

# ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Clara D. Bloomfield, MD

---

## Update on the Management of Pediatric Acute Promyelocytic Leukemia

Raul Ribeiro, MD

Member, Department of Hematology-Oncology and Director, the International Outreach Program St. Jude Children's Research Hospital  
Department of Pediatrics  
Professor, University of Tennessee  
College of Medicine

**H&O** What is the clinical presentation of pediatric acute promyelocytic leukemia and how does it differ from that of more common hematologic malignancies?

**RR** The initial clinical manifestation of pediatric acute promyelocytic leukemia (APL) does not differ much from that of acute myeloid leukemia (AML). However, severe bleeding is the hallmark of APL. About 80% of patients present with disseminated intravascular coagulation resulting from activation of the coagulation system, hyperfibrinolysis, and nonspecific protease activity. Coagulopathy may be exacerbated by infectious and hemodynamic complications and by thrombocytopenia. The initial treatment approach to APL differs from that used for most other types of pediatric leukemia, as APL should be considered a true hematologic emergency. If a child has acute lymphoblastic leukemia (ALL), it is possible to assess and stabilize the patient and plan treatment during the 24–48 hours required to gather all of the diagnostic information. In contrast, if APL is suspected, disease-specific treatment should begin within hours. Because APL is often associated with life-threatening bleeding, supportive measures to counteract coagulopathy are initiated immediately if laboratory evidence of coagulopathy is documented. Fresh frozen plasma, fibrinogen, and platelets are transfused to maintain a fibrinogen level above 150 mg/dL and a platelet count above  $50 \times 10^9/L$ . There is no need to wait for cytogenetic or molecular confirmation to

begin APL treatment. The morphologic and immunophenotypic features of the leukemia cells are highly specific and should prompt the initiation of treatment, although they are not sufficient for a definitive diagnosis. A recently introduced immunostaining technique provides a genetic diagnosis of APL. It is very rapid, simple to perform, and highly specific. This assay is particularly useful in settings where diagnostic resources are limited.

**H&O** What are the special considerations in treating APL in children versus adults?

**RR** APL has traditionally been managed similarly in children and adults. The major APL treatment protocols worldwide include both pediatric and adult patients. These are applied to studies by GIMEMA (Gruppo Italiano Malattie Ematologiche dell'Adulto) in Italy, PETHEMA (Programa para el Estudio de la Terapéutica en Hemopatía Maligna) in Spain, and the French APL Group. Although outcomes in children and adults with APL have been comparable, there is increasing concern that the anthracycline dose intensity of the above protocols may cause long-term cardiac dysfunction in a substantial proportion of patients. Pediatric oncology groups around the world have begun investigating other treatment strategies for pediatric patients with APL.

**H&O** Historically, what have been the treatment methods for pediatric APL?

**RR** Historically, most pediatric centers have used AML protocols to treat APL. Pediatric patients with APL have had overall survival rates of 45–50% with AML-oriented therapies. Bone marrow relapse has been the main cause of treatment failure, although many protocols reported a high rate of early mortality as well. After all-trans-retinoic acid (ATRA) was found to be highly effective against APL, pediatric patients began receiving ATRA as a single remission-induction agent followed by postremission

---

Supported in part by grant CA-21765 from the National Institutes of Health (US Department of Health and Human Services), a Center of Excellence grant from the State of Tennessee, and the American Lebanese Syrian Associated Charities (ALSAC).

chemotherapy (sequential therapy) or as a component of combination remission-induction chemotherapy (concurrent therapy). The introduction of ATRA resulted in survival rates of about 75%. Randomized studies in adults showed that intensive chemotherapy that included ATRA during early remission induction yielded a better outcome. In 1984, Marty and colleagues made the important observation that the duration of complete remission was much longer in patients receiving the combination of 6-mercaptopurine and methotrexate as maintenance therapy. Subsequently, two randomized studies showed a longer duration of complete remission in patients who received maintenance therapy; hence, this strategy has been adopted by most current treatment protocols for children and adults.

