The tricks of the trade for the appropriate management of newly diagnosed acute promyelocytic leukemia

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ABSTRACT

Most reviews on the state-of-the-art treatment in acute promyelocytic leukemia (APL) have focused mainly on the comparison of therapeutic approaches including ATRA and chemotherapy. However, outcome of individual patients also depends on appropriate knowledge of several aspects related to APL management which 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 (e.g induction, consolidation, maintenance), this article addresses the aforementioned issues on APL management (“the tricks of the trade”) with special emphasis on several peculiar aspects that distinguish APL from other acute myeloid leukemias.
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 using 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.1-8 Recently a number of exhaustive reviews have been published on the treatment progress achieved in this particular subtype of leukemia.9-12 However, these 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 (“the tricks of the trade”). Additional reasons for focusing on these aspects include the following: 1) APL is a rare disease and the majority of patients are currently treated in institutions with limited experience.; 2) The excellent outcome reported in recent studies using 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 AML subtypes.
Dealing with a suspected diagnosis of APL

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

1) 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 group, focused on analyzing the magnitude of this problem, showed that about 3% of all diagnosed patients die of hemorrhage before therapy has been started. In addition, approximately one half of the 5% 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 fresh frozen plasma and/or fibrinogen transfusions, as well as on aggressive platelet support to maintain the fibrinogen level and the platelet counts above 150 mg/dL and $30-50 \times 10^9$/L, respectively, until disappearance of all clinical and/or laboratory signs of coagulopathy. These supportive measures should be even more aggressive in patients with higher hemorrhagic risk (e.g. older patients, those with hyperleukocytosis, or manifest clinical and/or laboratory signs of coagulopathy, and abnormally increased level of serum creatinine). The benefit of heparin, tranexamic acid or other anticoagulant/antifibrinolytic therapy remains undetermined and should be a matter for clinical trial investigation.

2) 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 below in a separate paragraph.

3) *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 morphological features suggestive of APL yet lacking the PML/RARα rearrangement or, alternatively, patients whose morphologic aspects would not lead to suspect APL but present the specific genetic aberration have been described frequently in the literature.\(^{15}\) Due to 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/or molecular analyses in order 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\(^{15,16}\) and are summarized in Table 1 as well as in a dedicated paragraph.

As a further tool in the diagnostic evaluation, immunophenotyping by multiparameter flow cytometry can reinforce a morphological suspect of PML/RARα-positive APL among AML.

PML/RARα-positive leukemia blasts from APL typically show immunophenotypic features which are similar to those of normal promyelocytes (CD34-/+heterogeneous, CD117-/+dim, HLADR-/+dim, CD13+/++, CD11b-);\(^{17}\) however, unlike their normal counterpart, PML/RARα-positive promyelocytes display abnormally low levels of CD15 (CD15-/+dim vs CD15+++).\(^{17,18}\)
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 using 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 utilized 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/or FISH. Both RT-PCR and FISH have the additional advantage that no dividing cells are required for analysis and allow to obtain results in cases with few and/or poor quality metaphases. Due to the fact that RT-PCR is notoriously prone to contaminations and artifacts, the assay should be carried out by experienced hands. Therefore, it is advisable that diagnostic/monitoring samples from peripheral/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 using the immunofluorescence assay can be achieved in only two hours. In light of its very convenient cost/benefit ratio, the assay is highly recommended to rapidly confirm APL diagnosis at the genetic level, particularly in small centers not equipped and experienced for genetic analyses.
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.\textsuperscript{5,9,10} As to the type of anthracycline and whether or not it should be combined to other agents, both issues remain controversial. In the ATRA era, idarubicin has been more frequently used as monochemotherapy, 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 (e.g. severe organ failure, anticoagulant therapy, more than 80 years old, and others) would be candidates for induction with either differentiation therapy alone (ATRA), transcription modulation agents (ATO) or both.\textsuperscript{24} 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. Differentiating therapy, such as ATRA and/or ATO, 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). 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 (e.g. secondary chromosomal abnormalities, immunophenotypic markers, PML/RAR\textalpha 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.\textsuperscript{25} Recently, two large studies of the European APL and PETHEMA groups,\textsuperscript{26,27} 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/RAR\textalpha isoform have been reported in all major multicenter trials combining upfront ATRA and chemotherapy.\textsuperscript{2,4,7,8}
Supportive measures during induction therapy

