Tricks of the trade for the appropriate management of newly diagnosed acute promyelocytic leukemia

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

Most reviews on the state-of-the-art treatment in acute promyelocytic leukemia (APL) have focused mainly on the comparison of therapeutic approaches, including all-trans retinoic acid (ATRA) and chemotherapy. However, outcome of individual patients also depends on appropriate knowledge of several aspects related to APL management that are less appreciated and/or are underestimated in the literature. These aspects include appropriate diagnostic strategy, use of supportive care, early recognition and treatment of life-threatening complications typically associated with APL and its specific treatment, tools and timing for adequate evaluation of response, and, finally, management of the disease in special conditions such as older patients and pregnant women. Besides reviewing current consensus and controversies on the use of ATRA and chemotherapy in the distinct treatment phases (eg, induction, consolidation, maintenance), this article addresses the aforementioned issues on APL management (“tricks of the trade”) with special emphasis on several peculiar aspects that distinguish APL from other acute myeloid leukemias. (Blood. 2005;105:3019-3025) © 2005 by The American Society of Hematology

Introduction

The introduction of all-trans retinoic acid (ATRA) in initial therapy of acute promyelocytic leukemia (APL) represents one of the most spectacular advances in the treatment of human cancer. Over the past decade, several large multicenter trials that used various ATRA and anthracycline-based chemotherapy combinations have reported excellent outcome such that the estimated fraction of long-term survivors with APL exceeds 70% of patients in most contemporary studies. Recently, a number of exhaustive reviews have been published on the treatment progress achieved in this particular subtype of leukemia. However, these reviews have focused mainly on the comparison of therapeutic approaches, including ATRA and chemotherapy, without much attention given to several important apparently “minor” diagnostic and therapeutic aspects, which include supportive care, and could have a crucial importance in patient outcome.

In the present article, in addition to reviewing the current consensus and controversies on the most appropriate use of the armamentarium of drugs for the treatment of APL in the distinct phases, we aim to discuss some underestimated and less-appreciated aspects on the management of the disease that we consider important for the outcome of individual patients (tricks of the trade). Additional reasons for focusing on these aspects include the following. (1) APL is a rare disease and most patients are currently treated in institutions with limited experience. (2) The excellent outcome reported in recent studies that used various ATRA plus chemotherapy combinations may engender a sense of safety and complacency which may lead to underestimating other crucial aspects specifically related to the management of the disease. (3) Some other issues related to the treatment of APL are not well known and include the erroneous adoption of practices routinely used for the management of other acute myeloid leukemia (AML) subtypes.

Dealing with a suspected diagnosis of APL

Once a diagnosis of APL is suspected upon morphologic examination, the disease should be managed as a medical emergency that requires the following simultaneous and rapid actions.

What is the best way to prevent the life-threatening complications attributable to the coagulopathy?

The importance of rapidly providing adequate supportive therapy relies on the fact that a sizable fraction of patients develop fatal hemorrhages during the diagnostic evaluation before beginning antileukemic therapy or during the first days of induction. A recent survey of the PETHEMA (Programa de Estudio y Tratamiento de las Hemopatías Malignas) group, focused on analyzing the magnitude of this problem, showed that about 3% of all patients diagnosed with APL die of hemorrhage before therapy has been started. In addition, approximately one half of the 5% of hemorrhagic deaths recorded during induction occur during the first week of treatment. Therefore, it seems reasonable that rapid institution of supportive measures to reverse the coagulopathy may lower the risk of life-threatening hemorrhages in these patients. Treatment of the coagulopathy should be based on liberal transfusion of fresh frozen plasma, fibrinogen, or both, as well as on aggressive platelet support to maintain the fibrinogen level above 1.5 g/L (150 mg/dL) and the platelet counts above 30 to 50 × 10^9/L, until disappearance...
of all clinical and laboratory signs of coagulopathy. These supportive measures should be even more aggressive in patients with higher hemorrhagic risk (eg, older patients, patients with hyperleukocytosis or overt clinical or laboratory signs of coagulopathy, and patients with an abnormally increased level of serum creatinine). The benefit of heparin, tranexamic acid, or other anticoagulant or antifibrinolytic therapy remains undetermined and should be a matter for clinical trial investigation.

How important is starting therapy immediately?

