

### Practice Points, Consensus, and Controversial Issues in the Management of Patients with Newly Diagnosed Acute Promyelocytic Leukemia

MIGUEL A. SANZ,<sup>a</sup> MARTIN S. TALLMAN,<sup>b</sup> FRANCESCO LO-COCO<sup>c</sup>

<sup>a</sup>Hematology Service, University Hospital La Fe, Valencia, Spain; <sup>b</sup>Division of Hematology/Oncology, Feinberg School of Medicine, and Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, Illinois, USA; <sup>c</sup>Department of Biopathology, University "Tor Vergata", Rome, Italy

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#### LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Manage patients with a suspicion of APL.
2. Select appropriate diagnostic tools and strategies for rapid genetic diagnosis and molecular monitoring of minimal residual disease in APL patients.
3. Select appropriate frontline treatment and supportive care for patients with APL.
4. Provide practice points for appropriate evaluation of response.

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#### ABSTRACT

Recent reviews on acute promyelocytic leukemia (APL) treatment have focused on comparing therapeutic approaches, including all-*trans* retinoic acid (ATRA) and chemotherapy, and do not address several other aspects of APL management that are relevant to the outcome in individual patients. These aspects include appropriate diagnostic tools and strategies, supportive care, recognition and treatment of life-threatening

complications, evaluation of response, and, finally, management of the disease in special conditions such as older patients and pregnant women. In addition to reviewing current consensus and controversies of ATRA and chemotherapy treatment, this article addresses the above issues of APL management with special emphasis on aspects that distinguish APL from other acute myelogenous leukemias. *The Oncologist* 2005;10:806–814

#### INTRODUCTION

Recently, a number of exhaustive reviews have been published on the treatment progress achieved in acute promyelocytic leukemia (APL), representing one of the most spectacular advances in the treatment of human

cancer [1–4]. However, these have focused mainly on the comparison of therapeutic approaches, including all-*trans* retinoic acid (ATRA) and chemotherapy, without much attention given to several important, appar-

Correspondence: Miguel A. Sanz, M.D., Ph.D., Servicio de Hematología, Hospital Universitario La Fe, Avenida Campanar 21, 46009 Valencia, Spain. Telephone: +34-96-197 3057; Fax: +34-96-197 3281; e-mail: [msanz@uv.es](mailto:msanz@uv.es) Received March 30, 2005; accepted for publication August 23, 2005. ©AlphaMed Press 1083-7159/2005/\$12.00/0

ently “minor” diagnostic and therapeutic aspects that could have crucial importance in patient outcome.

In the present article, in addition to outline the current consensus and controversial issues in the management of patients with newly diagnosed APL, we aim to discuss some underestimated and less appreciated aspects specifically related to disease management that we consider important for the outcome of individual patients (“tricks of the trade”).

### APPROACH TO THE PATIENT WITH SUSPECTED APL

Although a general consensus exists on the need to confirm the diagnosis of APL at the genetic level, treatment of this leukemia should be started even before the results of genetic tests are available. Once the suspicion of APL is established on the basis on morphologic criteria, the disease should be managed as a medical emergency requiring the following rapid and simultaneous actions:

(a) Initiate supportive measures to counteract the coagulopathy and decrease the risk of fatal hemorrhage, an especially threatening complication that most frequently occurs before beginning ATRA treatment and during the first days of induction [5]. This support should consist of fresh frozen plasma, fibrinogen, and platelet transfusions to maintain fibrinogen and platelets above 150 mg/dl and  $30\text{--}50 \times 10^9$  per liter, respectively, until disappearance of all clinical and laboratory signs of coagulopathy (i.e., hypofibrinogenemia, increased fibrinogen-fibrin degradation products, elevated levels of D-dimer, and prolonged prothrombin and thrombin times). These measures should be more aggressive in patients with active bleeding or laboratory signs of severe coagulopathy and in those who are at higher hemorrhagic risk, such as older patients, patients with elevated WBC count at presentation, and patients with an abnormally increased level of serum creatinine [5]. The benefit of antifibrinolytic agents and heparin for the control of the coagulopathy remains uncertain.

(b) Start treatment with ATRA without waiting for genetic confirmation of diagnosis, preferably the same day that the diagnosis is suspected. ATRA is known to rapidly ameliorate the coagulopathy; hence, early initiation of ATRA is likely to decrease the risk of severe bleeding. The supportive measures to be adopted upon institution of ATRA treatment are discussed in “Supportive Measures” in the “Induction Therapy” section.

(c) Confirm diagnosis in bone marrow at the genetic level. Demonstration of the t(15;17) or its counterpart, the promyelocytic leukemia/retinoic acid receptor alpha (*PML/RAR $\alpha$* ) hybrid gene, by conventional karyotyping, fluorescence in situ hybridization (FISH), or reverse tran-

scription–polymerase chain reaction (RT-PCR) is mandatory because the efficacy of differentiation treatment based on retinoids is strictly dependent on the presence of the *PML/RAR $\alpha$*  fusion in leukemia cells. Nevertheless, it should be noted that all these methods are equally specific, but not equally sensitive to confirm the diagnosis.

