Standard practice and controversial issues in front-line therapy of acute promyelocytic leukemia

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In addition to choosing a state-of-the-art regimen including all-trans retinoic acid and anthracycline chemotherapy, modern management of acute promyelocytic leukemia (APL) implies the adoption of appropriate supportive measures, rapid establishment of an accurate genetic diagnosis, correct assessment of response to therapy and evaluation of the risk of disease recurrence by molecular monitoring. However, the general consensus about this overall strategy for APL treatment still leaves room for debate. In the present article, we review the current standard practice and controversial issues in the treatment of patients with newly diagnosed APL, including the management of special situations such as elderly patients, children and pregnant women.

Key words: hereditary hemorrhagic telangiectasia (HHT), angiogenesis, VEGF, TGF-β1, ALK1.

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The optimal management of patients with acute promyelocytic leukemia (APL) implies not only administration of the most appropriate anti-leukemic and supportive treatment, but also rapid establishment of the genetic diagnosis, adequate assessment of response to induction therapy, and molecular monitoring during the subsequent treatment phases. Some issues are undebated and should be included as current standard of care for treating this leukemia, whereas other more controversial points can only be clarified in the context of well designed clinical trials. In the present article we aim to outline the current general consensus and controversial issues in the management of patients with newly diagnosed APL.

Approach to the patient with suspected APL

Although there is a general consensus on the need to confirm the diagnosis of APL at the genetic level, differentiation and supportive therapy should be started even before the results of genetic tests are available. Once the suspicion of APL has been raised on the basis on morphologic criteria, patients should be managed as a medical emergency requiring the following rapid and simultaneous actions:

i) institution of supportive measures to counteract the coagulopathy. This support should consist of fresh frozen plasma, fibrinogen and platelet transfusions to maintain the fibrinogen concentration and platelets count above 150 mg/dL and 30-50×10^9/L, respectively, until disappearance of all clinical and laboratory signs of coagulopathy. 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 white blood cell (WBC) count at presentation and patients with an abnormally increased level of serum creatinine.[1] The use of antifibrinolytic agents and heparin is questionable and should be a subject of clinical research;

ii) initiation of treatment with all-trans retinoic acid (ATRA) without waiting for genetic confirmation of the diagnosis. ATRA is known to improve the biological signs of APL coagulopathy rapidly; hence early initiation of ATRA is likely to decrease the risk of severe bleeding;

iii) demonstration of the t(15;17) or its counterpart the PML/RARα hybrid gene by conventional karyotyping, fluorescent *in situ* hybridization (FISH), or reverse transcription polymerase chain reaction (RT-PCR). These are equally specific but not equally sensitive methods to confirm the diagnosis of APL. The use of immunostaining assays with anti-PML antibodies to detect the characteristic microparticulate nuclear pattern of the PML protein resulting

from the translocation, is another interesting option for a rapid and accurate diagnosis of APL.[2-5] Although this technique should not replace RT-PCR, which allows defintion of the type of PML/RARα isoform and the target for minimal residual disease evaluation in the individual patient, it can be particularly useful in cases in which RNA is not available or to confirm a diagnosis in institutions and developing countries where genetic tests are not routinely available.

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-containing regimens. Currently, there is a general agreement on the most appropriate induction therapy that should consist of simultaneous administration of ATRA and anthracycline-based chemotherapy.[6-8]

The choice of anthracycline and whether it should be combined with other agents, such as cytosine arabinoside, remain controversial. Recommended anthracycline doses are idarubicin 12 mg/m^2×4 (days 2, 4, 6, and 8) as in the AIDA regimen or daunorubicin 60 mg/m^2×4 consecutive days as in the European APL 93 study (in the latter regimen daunorubicin is given in combination with cytosine arabinoside). Exceptions to the use of anthracycline-based induction regimens should be considered only for individual patients in whom chemotherapy is contraindicated. This is the case of patients with certain clinical conditions such as severe organ failure, anticoagulant therapy, very elderly patients (more than 80 years old), and others. Treatment of APL in these and other special circumstances (*e.g.*, pregnant woman) is addressed in a separate paragraph (see *Management of special situations*).