In light of the reported improvement of the coagulopathy occurring early after the initiation of ATRA, tailored treatment should be started when APL is suspected without waiting for genetic confirmation of diagnosis, preferably the same day that diagnosis is suspected. Although there is no evidence supporting this assumption, it is reasonable to presume a favorable cost-benefit ratio associated with this approach. The supportive measures to be adopted upon institution of ATRA therapy are discussed in “Supportive measures during induction therapy.”

Is it important to confirm the diagnosis at the genetic level prior to starting therapy?

Although genetic confirmation of the diagnosis is mandatory, it can be carried out after starting tailored treatment with ATRA, which should not be delayed.

Morphologic diagnosis, although highly predictive of the specific genetic lesion in hypergranular (typical) cases, is considered insufficient. Patients with morphologic features suggestive of APL yet lacking the promyelocytic leukemia/retinoic acid receptor α (PML/RARα) rearrangement, or, alternatively, patients whose morphologic aspects would not lead to suspect APL but have the specific genetic aberration, have been described frequently in the literature. Because of the efficacy of differentiation treatment based on retinoids is strictly dependent on the presence of the PML/RARα fusion in leukemia cells, genetic confirmation of diagnosis is mandatory. Therefore, all patients, including those with typical hypergranular APL who have already started specific treatment, must be studied by karyotypic, and molecular analyses to confirm the presence of the specific gene fusion and to characterize its isoform for molecular monitoring of minimal residual disease (MRD). Advantages and pitfalls of the available methods for genetic diagnosis have been reviewed elsewhere and are summarized in Table 1 as well as in “Optimizing genetic diagnosis.”

As a further tool in the diagnostic evaluation, immunophenotyping by multiparameter flow cytometry can reinforce a morphologic suspicion of PML/RARα-positive APL among AML. PML/RARα-positive leukemia blasts from APL typically show immunophenotypic features that are similar to those of normal promyelocytes (CD34+/− heterogeneous, CD117+/− dim, HLA-DR+/− dim, CD13+/+++, CD11b−); however, unlike their normal counterpart, PML/RARα-positive promyelocytes display abnormally low levels of CD15 (CD15−/− dim versus CD15+/+).

### Optimizing genetic diagnosis

As shown in Table 1, the identification of the APL-specific genetic lesion in leukemic cells is feasible at chromosome, DNA, RNA, and protein level with the use of conventional karyotyping, FISH, RT-PCR, and anti-PML monoclonal antibodies, respectively. While either routine karyotyping or FISH are highly specific to confirm diagnosis at the genetic level, RT-PCR carries the additional advantage of defining the type of breakpoint and PML/RARα isoform to be used as a sensitive marker for response assessment and follow-up monitoring. Because molecular remission has been recently established as a therapeutic objective in APL, RT-PCR should be performed at presentation to precisely characterize the target for amplification, even in patients with confirmed t(15;17) by cytogenetics, and FISH. Both RT-PCR and FISH have the additional advantage that no dividing cells are required for analysis, and they allow results to be obtained in cases with few or poor-quality metaphases. Because RT-PCR is notoriously prone to contamination and artifacts, the assay should be carried out by experienced hands. Therefore, it is advisable that diagnostic and monitoring samples from peripheral and small institutions should be sent to reference laboratories where well-trained personnel has long-lasting experience on RT-PCR of PML/RARα. As to anti-PML immunostaining, this more recently introduced technique is very simple to perform and highly specific. It allows genetic diagnosis at very low cost by distinguishing the microgranular nuclear distribution of PML typical of APL from the staining pattern referred to as “nuclear bodies” characteristic of other leukemias and normal hematopoietic cells. Either indirect immunofluorescence or immunohistochemistry may be used as detection systems to unravel the type of PML nuclear distribution. Results from the immunofluorescence assay can be achieved in only 2 hours, whereas the immunohistochemical technique requires 48 hours.