Another interesting option for a rapid and accurate diagnosis of APL is the use of immunostaining assays with anti-PML antibodies to detect the characteristic microparticulate nuclear pattern of the PML protein resulting from the translocation [6–9]. Although this technique should not replace RT-PCR, which defines the type of *PML/RAR $\alpha$*  isoform and the target for minimal residual disease evaluation in the individual patient, it could be particularly useful in cases in which RNA is not available or to confirm diagnosis in institutions and developing countries where genetic tests are not routinely available.

Morphologic diagnosis in bone marrow, although highly predictive of the specific genetic lesion in hypergranular (typical) cases, is considered insufficient [10]. A morphological suspicion of *PML/RAR $\alpha$* –positive APL can be reinforced by the study of the characteristic immunophenotypic features of blast cells by multiparameter flow cytometry [11, 12]. *PML/RAR $\alpha$* –positive leukemia blasts from APL typically show immunophenotypic features that are similar to those of normal promyelocytes (i.e., CD34<sup>+/+</sup>–heterogeneous, CD117<sup>+/+</sup>–dim, HLADR<sup>+/+</sup>–dim, CD13<sup>+/2+</sup>, and CD11b<sup>-</sup>) [11]; however, unlike their normal counterpart, *PML/RAR $\alpha$* –positive promyelocytes display abnormally low levels of CD15 (CD15<sup>+/+</sup>–dim versus CD15<sup>3+</sup>) [11, 12].

### INDUCTION THERAPY

#### Targeted Treatment

Once a diagnosis of APL has been confirmed at the genetic level, targeted induction therapy should be promptly started with ATRA combined with anthracycline-based chemotherapy [1–3, 13]. As to the type of anthracycline, idarubicin has been more frequently used as a monochemotherapy option, whereas daunorubicin has been mainly used in combination with Ara-C. The role of Ara-C in this combination has been recently investigated by the European APL group in a randomized study that suggested a benefit from adding his agent [14]. However, the only randomized study comparing idarubicin monotherapy versus idarubicin plus Ara-C [15], although conducted in the pre-ATRA era, showed no advantage of adding Ara-C. Given these results reported with ATRA plus idarubicin alone, it is unlikely that any trial will randomly assign patients to this combination, with or without Ara-C.

Exceptions to the use of the anthracycline-based induction regimens should be considered only for individual cases in which chemotherapy is contraindicated. This is the case for patients with certain clinical conditions, such as severe organ failure, or anticoagulant therapy and for very elderly patients (older than 80 years) [16]. Treatment of APL in these and other special circumstances (e.g., pregnant women) is addressed in “Management of Special Situations.” Some patients with a temporary contraindication for chemotherapy (e.g., those with reversible organ dysfunction) could be induced with ATRA alone and given chemotherapy subsequently. Differentiation therapy, such as ATRA, arsenic trioxide (ATO), or both, followed by low-dose chemotherapy and intermittent ATRA maintenance might be adopted in the above patients as well as in other infrequent settings (e.g., Jehovah’s Witnesses).

The standard approach with ATRA and anthracycline-based chemotherapy should not be modified based on supposedly “adverse” prognostic factors such as additional chromosome aberrations other than t(15;17), CD56 expression, or short *PML/RAR $\alpha$*  isoform. In large cohorts of patients receiving modern ATRA plus chemotherapy regimens, the presence of additional chromosome lesions did not negatively affect the prognostic outcome [17–19]. Similarly, no significant differences in response to treatment according to the *PML/RAR $\alpha$*  isoform have been reported in all of the major multicenter trials combining ATRA and chemotherapy as initial therapy [13, 20–23].

### Supportive Measures

As mentioned above, supportive measures aimed at counteracting the coagulopathy should be started immediately after a suspected diagnosis of APL. Once the patient has initiated targeted treatment with ATRA, physicians caring for patients with APL should be aware of any symptom or sign suggestive of the retinoic acid syndrome (RAS), such as dyspnea, unexplained fever, weight gain, peripheral edema, pulmonary infiltrates, or pleuropericardial effusion [24]. Although none of the symptoms and signs that define the syndrome is pathognomonic, because they can be due to concurrent medical problems, such as bacteremia, sepsis, or congestive heart failure, specific treatment with dexamethasone at a dose of 10 mg twice a day intravenously for at least 4 days or until disappearance of symptoms should be initiated immediately at the very earliest suspicion of RAS. The rapid and life-threatening nature of the full-blown syndrome (referred to as *definite* RAS in the nomenclature proposed by Frankel et al. [24]) does not allow for any delay to start therapy. No consensus exists on the utility of discontinuing ATRA during the syndrome, although its withdrawal is advisable for patients developing severe RAS. Otherwise, ATRA could be maintained unless

progression to overt syndrome or lack of response to dexamethasone is observed. If a favorable response is obtained, ATRA should be resumed and dexamethasone maintained until complete disappearance of symptoms.