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 the short PML/RARα isoform. Additional chromosome lesions did not negatively affect the prognostic outcome when analyzed in large cohorts of patients receiving modern ATRA plus chemotherapy regimens.[9-11]

Supportive measures

As mentioned above, supportive measures aimed at counteracting the coagulopathy should be started immediately after a suspected diagnosis of APL has been formulated. Once the patient has initiated targeted treatment with ATRA, any symptom or sign suggestive of the retinoic acid syndrome (RAS) should be quickly recognized for immediate therapy. Although none of the symptoms and signs that define the syndrome[12] (i.e., dyspnea, unexplained fever, weight gain, peripheral edema, pulmonary nodular infiltrates or pleuropericardial effusion) is *per se* pathognonomic, treatment with high-dose steroids should be initiated immediately at the very earliest suspicion of RAS because of its rapid and potentially fatal course. The recommended treatment is dexamethasone at a dose of 10 mg twice a day intravenously for at least 4 days or until disappearance of symptoms.[12] There is no consensus on the utility of discontinuing ATRA or decreasing its dose during the syndrome, although its withdrawal is advisable for patients who develop severe RAS. Otherwise, ATRA can be maintained unless progression to the 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 for treating patients who develop RAS, there is at present no evidence that prophylactic corticosteroids are advantageous in reducing morbidity and mortality associated with this syndrome. Nevertheless, from uncontrolled studies,[13,14] the reported mortality rate due to RAS was very low when dexamethasone was administered prophylactically in patients with a WBC count greater than 5×10^9/L.

Besides specific measures to reduce RAS- and hemorrhage-associated morbidity and mortality, the policies for red cell transfusion, use of antibiotics, and other supportive measures, including hematopoietic growth factors, do not differ from those commonly adopted for patients with other subtypes of 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 the use of ATRA. However, a large study by the GIMEMA, carried out in patients treated with or without ATRA, failed to demonstrate this correlation.[15] Rather, it is conceivable that the longer exposure to the risk of relapse, due to the indisputably increased survival of patients treated with ATRA-based regimens, may account for the apparently higher prevalence of extramedullary disease, including CNS relapses, that otherwise would not have had the opportunity to emerge. At present, there is no consensus on the need for CNS prophylaxis and its benefit remains controversial. This notwithstanding, some groups include CNS prophylaxis for patients with hyperleukocytosis due to the fact that relapses in the CNS have been reported most frequently in this category of patients.

Because lumbar puncture at presentation and during induction is extremely hazardous, CNS prophylaxis should be performed after the achievement of complete remission. In the GIMEMA trial, CNS prophylaxis is given before each consolidation course with methotrexate 12 mg (total dose) and 6-methyl prednisolone 40 mg (total dose).

Assessment of induction response

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 (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 complete remission (CR) that invariably occurs in all patients with genetically proven APL who survive induction with ATRA and chemotherapy. In addition to these considerations on morphology, results of RT-PCR, karyotyping and FISH analyses performed early after induction may also be misleading. In fact, several large prospective studies have shown that early laboratory evaluation of residual disease is irrelevant with respect to the patients' subsequent outcome and clinicians should refrain from making therapeutic decisions based on laboratory results at this time point.[16-18]

Consolidation therapy

Given that several studies have shown a highly significant correlation between patients' molecular status detected at the end of consolidation and subsequent outcome,[19,20] current guidelines for the diagnosis and definition of treatment outcomes have established that molecular remission is a therapeutic objective in APL.[21] The achievement of PCR-negativity in 90-99% of patients receiving 2 or 3 intensive cycles of anthracycline-based chemotherapy for consolidation[8] has led to this strategy being adopted as the standard for this phase of therapy. Although the benefit provided by the addition of ATRA to consolidation chemotherapy has not been demonstrated in randomized studies, historical comparisons of consecutive studies carried out separately by the GIMEMA[22] and PETHEMA[13] groups suggest that the combination of ATRA and chemotherapy for consolidation may also contribute to improving therapeutic results in APL.