### Table 1. Methods for the genetic diagnosis of APL

<table>
<thead>
<tr>
<th>Cellular level</th>
<th>Target aberration</th>
<th>Methods</th>
<th>Time required, h</th>
<th>Main advantages</th>
<th>Main drawbacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosomes</td>
<td>t(15;17)</td>
<td>Karyotyping</td>
<td>16-48</td>
<td>Highly specific</td>
<td>24-48 h cultures needed; cryptic fusions undetected (false negatives); need of good quality metaphases</td>
</tr>
<tr>
<td>DNA</td>
<td>PML and RARα genes</td>
<td>FISH</td>
<td>6-24</td>
<td>No need of dividing cells</td>
<td>No information on the type of PML/RARα fusion</td>
</tr>
<tr>
<td>DNA</td>
<td>PML/RARα fusion</td>
<td>Southern blot</td>
<td>96-168</td>
<td>Highly specific</td>
<td>Time consuming; laborious</td>
</tr>
<tr>
<td>RNA</td>
<td>PML/RARα fusion</td>
<td>RT-PCR</td>
<td>4-6</td>
<td>Rapid; highly sensitive; defines targets for MRD</td>
<td>Poor RNA yield at dx; contamination and artifacts (false positives)</td>
</tr>
<tr>
<td>Nucleus</td>
<td>Microspeckled nuclear distribution of the PML protein</td>
<td>Immunofluorescence or immunohistochemistry</td>
<td>2-3</td>
<td>Rapid; simple; low cost</td>
<td>Artifacts due to cellular degradation, no information on the type of PML/RARα fusion</td>
</tr>
</tbody>
</table>

FISH indicates fluorescence in situ hybridization; RT-PCR, reverse transcription-polymerase chain reaction; MRD, minimal residual disease; dx, diagnosis.

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Targeted induction therapy

A consensus has now been reached on the most appropriate induction treatment that should consist on the simultaneous administration of ATRA and anthracycline-based chemotherapy. As to the type of anthracycline and whether it should be combined with other agents, both issues remain controversial. In the ATRA era, idarubicin has been more frequently used as monotherapcy, whereas daunorubicin has been mainly used in combination with other drugs. Exceptions to the use of the standard approach should be considered only for individual cases in which chemotherapy is contraindicated. Patients with certain clinical conditions (eg, severe organ failure, anticoagulant therapy, older than 80 years, and others) would be candidates for induction with either differentiation therapy alone (ATRA), transcription modulation agents (arsenic trioxide: ATO), or both. Some patients with a temporary contraindication for chemotherapy (eg, patients with reversible organ dysfunction) could be induced with ATRA alone and given chemotherapy subsequently. Differentiating therapy, such as ATRA, ATO, or their combination, followed by low-dose chemotherapy and intermittent ATRA maintenance might be adopted in the above-mentioned patients as well as in other infrequent settings (eg, Jehovah’s Witnesses). However, there is no reason for modifying the standard approach based on the presence of leukemia cell characteristics that have occasionally evoked an association with poor response to induction therapy (eg, secondary chromosomal abnormalities, immunophenotypic markers, PML/RARα isoform). In fact, the only study that reported an inferior survival for patients with secondary cytogenetic changes was carried out in a small series of patients treated in the pre-ATRA era. Two large studies of the European APL and PETHEMA groups, in which all patients received initial ATRA and chemotherapy, failed to demonstrate any difference in prognosis between patients with and without additional chromosomal abnormalities. Similarly, no significant differences in response to treatment according to the PML/RARα isoform have been reported in all major multicenter trials combining upfront ATRA and chemotherapy.

Supportive measures during induction therapy

In addition to the aforementioned supportive measures aimed at counteracting the coagulopathy, physicians caring for patients with APL should be aware of early symptoms or signs suggestive of the retinoic acid syndrome (RAS). Diagnosis of the RAS should be suspected clinically in the presence of 1 of the following symptoms and signs: dyspnea, unexplained fever, weight gain, peripheral edema, unexplained hypotension, acute renal failure or congestive heart failure, and particularly by a chest radiograph demonstrating pulmonary infiltrates, or pleuroperticardial effusion. Because of the life-threatening nature of the full-blown syndrome (referred to as definitive RAS in the nomenclature proposed by Frankel et al), specific treatment with dexamethasone at a dose of 10 mg twice daily by intravenous injection should be promptly started at the very earliest sign or symptom. This policy is highly recommended despite that none of the aforementioned symptoms is pathognomonic of the syndrome, and they can be due to concurrent medical problems, such as bacteremia, sepsis, or congestive heart failure. Temporary discontinuation of ATRA is indicated only in case of 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, dexamethasone should be maintained until complete disappearance of symptoms, and then ATRA should be resumed. While preemptive 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 to reduce rates of morbidity and mortality associated with this syndrome. Nevertheless, in uncontrolled studies, a very low mortality or morbidity rate was reported as a result of RAS by administering corticosteroids prophylactically in patients with white blood cell (WBC) count greater than 5 × 10^9/L.

Besides these specific measures to reduce the rates of RAS- and hemorrhage-associated morbidity and mortality, the policy for other supportive measures, including use of hematopoietic growth factors, does not differ from that commonly used for patients with other subtypes of AML.