Whereas therapy with dexamethasone currently represents the standard approach to treat patients who develop RAS, there is at present no evidence that prophylactic corticosteroid is advantageous in reducing morbidity and mortality associated with this syndrome. Nevertheless, in uncontrolled studies [25, 26], a very low mortality rate due to RAS has been reported by administering dexamethasone prophylactically in patients with a WBC count greater than  $5 \times 10^9$  per liter.

Besides specific measures to reduce RAS- and hemorrhage-associated morbidity and mortality, the policy for red cell transfusion, use of antibiotics, and other supportive measures, including use of hematopoietic growth factors, does not differ from that commonly used for patients with other subtypes of acute myelogenous leukemia (AML).

### Central Nervous System Prophylaxis

Although relapse in the central nervous system (CNS) is uncommon in patients with APL, an increasing number of cases of CNS involvement have been reported in recent years suggesting a possible association with ATRA use. However, a large study of the Italian Group of Malignant Hematological Diseases of the Adult (GIMEMA) carried out in patients treated with or without ATRA failed to demonstrate this correlation [27]. Rather, it is conceivable that an increased risk of relapse due to the indisputable increased survival of patients treated with ATRA-based regimens may account for the apparently higher prevalence of extramedullary disease, including CNS relapses, that otherwise, historically, did not have the opportunity to emerge.

Because the majority of CNS relapses occur in patients with hyperleukocytosis, some groups include CNS prophylaxis for patients in this particular high-risk setting. For such patients, because lumbar puncture at presentation and during induction is extremely hazardous, it is advisable to postpone CNS prophylaxis until after the achievement of complete remission (CR). However, the benefit of this policy has not been definitely established. In contrast, there is a general consensus to avoid CNS prophylaxis for patients without hyperleukocytosis, in whom the risk of CNS relapse is extremely low.

### Assessment of Induction Response

Whereas early response assessment by bone marrow aspirate (7–14 days after induction therapy) can provide useful prognostic information in other AML subtypes, in patients with APL receiving ATRA, this evaluation usually reveals

a relatively hypercellular pattern that reflects initial differentiation of leukemic cells. Moreover, cytomorphological features showing delayed blast maturation or persistence of atypical promyelocytes are occasionally detectable in patients with APL several weeks after the start of induction therapy with ATRA (up to 40–50 days). Such features have been occasionally misinterpreted and erroneously considered as indicating leukemia resistance. Irrespective of these findings, treatment should be continued until terminal differentiation of blasts and achievement of CR that invariably occurs in all patients with genetically proven APL who survive to induction with ATRA and chemotherapy. Results of RT-PCR, karyotyping, and FISH analyses performed early after induction may also be misleading. In fact, several large prospective studies have failed to demonstrate any correlation between the postinduction PCR status and successive patient outcome [20, 21, 23, 25]. Similarly, the results of both karyotyping and FISH analyses performed early after induction are not informative with respect to successive outcome and can be misleading. Therefore, clinicians should refrain from making therapeutic decisions based on any type of laboratory observations made at this time point. After the counts normalize, the persistence in bone marrow of any atypical morphological feature or cytogenetic or molecular abnormality should only lead to repeat a new marrow examination until CR is achieved.

### CONSOLIDATION THERAPY

Due to the presence of a specific marker amenable to PCR amplification, APL is the subtype of AML in which the benefit derived from consolidation has been more extensively assessed. This benefit has been demonstrated by the achievement of molecular remission in 90%–99% of patients receiving at least two or three intensive cycles of consolidation with anthracycline-based chemotherapy [3]. This high molecular remission rate has led to the adoption of this strategy as the standard for consolidation. Although the benefit provided by the addition of ATRA to chemotherapy for consolidation has not been demonstrated in randomized studies, historical comparisons of consecutive studies carried out separately by the GIMEMA [28] and Program for the Study and Treatment of Hematological Malignancies (PETHEMA) [25] groups suggest a synergistic effect of this combination that may also contribute to improve the outcomes in APL. In addition, the results of either studies have also questioned the role of non-anthracycline drugs for both induction and consolidation therapy, at least for low- and intermediate-risk patients.

### Risk-Adapted Consolidation

Another interesting issue addressed in the aforementioned GIMEMA and PETHEMA studies [25, 28] is the design of

risk-adapted approaches to modulate treatment intensity during consolidation according to predefined risk of relapse [29]. This tailored strategy seems an efficient approach to minimize therapy-related morbidity and mortality while maintaining the potential of cure for each relapse-risk group. It is remarkable that both studies reported low toxicity, high degree of compliance, and high antileukemic efficacy using ATRA combined with anthracycline monochemotherapy, especially in low- and intermediate-risk patients. The favorable long-term outcomes reported in these and other studies using state-of-the-art treatments do not leave room for more aggressive postremission therapy for low- and intermediate-risk patients in first CR. As to the high-risk group, recent data from the ongoing GIMEMA study [28] conducted in patients younger than 60 years suggest that this category can benefit from using ATRA combined with polychemotherapy regimens, including anthracyclines and nonintercalating agents such as high-dose cytarabine.

