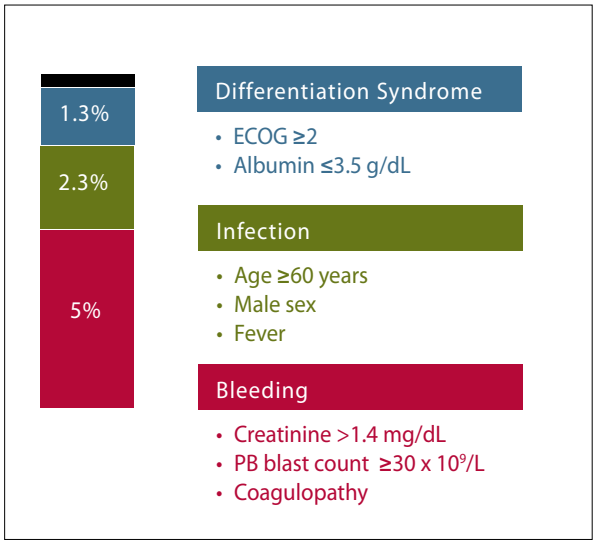


**Figure 1.** Predictive factors of induction death from the PETHEMA study.[3]

ECOG=Eastern Cooperative Oncology Group; PETHEMA=Programa para el Estudio de la Terapéutica en Hemopatía Maligna; PB=peripheral blood.

## Prognostic Factors of Early Death —The PETHEMA Experience

In 2 consecutive studies of the PETHEMA Group, both of which treated APL patients with ATRA and idarubicin induction therapy, a number of prognostic factors were identified for each of the causes of early death observed during induction therapy.[2] Overall, the factors that were found to be significantly prognostic for all-cause early death during induction therapy were abnormal creatinine level ($P$<.001), peripheral blood blast cell count exceeding 30 × $10^9$/L ($P$<.001), age older than 60 years ($P$<.001), male sex ($P$<.001), and WBC exceeding 10 × $10^9$/L ($P$=.04).

For the 5% of patients with early death due to bleeding, the prognostic factors with independent value identified were elevated creatinine (>1.4 mg/dL), peripheral blood blast cell count exceeding 30 × $10^9$/L, and the presence of coagulopathy. In the 2.3% of patients who died from infection, factors identified with independent prognostic value for early death included older age (>60 years), male sex, and fever at presentation. Among the 1.3% of patients who died due to differentiation syndrome, the independent prognostic factors identified were having an Eastern Cooperative Oncology Group (ECOG) status of 2 or greater and a low serum albumin level (≤3.5 g/dL).

Thus, in this large series of APL patients homogeneously treated with ATRA plus idarubicin as induction therapy, a characteristic pattern of causes of early death during induction therapy was established. Further, a specific set of prognostic variables was found, which may be used to identify patients most likely to fail induction therapy (Figure 1). In the future, these models may be useful for designing more appropriately risk-adapted treatment protocols aimed at reducing mortality from hemorrhage, infection, or differentiation syndrome.

## Discussion

**Francesco Lo-Coco, MD** In the PETHEMA analysis, the reported incidences of death were 57%, 19%, 19%, and 5% in the first, second, third, and fourth weeks of induction therapy, respectively.[2] Regarding the patients who died in the second, third, and fourth weeks, at what point did they experience a bleeding event?

**Miguel A. Sanz, MD, PhD** A significant fraction of patients who died in the later weeks of induction therapy actually developed a bleeding event first, and then died later. The median time interval from the start of induction therapy to the development of intracranial and pulmonary hemorrhage was 6 days (range, 1–21 days) and 9 days (range, 1–23 days), respectively.

**Martin S. Tallman, MD** Is there a theory as to why male sex was found to be prognostic for early death due to infection in the PETHEMA study?

**Miguel A. Sanz, MD, PhD** The reason for this finding remains unclear, but it may relate to an improved biologic status among women compared with men. Interestingly, other studies have shown a trend for improved outcomes overall in female versus male leukemia patients.

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# Can the Early Death Rate in APL Be Reduced?

Steven D. Gore, MD

With the introduction of ATRA and ATO as induction therapy for APL, the vast majority of patients—even those with high-risk disease—can achieve a CR without relapse. Thus, the risk of early death remains the last major hurdle in the management of these patients. Obviously, the earliest initiation of induction therapy with ATRA or ATO is vital to help mitigate coagulopathy in APL. However, while this therapy may work to resolve coagulopathy sooner, this outcome may not actually translate into a decrease in hemorrhagic deaths.