### **H&O** What has been the impact of ATRA on treatment of pediatric APL?

**RR** ATRA has had a marked clinical impact on the management of pediatric APL. Before this agent was used, severe bleeding complications were very common during the first few days of treatment. About 15% of patients died of hemorrhagic events. Most of the bleeding complications are now avoided with the use of ATRA. However, intracranial bleeding, particularly during early induction, continues to be a significant cause of mortality (3–5%). Aggressive and early introduction of supportive measures to counteract coagulopathy might further reduce the mortality rate. The main drawback of ATRA is the so-called retinoic acid syndrome (RAS)—respiratory distress, fever, weight gain, peripheral edema, hypotension, and renal and cardiac insufficiency—that develops a median of 7 days (range, 1–35 days) after ATRA is started. Chest radiographs reveal pulmonary infiltrates and/or pleuropericardial effusions. Early recognition and prompt treatment with dexamethasone is the mainstay of RAS management. Another relatively common adverse effect of ATRA in children, especially adolescents, is pseudotumor cerebri, which is characterized by headache, blurred vision, and papilledema. Although this complication has been attributed to the ATRA dosage, it is unclear whether dose reduction reduces its frequency.

### **H&O** What other therapies have been promising in pediatric APL?

**RR** There is much interest in introducing other effective compounds to reduce the toxicity of currently used agents, particularly high-dose anthracyclines. Two agents appear particularly promising for pediatric APL, based on the responses seen in adults with relapsed disease: arsenic trioxide (Trisenox, Cephalon) and gemtuzumab ozogamicin (Mylotarg, Wyeth). Arsenic trioxide has been investigated

as a single agent in newly diagnosed childhood APL in small studies in India. The Children's Oncology Group (COG) in the United States recently completed a randomized study of arsenic trioxide as consolidation therapy for children with APL; the results are not yet available, but preliminary information suggests that it is well tolerated.

The anti-CD33 monoclonal antibody gemtuzumab has been very effective in adults with relapsed APL, and it has been well tolerated by pediatric patients with other types of leukemia. The cytotoxic agent N-acetyl-gamma calicheamicin that is derived from gemtuzumab attaches to the anti-CD33 antibody, causing DNA double strand breaks. It has greater cytotoxicity to leukemia cells than does doxorubicin, but it is not cardiotoxic. Moreover, molecular profiling has identified additional pathways that can be targeted by therapies. For example, a subgroup of patients with APL has FLT3 internal tandem duplication (ITD). This pathway may be an effective target for small molecules and other novel agents. Prospective randomized trials in children with APL are necessary to define the role of these agents.

### **H&O** What prognostic factors have been identified in pediatric APL?

**RR** The most consistent prognostic indicator in pediatric patients with APL who receive contemporary treatment is white blood cell (WBC) count. WBC count greater than  $5-10 \times 10^9/L$  is associated with an increased risk of relapse. The M3 microgranular variant (M3v), which is more common in children, has also been found to be associated with a poor prognosis. Because M3v is commonly associated with a high WBC count, it is not clear whether it is an independent prognostic factor. Other markers such as FLT3 ITD and *PML/RAR $\alpha$*  isoform BCR3 have been considered prognostic factors, but their predictive value remains to be defined. Persistent polymerase chain reaction (PCR) evidence of the *PML/RAR $\alpha$*  chimeric transcript after induction/consolidation chemotherapy is associated with an increased likelihood of relapse. Because positive PCR after induction/consolidation identifies only a small minority of children at risk of relapse, it is possible that the kinetics of disappearance of the leukemia clone may be a more robust prognostic marker. The kinetics of blast cell clearance is the most reliable prognostic factor in childhood ALL and is very important in AML as well but has not been fully explored in pediatric APL.

### **H&O** When is hematopoietic stem cell transplantation used in the treatment of pediatric APL?

**RR** The role of hematopoietic stem cell transplantation (HSCT) in APL has not been completely elucidated.

Allogeneic HSCT is considered for patients who have PCR-positive residual disease in two successive bone marrow samples after induction/consolidation therapy. For patients in PCR-negative second remission, either autologous or allogeneic HSCT has been used. Alternative-donor transplantation, including cord blood and haploidentical HSCT, are considered experimental at this time.

### **H&O** Is research into pediatric APL limited by its low incidence?

**RR** The rarity of this disease is the main limitation in advancing its treatment. In the United States, only approximately 2–3% of patients with AML have APL (1% of all cases of pediatric leukemia). The disease is more prevalent in Mexico and Central America, where APL accounts for 20–25% of AML cases in the pediatric population. As a general rule, rare diseases are more difficult to investigate. Collaborative studies, such as those performed by COG and the international Berlin-Frankfurt-Munich consortium, perhaps in collaboration with investigators in regions with a high incidence of APL, will be needed to learn more about pediatric APL.