The small fraction of patients who test PCR-positive for the *PML/RAR $\alpha$*  hybrid gene at the end of consolidation (molecular persistence) have a dismal prognosis [30] and should receive additional therapy aimed at obtaining molecular remission, including novel agents such as gentuzumab ozogamycin (GO) and ATO, as well as allogeneic hematopoietic stem cell transplantation (HSCT).

As discussed for induction therapy, exceptions to the use of the standard approach for consolidation should be considered only for individual cases in which intensive chemotherapy is contraindicated. Alternative therapeutic options for consolidation in these patients may be the administration of ATO or GO.

### Molecular Assessment at the End of Consolidation

Unlike molecular assessment of response performed early after induction, RT-PCR evaluation after completion of consolidation is relevant to determine the short-term risk of relapse in the individual patient [10, 31]. However, it is important to recognize that this predictive value has only been demonstrated in studies in which low-sensitivity amplification techniques were used (sensitivity threshold between  $10^{-3}$  and  $10^{-4}$ ). As was discussed in the previous section (“Risk-Adapted Consolidation”), an accurate assessment of PCR status at the end of consolidation is crucial because patients who show residual *PML/RAR $\alpha$*  transcripts at this time point are candidates for further intensification, whereas those who test PCR-negative would proceed to receive maintenance. To minimize the risk of a false-positive result, the detection of residual transcripts should be confirmed by sending a new marrow sample to a highly experienced reference laboratory that uses a low-sensitivity assay.

Given the extremely low frequency of molecular persistence of residual disease after consolidation for patients enrolled in state-of-the-art protocols, this evaluation can be avoided whenever experienced laboratory support is not available for the analysis.

### Role of HSCT

The high cure rate obtained using upfront ATRA and chemotherapy indicates that there is no role for HSCT for patients who are in the first molecular remission at the end of consolidation. For the small fraction of patients with persistent minimal residual disease at this time point, given the overall poor prognosis of this subset of patients [30], new approaches such as ATO and/or GO followed by HSCT should be considered. Allogeneic HSCT is the recommended choice for patients with an available HLA-identical donor, whereas autologous HSCT is a valid alternative for patients ineligible for allogeneic transplant. In the latter case, however, the achievement of PCR-negativity prior to autologous transplantation is considered a mandatory requisite.

### MAINTENANCE THERAPY

Two randomized studies have shown a benefit from administering ATRA maintenance given intermittently [13] or continuously [32]. However, the continuous schedule for ATRA has been associated with significant toxicity [32] and does not seem to be supported by recent pharmacokinetic and pharmacodynamic data on this agent [33]. Besides the benefit of ATRA for maintenance, the APL93 study of the European group [13] showed an advantage in administering low-dose chemotherapy with methotrexate and 6-mercaptopurine. This study also reported an additional benefit from using the triple combination of ATRA, methotrexate, and 6-mercaptopurine that resulted in lower relapse rate and proved particularly effective for patients with an elevated WBC count at presentation. In contrast, results preliminarily reported, but still not published, from a similar study carried out by the GIMEMA group failed to demonstrate a benefit of maintenance in APL [34]. Although maintenance therapy remains at present a subject of investigation, particularly with respect to its optimal schedule and the target patient population, the majority of protocols include this approach into their overall therapeutic strategy.

Some physicians have raised concerns regarding the use of ATRA during the postremission period in patients who previously developed RAS during induction. However, ATRA can be used safely for either consolidation or maintenance therapy. In fact, no cases of RAS have been reported in patients receiving ATRA while in CR.

### Molecular Monitoring During Maintenance Therapy and Beyond

Although several studies have clearly demonstrated that repeatedly negative RT-PCR tests following consolidation correlate strongly with prolonged survival, whereas conversion to PCR-positivity is associated with impending hematologic relapse [10, 31], the increasing antileukemic efficacy reported with state-of-the-art treatments has currently questioned the benefit of an indiscriminate molecular monitoring. Nevertheless, for patients with hyperleukocytosis, it still seems reasonable to recommend a stringent monitoring, at least every 2 months in the early postconsolidation period and thereafter every 3 months for two additional years. By contrast, molecular monitoring of patients with an initial WBC count less than  $10 \times 10^9$  per liter appears questionable in terms of cost-effectiveness.

Considerations about the type and reliability of PCR techniques have been made previously (“Molecular Assessment at the End of Consolidation”). The clinical advantage of using quantitative RT-PCR in this situation remains to be determined.

### MANAGEMENT OF SPECIAL SITUATIONS

#### Treatment of the Older Patient with APL

Older patients (60 years or older) are usually treated with less intensive regimens [13, 21, 35] because of their vulnerability to therapy-related toxicity. However, based on the excellent tolerance and high degree of compliance observed in the PETHEMA studies using ATRA and anthracycline monochemotherapy for induction and consolidation therapy [21, 25], older patients were treated by this group with the same strategy, dose, and intensity of chemotherapy as used in younger patients, except for a small reduction of idarubicin during induction for patients 70 years or older. This approach provided excellent results comparable with those reported for younger patients [36].