Risk-adapted consolidation

Another interesting issue addressed in the aforementioned GIMEMA and PETHEMA studies[13,22] was the design of risk-adapted approaches to administer distinct treatment intensities for consolidation based on pre-defined risk of relapse.[23] According to these studies, this strategy seems a suitable 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 anthacycline monochemotherapy, especially in low- and intermediate-risk patients with APL. In both studies, ATRA was given at conventional oral doses of 45 mg/m^2 for 15 days during each of the 3 consolidation cycles. As to the high-risk group, recent data from the ongoing GIMEMA study[22] suggest that patients under 60 years old can benefit from a chemotherapy combination including both anthracyclines and non-intercalating agents with high-dose cytarabine in addition to ATRA.

Molecular assessment at the end of consolidation

Unlike RT-PCR analyses performed early after induction, molecular evaluation after completion of consolidation is regarded as extremely relevant for determining the short-term risk of relapse in the individual patient. However, it is important to remember that this predictive value has only been demonstrated in studies in which low-sensitivity amplification techniques (with sensitivity thresholds comprised between 10^{-3} and 10^{-4}) were used. An accurate assessment of PCR status at the end of consolidation is crucial because patients who show residual PML/RARα transcripts at this time point are candidates for further intensification therapy, whereas those who test PCR-negative would proceed to receive maintenance therapy. Nevertheless, to minimize the risk of false positive results, a PCR-positive result should be confirmed by sending a new marrow sample to a highly experienced reference laboratory where a low sensitivity assay is used. 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.

Maintenance therapy

Since the advent of ATRA, only two randomized studies have been published which investigated the role of maintenance therapy in APL.[6,24] These studies assessed the impact on relapse of maintenance therapy with ATRA alone[6,24] or in combination with low doses of methotrexate and mercaptopurine.[6] Both studies showed a benefit from maintenance with ATRA given intermittently or continuously. However, the continuous schedule does not seem to be supported by recent pharmacokinetic and pharmacodynamic

data on ATRA,[25] and has also been associated with significant toxicity.[24] In addition, the APL93 study of the European group[6] showed an advantage for administering maintenance therapy for 2 years in the form of low-dose chemotherapy including methotrexate 15 mg/m^2 and 6-mercaptopurine 50 mg/m^2. This study also reported an additional therapeutic benefit from using this chemotherapy plus intermittent ATRA (45 mg/m^2 for 15 days every 3 months), which resulted in a lower relapse rate, particularly in patients with elevated WBC count at presentation. In contrast, results that have been preliminarily reported but not yet published from a similar study carried out by the GIMEMA group failed to demonstrate a benefit of maintenance therapy.[26] 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 management strategies for APL.

Molecular monitoring during maintenance therapy and beyond

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.[19,20] Based on these findings, several groups have adopted the policy of anticipating administration of salvage treatment for patients showing reappearance of disease by RT-PCR (molecular relapse) during follow-up. However, the increasing antileukemic efficacy reported with state-of-the-art treatments has currently questioned the benefit of molecular monitoring, in terms of cost-effectiveness, for patients with a low risk of relapse (ie, patients with an initial WBC count less than 10×10^9/L). In contrast, for patients with hyperleukocytosis, it seems reasonable to recommend monitoring every 1-2 months in the early post-consolidation phase and thereafter every 3 months for another two years. 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 real-time quantitative-RT-PCR in this situation remains to be determined.

