Published in final edited form as:

Hematol Oncol Clin North Am. 2011 December ; 25(6): 1215–viii. doi:10.1016/j.hoc.2011.10.002.

Curing All Patients with Acute Promyelocytic Leukemia: Are We There Yet?

Muhammed Baljevic, MD^a, Jae H. Park, MD^b, Eytan Stein, MD^c, Dan Douer, MD^{c,d}, Jessica K. Altman, MD^e, and Martin S. Tallman, MD^{b,c,*}

^a Department of Medicine, New York-Presbyterian Hospital/Weill Cornell Medical Center, 525 East 68th Street, Box 130, New York, NY 10065, USA

^b Leukemia Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, Weill Cornell Medical College, 1275 York Avenue, New York, NY 10065, USA

^c Department of Medicine, Memorial Sloan-Kettering Cancer Center, Weill Cornell Medical College, 1275 York Avenue, New York, NY 10065, USA

^d Acute Lymphoblastic Leukemia Program, Department of Medicine, Memorial Sloan-Kettering Cancer Center, Weill Cornell Medical College, 1275 York Avenue, New York, NY 10065, USA

^e Department of Medicine, Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Abstract

Acute promyelocytic leukemia (APL) is a distinct morphologic variant of acute myeloid leukemia (AML), accounting for approximately 10% to 15% of the adult cases of AML diagnosed in the United States annually.¹ The leukemia cells are usually easy to distinguish morphologically from others² and are characterized by a specific reciprocal translocation t(15;17),³ which fuses the PML (promyelocyte) gene from chromosome 15 to the RAR- α (retinoic acid receptor- α) gene of chromosome 17.⁴ Consistently found in all cases of t(15;17) APL, the resulting PML-RAR α fusion gene on der(15) encodes a chimeric transcript of the 2 DNA-binding domains that shows altered transcriptional regulatory properties, eventually leading to the block of retinoic-acid-induced myeloid differentiation.⁴

Keywords

Acute promyelocytic leukemia; All-*trans* retinoic acid; Arsenic trioxide; Targeted therapies; Cure

Ever since the seminal description by Hillestad in 1957,⁵ APL has been well recognized as one of the most fatal forms of acute leukemia at presentation or during induction, primarily because of an associated complex and often catastrophic bleeding disorder.¹ However, the

introduction of all-*trans* retinoic acid (ATRA) in 1985, combined with anthracycline-based chemotherapy, has revolutionized the prognosis of this disease, with unprecedented complete response (CR) rates in excess of 90%, and cure rates of approximately 80%. The pharmacologic concentrations of ATRA used in the treatment of APL lead to dissociation of N-CoR (nuclear corepressor) (a ubiquitous nuclear protein that mediates transcriptional repression) presumably permitting differentiation of the leukemic cells.⁶ As a result, the long-term outcome in most patients with APL is favorable. Nevertheless, a small percentage of patients have a variant form of the disease with different fusion transcripts such as PLZF/RAR- α ⁷ or STAT5b/RAR- α ⁸ coding for fusion proteins that are almost invariably resistant to initial treatment with ATRA, necessitating the accurate baseline identification of candidates who can be expected to benefit from induction therapy with ATRA. FLT-3 mutations, particularly the internal tandem duplication (ITD) mutations, are also common in APL and seem to be present in approximately 40% of patients. These variants are often also characterized by the high white blood cell (WBC) count and the bcr3 PML breakpoint. Several retrospective studies have reported that the subgroup of patients with FLT-3 mutation have a higher death rate during induction chemotherapy without a significant difference in relapse rate or 5-year overall survival (OS).⁹ Nevertheless, there have been reports that through univariate analysis showed higher relapse and lower survival rates in patients with an FLT3-ITD.¹⁰

The subsequent introduction of arsenic trioxide (ATO) further redefined the course of APL from a highly fatal to the most curable subtype of AML in adults. After several studies reported that the combination of ATRA and ATO is a highly effective and potentially curative treatment, an exciting new treatment strategy has emerged, which aims to eliminate exposure to conventional cytotoxic chemotherapy in treatment of many, if not most, patients with APL. Despite the advances in molecular biology and treatment approaches that have led to substantially decreased relapse rates, even among high-risk patients, the persistent challenge of the complex and life-threatening coagulopathy¹¹ before and during induction therapy has remained the principal cause of early death and has emerged as the major cause of treatment failure among patients with APL. Other questions of importance in APL are centered on defining the best treatment of patients with high-risk disease, the role of ATO in initial therapy, and the roles of maintenance therapy and molecular monitoring. Nevertheless, implementing rapid, aggressive, and comprehensive strategies that mitigate early death has become one of the most important goals in APL treatment and is sure to further increase the cure rate of APL.