#### Patients with Severe Comorbidities

Older and younger patients with severe comorbidities in which intensive chemotherapy is contraindicated (e.g., patients with cardiomyopathy or other severe organ dysfunction) are candidates for alternative front-line approaches using ATRA, ATO, and GO. A study presently conducted at the M.D. Anderson Cancer Center (Houston, TX) in which an ATO plus ATRA combination is used to avoid front-line chemotherapy may serve as a reference in this context, although its results are still preliminary [37].

### Management of APL in Children

To our knowledge, only four studies including 22, 31, 66, and 110 children from the German-Austrian-Swiss, European APL, PETHEMA, and GIMEMA groups [38–41], respectively, have reported therapeutic results using combinations of ATRA and anthracycline-based chemotherapy. In general, outcome results in children with APL, with CR and disease-free survival rates above 90% and 75%, respectively, are comparable with those reported in adult patients.

To decrease the risk of pseudotumor cerebri during ATRA treatment, a side effect frequently observed in children [42], some groups have used a reduced dose of ATRA for the treatment of children and adolescents with APL [38, 40, 41]. The apparently lower incidence of pseudotumor cerebri and headache, together with the excellent therapy results obtained with ATRA at 25 mg/m<sup>2</sup> per day, when compared with the administration of ATRA at 45 mg/m<sup>2</sup> per day [39], suggests that 25 mg/m<sup>2</sup> could be the recommended dose, at least for children. Pseudotumor cerebri is characterized by increased intracranial pressure, headache, nausea, and vomiting that may be accompanied by vision disturbances and papilledema. Treatment of this complication consists of temporary discontinuation or dose reduction of ATRA and administration of dexamethasone, osmotic diuretics (mannitol), and analgesics.

### Management of Pregnant Patients with APL

Management of APL during pregnancy is always a cause of major concern because of the hemorrhagic risk and the potential teratogenicity of ATRA and chemotherapy. However, no serious complications have been reported in the mother or the fetus for patients receiving ATRA alone or combined with chemotherapy [43]. In spite of the limited experience, such treatments seem reasonably safe when applied to patients with APL during the second or third trimester of pregnancy, as they do not seem to compromise the delivery of a healthy newborn. In fact, the products of all the pregnancies reported, although premature, survived and developed normally. Nevertheless, stringent fetal monitoring, with particular emphasis on cardiac function, is recommended for patients receiving ATRA during pregnancy because some cases of reversible fetal arrhythmias have been reported [44, 45]. By contrast, although specific information regarding teratogenicity of ATRA is lacking, its use during the first trimester of pregnancy should take into account the known teratogenic action of retinoids.

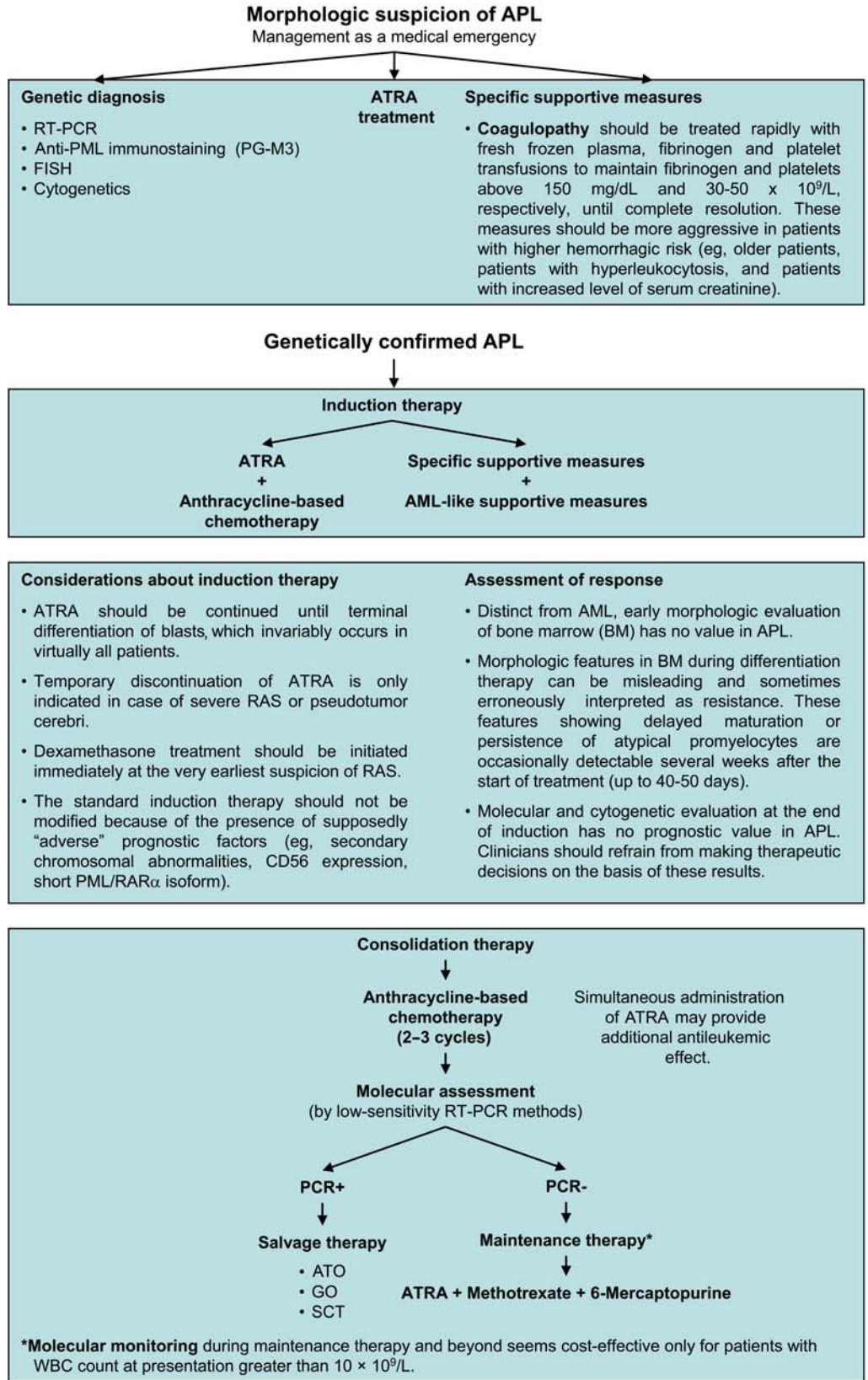
### Management of Hyperleukocytosis, the APL Differentiation Syndrome, and Prolonged QT Interval Associated with ATO