Evaluation of induction response

Morphologic evaluation

A relatively frequent error in the management of APL is the misinterpretation of marrow aspirates collected during or at the end of induction treatment with ATRA. While in other AML subtypes the bone marrow aspirate performed 7 to 14 days after induction therapy may be informative for early response assessment, for patients with APL receiving ATRA, this evaluation usually reveals a relatively hypercellular pattern which reflects initial differentiation of leukemic cells. This finding may lead to erroneously labeling as resistant some individual patients showing delayed maturation features, persistence of atypical promyelocytes, or both. These cytomorphologic features that are occasionally detectable several weeks after the start of treatment (up to 40-50 days) should in no way lead to therapeutic changes. Rather, treatment should be continued until terminal differentiation of blasts and achievement of complete remission (CR) that invariably occurs in all patients with genetically proven APL who survive after ATRA-based induction.

Molecular and cytogenetic evaluation

Another common cause of hematologists’ concern and misinterpretation derives from the significance attributed to PML/RARα residual transcripts detected by RT-PCR at the end of induction. At this time point, about one half of the patients in CR after ATRA and chemotherapy test PCR positive in the marrow, even using low-sensitivity methods (ie, with detection threshold between 10^-3 and 10^-4). Several clinical trials, including the Gruppo Italiano Malattie Ematologiche Maligne dell’Adulto (GIMEMA), PETHEMA, Medical Research Council (MRC), and North American Intergroup studies, have failed to find any correlation between the postinduction PCR status and subsequent patient outcome. Hence, there is no indication to either increase treatment intensity or to change therapy for patients who test PCR positive at the end of induction prior to consolidation. 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.

In summary, early laboratory evaluation of MRD after ATRA-based induction should only be part of investigational studies, and clinicians should refrain from making therapeutic decisions on the basis of their results.

**What is the optimal consolidation therapy?**

Because of the presence of a disease-specific marker that is amenable to sensitive PCR amplification, APL is the subtype of AML in which the benefit derived from consolidation has been thoroughly evaluated. This benefit has been demonstrated in the laboratory with the achievement of molecular remission in 90% to 99% of patients receiving 2 to 3 intensive cycles of postremission chemotherapy, irrespective of type of drugs combined with anthracyclines during consolidation. However, a study by the PETHEMA group has questioned the role of nonanthracycline drugs for both induction and consolidation therapy and suggests a synergistic effect of ATRA and chemotherapy given simultaneously in consolidation. Although the antileukemic benefit provided by the addition of ATRA to consolidation therapy should be definitively established in randomized studies, the results of this study suggest that a risk-adapted strategy for consolidation, including distinct treatment intensities according to the relapse risk, improves the overall results in APL.

The favorable long-term outcomes reported in all recent series using state-of-the-art treatments do not leave room for more aggressive options to intensify therapy for patients in first CR, except for the small fraction of patients with persistence of molecular disease (PCR positive) at the end of consolidation. Because of their very poor prognosis, these patients should receive further aggressive therapy, including novel agents such as gentuzumab ozogamicin and ATO, as well as allogeneic hematopoietic stem cell transplantation. Alternatively, 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. A possible alternative for consolidation in these patients would be the administration of ATO or gentuzumab ozogamicin.

**Maintenance therapy**

Since the advent of ATRA, only 2 randomized studies have been reported that investigated the role of maintenance therapy in APL. Both studies showed a benefit from administering ATRA maintenance given intermittently or continuously. However, the continuous schedule for ATRA maintenance does not seem to be supported by recent pharmacokinetic and pharmacodynamic data on ATRA and has also been associated with significant toxicity. In addition, the APL93 study of the European group showed an advantage in administering low-dose chemotherapy with methotrexate and 6-mercaptopurine and reported an additional therapeutic benefit from using this chemotherapy plus ATRA combination. In fact, the triple combination (ATRA plus methotrexate and 6-mercaptopurine) resulted in lower relapse rate and proved particularly effective for patients with elevated WBC count at presentation. Although maintenance therapy remains at present a subject of investigation, particularly with respect to its optimal schedule and the target patient population, most groups have incorporated this approach into their APL therapeutic strategies.