## Options for Treating Coagulopathy

One of the more controversial options that may be explored to mitigate early death in APL is a re-examination of the use of heparin in a limited patient population. In previous studies that found there was no benefit to heparin treatment of APL patients, patient selection did not occur.[1] It is possible that careful selection of high-risk patients and use of the identified prognostic factors for early death due to coagulopathy could help to define a population that would indeed benefit from heparin therapy with proper monitoring. Although controversial, it is clear that the current interventions to prevent early death (platelet transfusions and cryoprecipitation) are not adequate.

As an alternative, data from a Japanese study presented at the 2010 ASH annual meeting demonstrated that recombinant human soluble thrombomodulin (rTM) could enhance the antifibrinolytic and antileukemia effects of ATRA in APL cells.[2] rTM is the active extracellular domain of thrombomodulin that normally binds to thrombin, inactivating coagulation. This molecule also inhibits thrombin formation by activating protein C (producing activated protein C), which together with protein S inactivates VIIIa and Va. Although rTM is not approved in the United States, in Japan it is approved for the treatment of DIC related to hematologic malignancies or infections. In this Japanese study, the effects of rTM on the plasmin activity in the APL NB4 cell line were investigated, showing a 35% rate of inhibition compared with controls. When combined with ATRA, this inhibition rate was increased to 60% (inhibition with ATRA alone was 40%). Further, rTM significantly improved the ability of ATRA to induce growth arrest, differentiation, and apoptosis in these cells. When rTM was combined with ATRA and chemotherapy (idarubicin and cytarabine) in the treatment of 4 patients with DIC caused by APL, patients were rescued from DIC earlier than when compared with ATRA-treated historical controls (8.3 ±4.5 vs 12.5 ±5.2 days). Patients also had a significantly reduced need for cryoprecipitation to maintain plasma levels of fibrinogen (0.13 ±0.25 vs 3.93 ±1.18 U/day; $P$=.0131). Thus, this therapy may be of potential interest as a novel investigative agent.

## Options for Treating Differentiation Syndrome

Steroid prophylaxis is routinely used in patients considered at high risk for differentiation syndrome. However, this approach has never been shown to be effective in a randomized trial. Some APL patients present with effective differentiation syndrome already occurring. In many cases, supportive care may be the best intervention available.

A significant proportion of high-risk APL patients are positive for FLT3 ITD. In an interesting study presented at the 2010 ASH annual meeting, patients with an FLT3-ITD:wild-type allelic burden that was greater than 0.5 had a significantly inferior rate of event-free survival than those patients with an allelic burden less than 0.5 (2-year event-free survival: 61.2% vs 83.5%; $P$=.009).[3] Thus, these data suggest that an FLT3 inhibitor may act to abrogate differentiation syndrome or coagulopathy. This possibility has yet to be evaluated in preclinical or clinical studies.

## Discussion

**Martin S. Tallman, MD** If we can do anything at the moment, we can start ATRA early, at the very earliest suspicion of APL and before genetic diagnosis. Despite the

critical need to initiate induction therapy at the earliest suspicion of APL, it often does not happen. I think that physicians still wait a number of hours to do a bone marrow. Then they have to wait another day to get the core biopsy back. Some physicians still wait for genetic test results. Thus, there is a clear need to improve education regarding the treatment of this disease. However, given its relative rarity, how feasible is this?

**Francesco Lo-Coco, MD** I understand your concern, being that APL is a very rare condition.

**Steven D. Gore, MD** It is an emergency room diagnosis.

**Francesco Lo-Coco, MD** I think it is a matter of educating not only emergency room physicians, but also hematologists.

**Steven D. Gore, MD** Patients who are most at risk of early death are those with higher WBCs. I think that in such cases, the hematologist or oncologist is usually called in with some speed now.

**Martin S. Tallman, MD** Is high-risk APL biologically distinctive from other types of APLs?

**Miguel A. Sanz, MD, PhD** There may be some biologic characteristics that are more frequent in high-risk APL. These patients more frequently express FLT3 ITD, which suggests that there may be some unique biologic features of high-risk disease. But to say that high-risk APL is a different disease is too much.

**Francesco Lo-Coco, MD** We know that FLT3 is not a primary issue. It is definitely an acquired issue.

**Martin S. Tallman, MD** Do you think all low-risk patients will develop high-risk disease in time?

**Miguel A. Sanz, MD, PhD** It is difficult to say. I think there is no answer to this question, which remains an interesting issue for investigation. Sometimes, a patient will present to the hospital with high-risk APL, but in the history you will see signs of intermediate or even low-level disease. Other patients may have a biologically different disease.

My colleagues and I have done a study on whether the place of treatment affects outcome. We found that there was no relationship between improved outcome and the size of the city or the size of the hospital; a small hospital can have very good results. Outcome seems to be based on the individual patient.