The high response rate reported with ATO in patients with APL in relapse [46, 47] has suggested a role for this drug as an alternative for patients in whom chemotherapy is contraindicated. ATO is administered as a single agent and is quite well tolerated. Hyperleukocytosis, similar to that observed in patients receiving ATRA alone, occurs, and, in general, ATO may be continued with careful observation [48]. Approximately 50% of patients develop leukocytosis with ATO with a peak WBC count at approximately 20 days after the first dose. Such leukocytosis resolves at a median of 10.5 days after the peak, despite continuation of ATO. Diagnosis and management of the APL differentiation syndrome, which appears in approximately 30% of patients treated with ATO, are identical to those described for ATRA (see “Supportive Measures”). If the patient has persistent hyperleukocytosis despite resolution of the syndrome, it may be prudent to continue dexamethasone until the hyperleukocytosis resolves to less than 10,000 per  $\mu$ l. No additional cytotoxic therapy is required. ATO is also associated with prolongation of the QT interval, and careful monitoring is required [49]. In addition, maintenance of the serum potassium and serum magnesium well above the lower limit of normal is indicated. Both are recommended to be above 4 mmol/l (4 mEq/l) and 0.82 mmol/l (2 mg/dl), respectively. For patients with a heart rate of above 60 beats per minute, if the QTc (heart rate corrected) interval is prolonged more than 500 ms, ATO should be held, the electrolytes repleted (potassium and magnesium), and other medications that may cause prolonged QTc interval searched for and discontinued. For patients with a heart rate of 60 beats per minute or fewer, the absolute QT (uncorrected for the heart rate) interval can be used. Once the QT/QTc returns to approximately 460 ms and the electrolytes are repleted, the ATO may be resumed. In addition to the prolongation of the QT/QTc interval, and the APL differentiation syndrome mentioned earlier in this paragraph, approximately 13% of patients may develop hypokalemia or hyperglycemia.

An algorithm of practice points is summarized in Figure 1.

### DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.



**Figure 1.** Abbreviations: AML, acute myelogenous leukemia; APL, acute promyelocytic leukemia; ATO, arsenic trioxide; ATRA, all-*trans* retinoic acid; FISH, fluorescence in situ hybridization; GO, gentuzumab ozogamycin; PML, promyelocytic leukemia; RAR, retinoic acid receptor; RAS, retinoic acid syndrome; RT-PCR, reverse transcription–polymerase chain reaction; SCT, stem cell transplantation.