In addition to the aforementioned supportive measures aimed at counteracting the coagulopathy, attending physicians caring for APL patients 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 one 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 nodular infiltrates and/or pleuropericardial effusion. Due to the life-threatening nature of the full-blown syndrome (referred to as definite RAS in the nomenclature proposed by Frankel et al\textsuperscript{28}), 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 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 pre-emptive 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 morbidity and mortality associated with this syndrome.\textsuperscript{8,29} Nevertheless, in uncontrolled studies,\textsuperscript{6,8} it has been reported a very low mortality rate due to RAS by administering dexamethasone prophylactically in patients with WBC count greater than $5 \times 10^9$/L.
Besides these specific measures to reduce 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**

1) *Morphological 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, in APL patients 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 and/or persistence of atypical promyelocytes. These cytomorphological features which are occasionally detectable several weeks after the start of treatment (up to 40-50 days), should in no way lead to therapeutical 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.

2) *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 a half of the patients in CR after ATRA and chemotherapy test PCR positive in the marrow, even using low sensitivity methods (i.e. with detection threshold comprised between $10^{-3}$ and $10^{-4}$). Several clinical trials including the GIMEMA, PETHEMA, MRC and North American Intergroup studies have failed to find any correlation between the post-induction PCR status and successive 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 based on their results.

**What is the optimal consolidation therapy?**

Due to the presence of a disease-specific marker which is amenable to sensitive PCR amplification, APL is the subtype of AML where the benefit derived from consolidation has been thoroughly evaluated. This benefit has been demonstrated in the laboratory with the achievement of *molecular remission* in 90-99% of patients receiving 2-3 intensive cycles of postremission chemotherapy, irrespective of type of drugs combined with anthracyclines during consolidation.9,10 However, a recent study by the PETHEMA group8 has questioned the role of non-anthracycline 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.

**Molecular evaluation at the end consolidation**

While, as discussed above, RT-PCR studies carried out at the end of induction are uninformative with respect to clinical outcome and should not lead to any treatment modification, the same analysis performed after completion of consolidation is regarded by most investigators as
mandatory and extremely relevant to determine the relapse risk in the individual patient. As a consequence, in several trial designs RT-PCR results following consolidation are taken into account to address further treatment, whereas patients who show residual PML/RARα transcripts are candidates to further intensification and those who test PCR-negative would proceed to receive maintenance only. Hence, molecular remission as a therapeutic objective in APL has to be regarded as a status to be assessed at completion of consolidation.

From a technical viewpoint, it is important to remind that, in APL, analysing bone marrow for RT-PCR evaluation of PML/RARα is advantageous over examining peripheral blood, due to the higher likelihood to detect residual aberrant transcript in the former site (Lo Coco, unpublished observations). Furthermore, as already mentioned the use of low-sensitivity amplification techniques has proved more informative in assessing the relapse risk as compared to methods with sensitivity threshold greater than $10^{-4}$. For this reason, and in order to minimize the risk of false positive results due to contamination, it is advisable to confirm a post-consolidation PCR-positive result by sending a new marrow sample to a highly experienced reference laboratory using the low sensitivity assay.

**Maintenance therapy**

Since the advent of ATRA only two randomized studies have been reported which investigated the role of maintenance therapy in APL.\textsuperscript{5,31} These studies assessed the impact on relapse of ATRA alone or in combination with low doses of methotrexate and mercaptopurine.\textsuperscript{5} 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,\textsuperscript{32} and has also been associated with significant toxicity.\textsuperscript{31} 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 white blood cell 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, the majority of groups have incorporated this approach into their APL therapeutic strategies.

**Molecular monitoring during post-consolidation follow-up**

As shown by two large prospective trials and confirmed in many longitudinal studies on MRD monitoring in APL (reviewed in references 14 and 15), repeatedly negative RT-PCR tests following consolidation correlate strongly with prolonged survival, whereas conversion to PCR-positivity is associated with impending hematologic relapse. Based on 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 (i.e. those with WBC count at presentation less than $10 \times 10^9$/L). In this view, patients with elevated WBC count at presentation should be monitored every 1-2 months early following consolidation and every 3 months during the second and third year.