In this review, the therapeutic approaches that have led to the current frontline treatment in APL are summarized, focusing on development of new and rationally targeted therapeutic approaches that aim to eliminate toxicities of conventional chemotherapy without compromising cure rates; the importance of strategies to further increase the cure rate of APL by addressing early hemorrhagic deaths is also highlighted.

INDUCTION THERAPY

In the age preceding the therapeutic use of ATRA, APL was treated much like other subtypes of AML, with the standard induction regimens based on an anthracycline and

cytarabine (Ara-C) yielding 70% CR rates among newly diagnosed patients.^{12–14} However, even among those patients who initially achieved CR, between 50% and 65% subsequently relapsed, whereas only 30% to 50% remain alive at 2 years.^{12,15}

Initial Studies of ATRA in APL

The evolution of creative treatment approaches for APL was spurred by an initial report, which documented CR rates of 85% with ATRA as a single induction agent.¹⁶ Among the first large studies to explore the role of ATRA either as a single agent or in combination with chemotherapy,^{16–19} the first North American Intergroup study I0129/E2491 reported an equivalent remission rate of 70% with single-agent ATRA compared with induction with Ara-C and daunorubicin.¹⁷ These encouraging results were tempered by studies of ATRA as a single agent that reported relapse of these patients from CR without further chemotherapy. As a result, subsequent trials such as that conducted by the European APL (EAPL) group focused on improving the clinical outcome through a combination of ATRA and chemotherapy. These investigators reported equal remission rates of 92% among the groups randomized to induction with concurrent therapy with ATRA plus chemotherapy with Ara-C and daunorubicin, versus sequential ATRA followed by chemotherapy.²⁰ However, a reduced relapse rate at 2 years (6% vs 16%) was observed in the arm with concurrent versus sequential therapy. After validation in multiple large multicenter trials^{21–24} (Table 1), these results led to the simultaneous administration of ATRA and anthracycline-based chemotherapy as the current standard induction approach in newly diagnosed patients with APL, with outstanding disease-free survival (DFS) rates (Fig. 1).

Choice of Anthracyclines

There is no clear evidence that one anthracycline is superior to another when combined with ATRA because no prospective randomized trials have directly compared daunorubicin and idarubicin in the ATRA era. The best available evidence stems from the pre-ATRA era. Even though it seems to suggest that idarubicin is associated with an improved outcome compared with daunorubicin or amsacrine,²⁵ there is no distinct superiority between the two because both seem equally effective in APL.

Role of Ara-C in Initial Therapy

The question of the importance of the addition of Ara-C to anthracyclines in the induction regimen has been addressed with disparate results. The cooperative groups Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) and the Programa Español de Tratamientos en Hematología (PETHEMA) omitted Ara-C during induction in nonrandomized prospective clinical trials, showing that ATRA plus idarubicin (AIDA) is as effective in inducing CR as a regimen containing Ara-C, with CR rates of 89% to 95% that were not influenced by the presenting WBC count.^{24,26} The National Cancer Research Institute (NCRI) in the United Kingdom (UK) reported no overall difference in response, relapse, or survival rates between the arms randomized to AIDA and ATRA plus daunorubicin and Ara-C. However, they did observe less myelosuppression without the use of cytarabine.²⁷ In a contrasting report, the EAPL group (APL 2000) in a randomized study observed a statistically significant increase in relapse risk (13.4% vs 29%) and OS (92.9% vs 83.3%) without the addition of Ara-C in both induction and consolidation regimens.^{28,29} Despite the

discrepancy of these reports, which can be attributed possibly to the choice and cumulative doses of anthracyclines, as well as differences in the consolidation regimens and the number of total consolidation courses, the choice of induction therapy is defined by the ability to tolerate anthracyclines and by whether the patient had high-risk or low-risk disease based on the WBC count at diagnosis.³⁰ It seems that Ara-C can be omitted from ATRA plus anthracycline-based induction regimen in most patients, even those considered high-risk (WBC count >10,000/ μ L). The optimal anthracycline has not been determined. However, idarubicin seems to be sufficient to induce CR in almost all patients who survive the initial risk of early death during induction.³¹