## REFERENCES

- 1 Tallman MS, Nabhan Ch, Feusner JH et al. Acute promyelocytic leukemia: evolving therapeutic strategies. *Blood* 2002;99:759–767.
- 2 Ohno R, Asou N, Ohnishi K. Treatment of acute promyelocytic leukemia: strategy toward further increase of cure rate. *Leukemia* 2003;17:1454–1463.
- 3 Sanz MA, Martín G, Lo-Coco F. Choice of chemotherapy in induction, consolidation and maintenance in acute promyelocytic leukemia. *Baillieres Best Pract Res Clin Haematol* 2003;16:433–451.
- 4 Douer D. New advances in the treatment of acute promyelocytic leukemia. *Int J Hematol* 2002;76(suppl 2):179–187.
- 5 Tallman MS, Brenner B, de la Serna J et al. APL coagulopathy workshop, 21 January 2004, London, England. *Leuk Res* 2005;29:347–351.
- 6 Falini B, Flenghi L, Fagioli M et al. Immunocytochemical diagnosis of acute promyelocytic leukemia (M3) with the monoclonal antibody PG-M3 (Anti-PML). *Blood* 1997;90:4046–4053.
- 7 Villamor N, Costa D, Aymerich M et al. Rapid diagnosis of acute promyelocytic leukemia by analyzing the immunocytochemical pattern of the PML protein with the monoclonal antibody PG-M3. *Am J Clin Pathol* 2000;114:786–792.
- 8 Samoszuk MK, Tynan W, Sallash G et al. An immunofluorescent assay for acute promyelocytic leukemia. *Am J Clin Pathol* 1998;109:205–210.
- 9 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.
- 10 Lo-Coco F, Diverio D, Falini B et al. Genetic diagnosis and molecular monitoring in the management of acute promyelocytic leukemia. *Blood* 1999;94:12–22.
- 11 Orfao A, Ortuño F, de Santiago M et al. Immunophenotyping of acute leukemias and myelodysplastic syndromes. *Cytometry* 2004;58A:62–71.
- 12 Orfao A, Chillón MC, Bortoluci AM et al. The flow cytometric pattern of CD34, CD15 and CD13 expression in acute myeloblastic leukemia is highly characteristic of the presence of PML/RARalpha gene rearrangements. *Haematologica* 1999;84:405–412.
- 13 Fenaux P, Chastang C, Sanz MA et al. A randomized comparison of ATRA followed by chemotherapy and ATRA plus chemotherapy, and the role of maintenance therapy in newly diagnosed acute promyelocytic leukemia. *Blood* 1999;94:1192–1200.
- 14 Ades L, Raffoux E, Chevret S et al. Is Ara-C required in the treatment of newly diagnosed APL? Results of a randomized trial (APL 2000). *Blood* 2004;104(suppl 1):391.
- 15 Avvisati G, Petti MC, Lo-Coco F et al. Induction therapy with idarubicin alone significantly influences event-free survival duration in patients with newly diagnosed hypergranular acute promyelocytic leukemia: final results of the GIMEMA randomized study LAP 0389 with 7 years of minimal follow-up. *Blood* 2002;100:3141–3146.
- 16 Sham RL, Tallman MS. Treatment of acute promyelocytic leukemia in the very elderly: case report and review of the literature. *Leuk Res* 2004;28:1347–1350.
- 17 De Botton S, Chevret S, Sanz M et al. Additional chromosomal abnormalities have no effect on the clinical outcome of patients with acute promyelocytic leukemia. *Br J Haematol* 2000;111:801–806.
- 18 Hernández JM, Martín G, Gutiérrez NC et al. Additional cytogenetic changes do not influence the outcome of patients with newly diagnosed acute promyelocytic leukemia treated with an ATRA plus anthracyclin based protocol. A report of the Spanish group PETHEMA. *Haematologica* 2001;86:807–813.
- 19 Cervera J, Martín G, Hernández JM et al. Additional chromosome abnormalities have no prognostic value in acute promyelocytic leukemia patients treated with simultaneous ATRA and anthracycline-based chemotherapy: an update of the LPA96 and LPA99 PETHEMA protocols. *Blood* 2004;104(suppl 1):2019.
- 20 Mandelli F, Diverio D, Avvisati G et al. Molecular remission in PML/RAR alpha-positive acute promyelocytic leukemia by combined all-trans retinoic acid and idarubicin (AIDA) therapy. *Blood* 1997;90:1014–1021.
- 21 Burnett AK, Grimwade D, Solomon E et al. Presenting white blood cell count and kinetics of molecular remission predict prognosis in acute promyelocytic leukemia treated with all-trans retinoic acid: result of the randomized MRC trial. *Blood* 1999;93:4131–4143.
- 22 Lengfelder E, Reichert A, Schoch C et al. Double induction strategy including high dose cytarabine in combination with all-trans retinoic acid: effects in patients with newly diagnosed acute promyelocytic leukemia. *Leukemia* 2000;14:1362–1370.
- 23 Sanz MA, Martín G, Rayón C et al. A modified AIDA protocol with anthracycline-based consolidation results in high antileukemic efficacy and reduced toxicity in newly diagnosed PML/RAR alpha-positive acute promyelocytic leukemia. *Blood* 1999;94:3015–3021.
- 24 Frankel SR, Eardley A, Heller G et al. All-trans retinoic acid for acute promyelocytic leukemia. Results of the New York study. *Ann Intern Med* 1994;120:278–286.
- 25 Sanz M, Martín G, Gonzalez M et al. Risk-adapted treatment of acute promyelocytic leukemia with all-trans-retinoic acid and anthracycline monochemotherapy: a multicenter study by the PETHEMA group. *Blood* 2004;103:1237–1243.
- 26 Wiley JS, Firkin FC. Reduction of pulmonary toxicity by prednisolone prophylaxis during all-trans retinoic acid treatment of acute promyelocytic leukemia. Australian Leukaemia Study Group. *Leukemia* 1995;9:774–778.
- 27 Specchia G, Lo-Coco F, Vignetti M et al. Extramedullary involvement at relapse in acute promyelocytic leukemia patients treated or not with ATRA. A report by the GIMEMA Group. *J Clin Oncol* 2001;19:4023–4028.
- 28 Lo-Coco F, Avvisati G, Vignetti M et al. Front-line treatment of acute promyelocytic leukemia with AIDA induction followed by risk-adapted consolidation: results of the AIDA-2000 trial of the Italian GIMEMA group. *Blood* 2004;104:392a.
- 29 Sanz MA, Lo-Coco F, Martín G et al. Definition of relapse risk and role of non-anthracycline drugs for consolidation in patients with acute promyelocytic leukemia: a joint study of the PETHEMA and GIMEMA cooperative groups. *Blood* 2000;96:1247–1252.
- 30 Breccia M, Diverio D, Noguera NI et al. Clinico-biological features and outcome of acute promyelocytic leukemia patients with persistent polymerase chain reaction-detectable disease after the AIDA front-line induction and consolidation therapy. *Haematologica* 2004;89:29–33.
- 31 Grimwade D, Lo-Coco F. Acute promyelocytic leukemia: a model for the role of molecular diagnosis and residual disease monitoring in directing treatment approach in acute myeloid leukemia. *Leukemia* 2002;16:1959–1973.
- 32 Tallman MS, Andersen JW, Schiffer CA et al. All-trans retinoic acid in acute promyelocytic leukemia. *N Engl J Med* 1997;337:1021–1028.
- 33 Muindi J, Frankel SR, Miller WH et al. Continuous treatment with all-trans RA progressively decreases plasma drug concentrations: implications for relapse and resistance in acute promyelocytic leukemia. *Blood* 1992;79:299–307.