While non-quantitative RT-PCR assays are characterized by poor accuracy and little reproducibility, they still hold clinical value particularly if performed in experienced laboratories. The clinical advantage of using 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 postremission 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.

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 treatment for patients in first CR, except for the small fraction of patients with persistence of molecular disease (PCR-positive) at the end of consolidation. Due to their very poor prognosis, these patients should receive further aggressive therapy, including novel agents such as gentuzumab ozogamycin 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 ozogamycin.

**What is the best therapy for the older APL patients?**

Due to the vulnerability of older (≥ 55-60 years old) patients in terms of treatment-related toxicity, a reduction of chemotherapy intensity has been generally proposed for this age group. 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, older patients were treated 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 to those reported for younger patients. Older and younger patients with severe comorbidities are candidates to be treated with arsenic trioxide.
Management of APL in children

The presenting characteristics and response to therapy of children included the European-APL’93, GIMEMA and PETHEMA studies have been reported in detail.\textsuperscript{36-38} Compared to adults, children with APL more frequently present with hypeleukocytosis (approximately 40\% vs. 25\%). In spite of this, and probably due to better compliance to therapy and reduced toxicity, outcome results in children and adults receiving the same treatment are comparable, with CR and DFS rates above 90\% and 75\% respectively.\textsuperscript{36-38} Due to concerns related to the development of pseudotumor cerebri during ATRA,\textsuperscript{39} some groups have used lower doses (i.e. 25mg/m2) of ATRA during induction, although it is not clear if this dose reduction results in a decreased incidence and less morbidity of this side effect. Pseudotumor cerebri is characterized by increased intracranial pressure resulting in headache, nausea and vomiting that may be accompanied to vision abnormalities and papilledema. Management of pseudotumor cerebri consists of discontinuation of ATRA\textsuperscript{2} or dose reduction\textsuperscript{36} and administration of dexamethasone, osmotic diuretic such as mannitol, and analgesics.

Management of pregnant APL patients

Management of APL during pregnancy is always a cause of major concern due to the hemorrhagic risk and the potential teratogenicity of ATRA and chemotherapy. However, in contrast to the experience reported in the pre-ATRA era,\textsuperscript{40} all cases described so far in which ATRA was used alone or in combination with chemotherapy attained CR and no serious adverse effect were recorded for either the mother or the fetus.\textsuperscript{41} The limited experience available from the literature suggests that both ATRA and anthracycline-based chemotherapy appear reasonably safe for APL patients 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 premature, survived and developed normally. 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 teratogenity of ATRA, its use during the first trimester of pregnancy is not recommended because retinoids are known teratogenics.

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

Mainly based on the experience in relapsed patients with APL, in whom ATO induces complete hematologic and morphologic remission in approximately 85% of patients, and approximately 50% of patients achieve a molecular remission after one 25-day course, it is conceivable that this drug 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 white blood cell 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 cardiorespiratory distress syndrome, the APL differentiation syndrome, in approximately 30%, dexamethasone is instituted at the earliest sign or symptom, and usually results in 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 < 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 mEq/L and serum magnesium above 2.0 mg/dL, well above the lower limit of normal is indicated. For patients with a heart rate of above 60 beats per minute, if the QTc (heart rate corrected) interval is prolonged more than 500 msec, ATO should be held, the electrolytes
repleted (potassium and magnesium), and other medications which 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 QT/QTc returns to approximately 460 milliseconds, 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 above, patients may develop hypokalemia or hyperglycemia in approximately 13% of patients.
OUTLINED PRACTICE POINTS

Preinduction phase

- Once a diagnosis of APL is suspected upon morphological examination, the disease should be managed as a medical emergency.

- Genetic confirmation of diagnosis is mandatory.

- Rapid institution of supportive measures to reverse the coagulopathy and the associated risk of life-threatening hemorrhages. Liberal fresh frozen plasma and/or fibrinogen transfusions, as well as on platelet support to maintain the fibrinogen level and the platelet counts above 150 mg/dL and 30-50 \( \times 10^9 / L \) until disappearance of all clinical and/or laboratory signs of coagulopathy are fundamental measures in this respect.