**Molecular monitoring during postconsolidation follow-up**

As shown by 2 large prospective trials and confirmed in many longitudinal studies on MRD monitoring in APL (reviewed in Lo Coco et al and Grimwade and Lo Coco), repeatedly negative RT-PCR tests following consolidation correlate strongly with prolonged survival, whereas conversion to PCR positivity is associated with impending hematologic relapse. On the basis of these findings, some groups have elected to administer salvage treatment at time of molecular relapse prior to development of overt disease recurrence. However, while molecular monitoring in this phase can be particularly useful in patients with WBC count at presentation greater than $10 \times 10^9/L$, it is currently questioned for patients with low risk of relapse (ie, patients with WBC count at presentation fewer than $10 \times 10^9/L$). In this view, patients with elevated WBC count at presentation should be monitored every 1 to 2 months early following consolidation and every 3 months during the second and third year.

While nonquantitative RT-PCR assays are characterized by poor accuracy and little reproducibility, they still hold clinical
value, particularly when performed in experienced laboratories. The clinical advantage of using quantitative (QT)–RT-PCR remains to be determined.

What is the risk of developing the RAS during postremission therapy with ATRA if a patient had the RAS during induction?

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.

Management of APL in children

The presenting characteristics and response to therapy of children who were included in the European-APL93, GIMEMA, and PETHEMA studies, have been reported in detail. Compared with adults, children with APL more frequently present with hyperleukocytosis (approximately 40% versus 25%). Despite this, and probably because of better compliance to therapy and reduced toxicity, outcome results in children and adults receiving the same treatment are comparable, with CR and disease-free survival rates more than 90% and 75%, respectively.

Because of concerns related to the development of pseudotumor cerebri during ATRA, some groups have used lower doses (ie, 25 mg/m²) of ATRA during induction, although it is not clear whether this dose reduction results in a decreased incidence and rate of morbidity of this side effect. Pseudotumor cerebri is characterized by increased intracranial pressure, resulting in headache, nausea, and vomiting, that may be accompanied with vision abnormalities and papilledema. Management of pseudotumor cerebri consists of discontinuation of...
osmotic diuretic such as 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, in contrast to the experience reported in the pre-ATRA era, all cases described so far in which ATRA was used alone or in combination with chemotherapy attained CR, and no serious adverse effects were recorded for either the mother or the fetus. The limited experience available from the literature suggests that both ATRA and anthracycline-based chemotherapy appear reasonably safe for patients with APL diagnosed in 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 they do not seem to compromise the delivery of a healthy newborn. Nevertheless, close fetal cardiac monitoring to unravel complications has been strongly recommended throughout the pregnancy because some cases of reversible cardiac arrhythmia were reported. By contrast, although there is scarce information regarding the teratogenicity of ATRA, its use during the first trimester of pregnancy is not recommended because retinoids are known teratogens.

What is the best management for hyperleukocytosis, the APL differentiation syndrome, and prolonged QT interval associated with ATO?

According to the experience in patients with APL in relapse, ATO induces complete hematologic and morphologic remission in approximately 85% of patients. Approximately 50% of patients with APL in relapse achieve a molecular remission after one 25-day course of ATO. Therefore, it is conceivable that ATO can be used as an alternative in patients in whom conventional treatment with ATRA plus chemotherapy is contraindicated. ATO is administered as a single agent and is quite well tolerated. Hyperleukocytosis, similar to that observed in patients receiving ATRA, occurs, and, in general, ATO may be continued with careful observation. 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. With the development of the cardiopulmonary distress syndrome, the APL differentiation syndrome, in approximately 30%, dexamethasone is instituted at the earliest sign or symptom and usually promotes rapid resolution. Dexamethasone may be tapered and then discontinued when the signs and symptoms resolve. 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/μL. No additional cytotoxic therapy is required. ATO is also associated with prolongation of the QT interval, and careful monitoring is required. In addition, maintenance of the serum potassium above 4.0 mmol/L (4.0 mEq/L) and serum magnesium above 0.82 mmol/L (2.0 mg/dL), well above the lower limit of normal, is indicated. For patients with a heart rate of greater than 60 beats per minute, if the QTc (heart rate corrected) interval is prolonged longer than 500 millisecond, 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 less, the absolute QT (uncorrected for the heart rate) interval can be used. Once the QTc returns to approximately 460 milliseconds, and the electrolytes are repleted, the ATO may be resumed. In addition to the prolongation of the QTc interval, and the APL differentiation syndrome mentioned earlier in this paragraph, approximately 13% of patients may develop hypokalemia or hyperglycemia.

An outline of practice points is summarized in Table 2.

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