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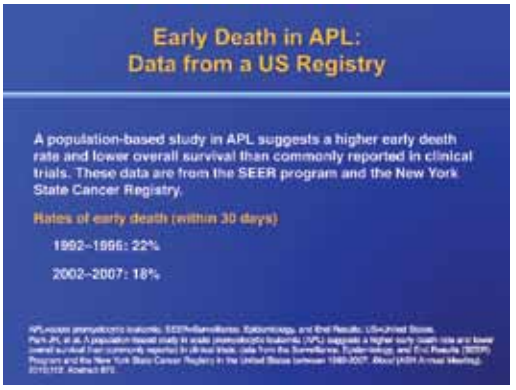



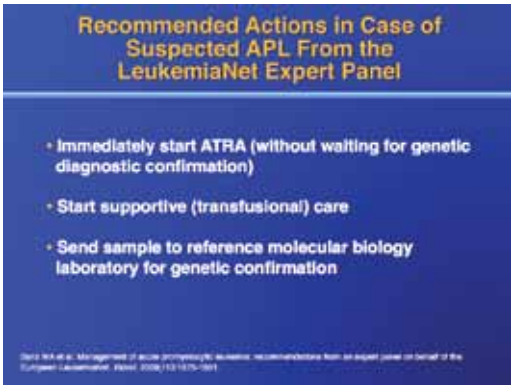




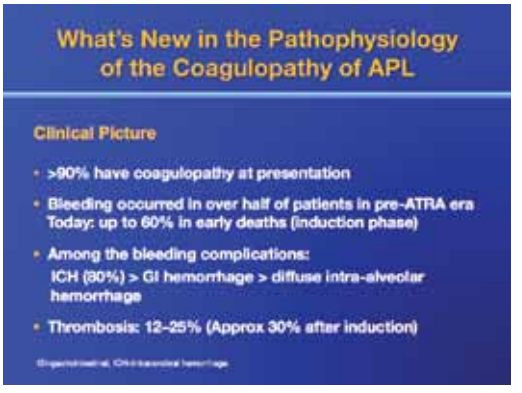

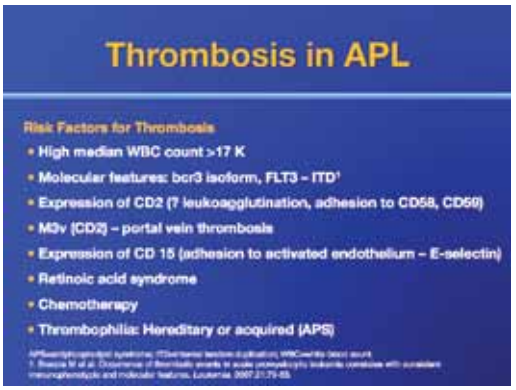



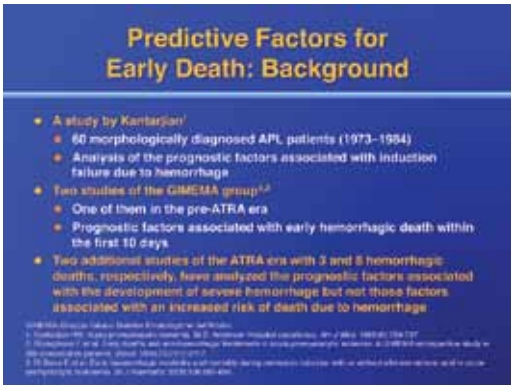


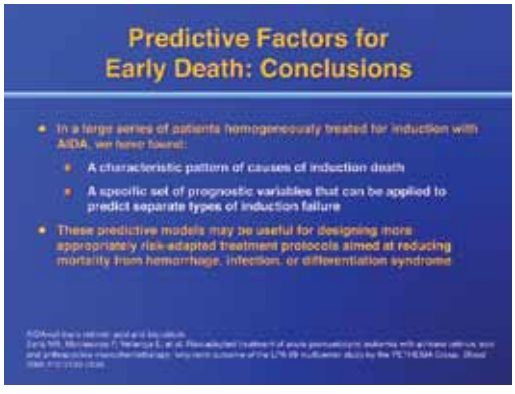



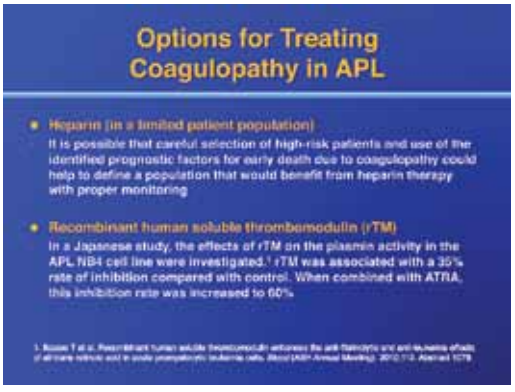


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