### **H&O** What do you foresee for the future in the treatment of APL?

**RR** To decrease the anthracycline dose intensity, it is important to continue to explore the role of effective compounds that are already available, such as cytarabine, arsenic trioxide, and gemtuzumab ozogamicin, in children with newly diagnosed APL. Novel compounds such as FLT3 inhibitors can be investigated in relapsed disease. Non-leukemia-associated mortality continues to be high and should be reduced substantially. Some patients die before treatment is started, usually of intracranial hemorrhage. It is important to precisely define the events that precede this complication to learn how to prevent them. Understanding the mechanisms of RAS and the pharmacokinetics and pharmacodynamics of ATRA can lead to more rational use of this agent in pediatric APL. I look forward to better supportive care, the introduction of therapies that have been tested in clinical trials, and the

incorporation of new technology, including profiling, to better define prognostic groups. Pediatric APL already has a survival rate of 80–85%. With available therapies and available knowledge, this rate can be increased to 90% or higher.

### **Suggested Reading**

de Botton S, Coiteux V, Chevret V, et al. Outcome of childhood acute promyelocytic leukemia with all-trans-retinoic acid and chemotherapy. *J Clin Oncol*. 2004;22:1404-1412.

Falanga A, Rickles F. Pathogenesis and management of the bleeding diathesis in acute promyelocytic leukaemia. *Best Pract Res Clin Haematol*. 2003;16:463-482.

Feusner J, Gregory J Jr. Acute promyelocytic leukemia in children. *Best Pract Res Clin Haematol*. 2003;16:483-494.

Gale RE, Hills R, Pizzey AR, et al. Relationship between FLT3 mutation status, biologic characteristics, and response to targeted therapy in acute promyelocytic leukemia. *Blood*. 2005;106:3768-3776.

George B, Mathews V, Poonkuzhali B, et al. Hepatotoxicity profile of single agent arsenic trioxide in the treatment of newly diagnosed acute promyelocytic leukemia, its impact on clinical outcome and the effect of genetic polymorphisms on the incidence of hepatotoxicity. *Leukemia*. 2006 Mar 9; [Epub ahead of print].

Gomis F, Sanz J, Sempere A, et al. Immunofluorescent analysis with the anti-pml monoclonal antibody (PG-M3) for rapid and accurate genetic diagnosis of acute promyelocytic leukemia. *Ann Hematol*. 2004;83:687-690.

Lo Coco F, Ammatuna E, Noguera N. Treatment of acute promyelocytic leukemia with gemtuzumab ozogamicin. *Clin Adv Hematol Oncol*. 2006;4:57-62, 76-77.

Lo Coco F, Breccia M, Diverio D. Diagnostic value of detecting fusion proteins derived from chromosome translocations in acute leukaemia. *Best Pract Res Clin Haematol*. 2003;16:653-670.

Marty M, Ganem G, Fisher J, et al. Acute promyelocytic leukemia: retrospective study of 119 patients treated with daunorubicin. *Nouv Rev Fr Hematol*. 1984;26:371-378.

Ortega JJ, Madero L, Martin G, et al. Treatment with all-trans retinoic acid and anthracycline monochemotherapy for children with acute promyelocytic leukemia: a multicenter study by the PETHEMA Group. *J Clin Oncol*. 2005;23:7632-7640.

Sanz M, Tallman M, Lo-Coco F. Trick of the trade for the appropriate management of newly diagnosed acute promyelocytic leukemia. *Blood*. 2005;105:3019-3025.

Sanz M, Tallman M, Lo-Coco F. Practice points, consensus, and controversial issues in the management of patients with newly diagnosed acute promyelocytic leukemia. *Oncologist*. 2005;10:806-814.

Shen ZX, Shi ZZ, Fang J, et al. All-trans retinoic acid/As2O3 combination yields a high quality remission and survival in newly diagnosed acute promyelocytic leukemia. *Proc Natl Acad Sci U S A*. 2004;101:5328-5335.

Testi AM, Biondi A, Lo Coco F, et al. GIMEMA-AIEOPAIDA protocol for the treatment of newly diagnosed acute promyelocytic leukemia (APL) in children. *Blood*. 2005;106:447-453.