- The benefit of heparin, tranexamic acid or other anticoagulant/antifibrinolytic therapy remains undetermined.

- Treatment with ATRA should be started immediately when diagnosis of APL is suspected.

- In addition to conventional karyotyping, FISH and RT-PCR, immunoassay with anti-PML can be used for rapid diagnosis of APL.

Induction phase

- Induction therapy should consist of simultaneous administration of ATRA and anthracycline-based chemotherapy.

- Standard induction therapy should not be “reinforced” based on the presence of secondary chromosomal abnormalities or other leukemia cell characteristics evoking an association with poor response. No presenting features predict for unfavorable response to induction APL.

- Pre-emptive therapy with dexamethasone should be started when the diagnosis of RAS is suspected in the presence of any symptom or sign that characterize the syndrome.
• Treatment with ATRA should be continued until terminal differentiation of blasts and achievement of CR, which invariably occurs in all patients. Temporary discontinuation of ATRA is only indicated in case of severe RAS.

• Morphological features in bone marrow during differentiation therapy with ATRA can lead to erroneously labeling some patients as resistant by inexperienced pathologists. These misleading cytomorphological features, which are occasionally detectable several weeks after the start of treatment (up to 40-50 days), should not lead to therapeutical changes.

• Early morphological evaluation in bone marrow, as well as molecular and cytogenetic evaluation at the end of induction has little or no value in APL. Clinicians should refrain from making therapeutic decisions based on these results.

Consolidation phase

• Two or three courses of anthracycline-based chemotherapy is considered the standard approach for consolidation therapy. Simultaneous administration of ATRA seems to provide a clinical benefit.

• Molecular remission should be assessed at completion of consolidation by low sensitivity RT-PCR methods.

• The small fraction of patients with confirmed molecular persistence (as assessed in two successive bone marrow samples) should be considered for allogeneic SCT. Alternatively of ATO or gentuzumab ozogamycin may be considered in these patients.

Maintenance phase

• The combination of ATRA with or without low-dose chemotherapy has been adopted as the standard maintenance therapy by the majority of groups.
Molecular monitoring in this phase seems cost-effective only for patients with WBC count at presentation greater than $10 \times 10^9/L$, while its utility is questionable for patients with low risk of relapse (i.e. those with WBC count at presentation less than $10 \times 10^9/L$).

**Special situations**

- Elderly patients in good clinical conditions should be managed with a treatment approach similar to that used in younger patients.

- Elderly and younger patients with severe comorbidities are candidates to receive arsenic trioxide.

- Both ATRA and anthracycline-based chemotherapy appear reasonably safe for APL patients diagnosed in the second or third trimester of pregnancy. By contrast, the use of ATRA therapy in the first trimester of pregnancy is not recommended because retinoids are known teratogenics.
REFERENCES


with acute promyelocytic leukemia enrolled in the GIMEMA-AIEOP multicenter "AIDA" trial.

significance of minimal residual disease detection and PML/RAR-alpha isoform type: long-term

35. 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.


monochemotherapy in children with acute promyelocytic leukemia: a multicenter study by the


40. Giagounidis AAN, Beckmann MW, Giagounidis AS, et al. Acute promyelocytic leukemia and

41. Fadilah SAW, Hatta AZ, Keng CS, Jamil MA, Singh S. Successful treatment of acute

42. Lipovsky MM, Biesma DH, Christiaens GCML, et al. Successful treatment of acute
94:699-701.


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</th>
<th>Main advantages</th>
<th>Main drawbacks</th>
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<td>Chromosomes</td>
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<td>Karyotyping</td>
<td>16-48 h</td>
<td>Highly specific</td>
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<td>Southern blot</td>
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<tr>
<td>RNA</td>
<td>PML/RARα fusion</td>
<td>RT-PCR</td>
<td>4-6 h</td>
<td>Rapid; highly sensitive; Defines targets for MRD*</td>
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<td>Nucleus</td>
<td>Microspeckled nuclear</td>
<td>Immunofluorescence</td>
<td>2-3 h</td>
<td>Rapid; simple; low cost</td>
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MRD*, minimal residual disease
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