Role of hematopoietic stem cell transplantation (HSCT)

In the light of the long-term results obtained with upfront ATRA and chemotherapy, there are currently no indications for using either autologous or allogeneic HSCT for patients who are in first molecular remission at the end of consolidation. As discussed later, new approaches such as arsenic trioxide and/or gemtuzumab-ozogamicin followed by HSCT may be considered for the small fraction of patients showing persistent minimal residual disease after front line consolidation. Given the overall poor prognosis of this subset of patients,[27] allogeneic HSCT should be the preferred choice for those with an available HLA-identical donor. Autologous HSCT might represent a valid approach to consolidate remission for patients ineligible for allogeneic HSCT, provided that PCR-negativity is achieved prior to transplantation.

Management of special situations

Patients with persistent molecular residual disease at the end of consolidation

Because of their very poor prognosis,[27] patients who show molecular persistence of residual disease at the end of consolidation should receive additional therapy aimed at obtaining molecular remission. As salvage therapy for these patients, arsenic trioxide, gemtuzumab ozogamicin, and allogeneic stem cell transplantation can be considered.

Elderly patients

Given their vulnerability to therapy-related toxicity, elderly patients (60 years or older) are usually treated with less intensive regimens.[6,17,28] However, the PETHEMA group has recently reported excellent results, accompanied by a high degree of compliance and very good tolerance,[29] from administering to elderly patients the same protocol as that used for younger adults (i.e. ATRA with anthracycline monochemotherapy).[13,18]

Patients with severe comorbidities

Exceptions to the standard treatment approach for induction and consolidation should be considered solely for individual patients with absolute contraindications to intensive chemotherapy (eg, patients with cardiomyopathy or other severe organ dysfunction). In these settings, alternative front-line approaches using ATRA, arsenic trioxide and gemtuzumab ozogamicin should be explored. A study presently being conducted at the MD Anderson Cancer Center in USA in which an arsenic trioxide plus ATRA combination is being used to avoid front-line chemotherapy may serve as a reference in this context, although its results are still preliminary.[30]

Children

Information about therapeutic results with combinations of ATRA and anthracycline-based chemotherapy in children with APL is still scarce. To our knowledge, only four studies including 22, 31, 66 and 110 children from the German-Austrian-Swiss, European APL, PETHEMA and GIMEMA groups,[31-34] respectively, have reported therapeutic results using such an approach.

Compared to the disease in adults, APL diagnosed in childhood more frequently presents with hyperleukocytosis (approximately 40% versus 25%). In spite of the higher frequency of patients with an elevated WBC in the pediatric population, outcome results are comparable in cohorts of adults and children.

With the aim of decreasing the risk of pseudotumor cerebri, a side effect frequently observed in children,[35] the dose of ATRA used for the treatment of children and adolescents with APL has generally been reduced. The outstanding complete remission rates achieved with ATRA 25 mg/m^2/day combined with distinct anthracycline-based chemotherapy schemes, together with the apparently lower incidence of pseudotumor cerebri and headache when compared with the administration of ATRA 45 mg/m^2/day, suggest that 25 mg/m^2 could be the recommended dose, at least for children.

Treatment of pseudotumor cerebri, which is characterized by increased intracranial pressure, headache, nausea and vomiting that may be accompanied by visual disturbances and papilloedema, relies on discontinuation or dose reduction of ATRA and administration of dexamethasone, osmotic diuretics (mannitol) and analgesics.

Pregnant women

Both the coagulopathy and the teratogenic risk of ATRA and chemotherapy have been matters of major concern when treating APL during pregnancy. However, based on the limited experience reported, such treatments are reasonably safe when applied to APL patients diagnosed in the second or third trimester of pregnancy. No serious complications have been observed in the mother or the fetus for patients receiving ATRA alone or combined with chemotherapy.[36] Nevertheless, although fetal survival and normal development of neonates have always been reported in these cases, 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.[37,38] In contrast, although specific information on the use of ATRA during the first trimester is lacking, the use of this drug this period is not recommended because of the known teratogenic action of retinoids.

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