- 34 Avvisati G, Petti MC, Lo-Coco F et al. The Italian way of treating acute promyelocytic leukemia. *Blood* 2003;102(suppl 1):142.
- 35 Mandelli F, Latagliata R, Avvisati G et al. Treatment of elderly patients ( $\geq 60$  years) with newly diagnosed acute promyelocytic leukaemia. Results of the Italian multicenter group GIMEMA with ATRA and idarubicin (AIDA) protocols. *Leukemia* 2003;17:1085–1090.
- 36 Sanz MA, Vellenga E, Rayon C et al. All-trans retinoic acid and anthracycline monochemotherapy for the treatment of elderly patients with acute promyelocytic leukemia. *Blood* 2004;104:3490–3493.
- 37 Estey EH, Garcia-Manero G, Ferrajoli A et al. Use of all-trans retinoic acid + arsenic trioxide to eliminate or minimize use of chemotherapy in untreated acute promyelocytic leukemia. *Blood* 2004;104:393a.
- 38 Mann G, Reinhardt D, Ritter J et al. Treatment with all-trans retinoic acid in acute promyelocytic leukemia reduces early deaths in children. *Ann Hematol* 2001;80:417–422.
- 39 De Botton S, Coiteux V, Chevret S et al. Outcome of childhood acute promyelocytic leukemia with all-trans-retinoic acid and chemotherapy. *J Clin Oncol* 2004;22:1404–1412.
- 40 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.
- 41 Testi AM, Lo-Coco F, Biondi A, et al. GIMEMA-AIEOP AIDA protocol for the treatment of newly diagnosed promyelocytic leukemia in children. *Blood* 2005;106:447–453.
- 42 Mahmoud HH, Hurwitz CA, Roberts WM et al. Tretinoin toxicity in children with acute promyelocytic leukemia. *Lancet* 1993;342:1394–1395.
- 43 Fadilah SAW, Hatta AZ, Keng CS et al. Successful treatment of acute promyelocytic leukemia in pregnancy with all-trans retinoic acid. *Leukemia* 2001;15:1665–1666.
- 44 Lipovsky MM, Biesma DH, Christiaens GCML et al. Successful treatment of acute promyelocytic leukemia with all-trans retinoic acid during late pregnancy. *Br J Haematol* 1996;94:699–701.
- 45 Terada Y, Shindo T, Endoh A et al. Fetal arrhythmia during treatment of pregnancy-associated acute promyelocytic leukemia with all-trans retinoic acid and favorable outcome. *Leukemia* 1997;11:454–455.
- 46 Niu C, Yan II, Yu T et al. Studies on treatment of acute promyelocytic leukemia with arsenic trioxide: remission induction, follow-up and molecular monitoring in 11 newly diagnosed and 47 relapsed acute promyelocytic leukemia patients. *Blood* 1999;94:3315–3324.
- 47 Soignet S, Frankel S, Douer D et al. United States multicenter study of arsenic trioxide in relapsed acute promyelocytic leukemia. *J Clin Oncol* 2001;19:3852–3860.
- 48 Camacho L, Soignet S, Chanel S et al. Leukocytosis and the retinoic acid syndrome in patients with acute promyelocytic leukemia treated with arsenic trioxide. *J Clin Oncol* 2000;18:2620–2625.
- 49 Barbey J, Pezzullo J, Soignet S. Effect of arsenic trioxide on QT interval in patients with advanced malignancies. *J Clin Oncol* 2003;21:3609–3615.

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Miguel A. Sanz, Martin S. Tallman and Francesco Lo-Coco

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