CONSOLIDATION THERAPY

Unlike the aim of induction therapy, which focuses on reduction of the total disease burden to less than the cytologically detectable level of approximately 10^9 cells, the goal of consolidation therapy in APL is to eliminate the remaining malignant leukemic stem cells that through replicative resilience lead to eventual relapse. Induction failure of any subgroup of patients with APL is generally related to bleeding, the APL differentiation syndrome, or infection and not disease progression.³¹ There is essentially no primary resistance in APL. Although ATRA-based induction therapy has a greater than 90% CR rate in APL,²² patients are invariably destined to relapse, necessitating effective consolidation therapy that provides durable remission. The benefit of adding ATRA in induction in improving DFS and OS by reducing relapse has been amply reported. Although not shown in any randomized trial, consecutive trials by the GIMEMA³² and PETHEMA groups³³ have shown improvement in outcome by the addition of ATRA in consolidation. The optimal choice and intensity of consolidation regimens remain controversial, because many of the investigative efforts of the past decade have promoted the development of risk-adapted approaches that guide the treatment intensity as defined by the risk factors predictive of relapse.

Risk-adapted Approach to Consolidation Therapy

The necessity for a risk-adapted approach is reflected in the higher mortality of 19% in patients in CR older than 70 years, compared with mortality of 1% in those younger than 60 years.³⁴ The currently used risk model stems from the 2 PETHEMA trials,^{33,35} which have identified 3 different groups of patients at risk for relapse: high-risk defined by presenting WBC counts 10,000/ μ L or greater and platelet count less than 40,000/ μ L; intermediate-risk with WBC count less than 10,000/ μ L and platelet count less than 40,000/ μ L and a low-risk with WBC count less than 10,000/ μ L and platelet count greater than 40,000/ μ L.

The results of the LPA99 trial of significantly improved outcome with the inclusion of ATRA in consolidation treatment were confirmed by the new AIDA-2000 trial of the Italian GIMEMA group.³² The PETHEMA group study (LPA2005) randomized high-risk patients younger than 60 years to receive Ara-C combined with ATRA and idarubicin in the first and third consolidation courses, reporting significantly lower relapse rate of 11% at 3 years (this is compared with 26% relapse rate in the historical cohort in the LPA99 trial, $P = .03$).³¹ More importantly, the study also investigated reducing the overall toxicity in low-risk and intermediate-risk patients by lowering the dose of mitoxantrone for the second consolidation course and eliminating Ara-C during the 3 consolidation courses. This treatment resulted in

a comparable clinical outcome but with a significant reduction of toxicity (as reflected in the duration of neutropenia and thrombocytopenia) and a shorter overall hospital stay (17 days vs 22 days in the LPA99 trial; $P < .001$).³¹ The GIMEMA group (AIDA2000), which also included ATRA as a part of the consolidation regimen, similarly reported no difference in OS and a significant reduction of infections (40% vs 80%) and prolonged neutropenia with improved DFS at 6 years (85.9% vs 76.6% in the AIDA0493) for the low-risk and intermediate-risk patients who had Ara-C omitted from their consolidation courses.³² An additional study conducted by the UK NCRI failed to show any benefit of Ara-C regardless of risk stratification.²⁷ With the goal of further reduction in toxicity, the North American Intergroup Trial C9710 randomized patients after CR to receive either 2 courses of 25 days of ATO (5 days a week for a total of 5 weeks) followed by a standard postremission regimen with 2 courses of ATRA plus daunorubicin, or postremission therapy alone. Treatment with ATO, particularly in the high-risk subgroup, showed significantly better event-free survival (EFS) and OS.³⁶ This finding represents an attractive alternative among those patients with a high-risk disease who may be in particular need of a less cardiotoxic consolidation regimen.

Given the overall body of evidence, it seems that high-risk patients benefit from either the addition of intermediate-dose Ara-C to consolidation or ATO as an early consolidation course with synergistic antileukemic effect of combination therapy.³⁷

MAINTENANCE (POSTCONSOLIDATION) THERAPY

The response to completed consolidation therapy is routinely assessed using reverse transcriptase-polymerase chain reaction (RT-PCR) in the bone marrow, the goal being complete molecular remission (MR). The best therapeutic approach to maintenance therapy was controversial even in the pre-ATRA era, and despite the 2 randomized controlled trials that have reported a substantial benefit with ATRA-based maintenance therapy,^{20,38} its systematic use remains controversial. This situation is particularly true for those patients considered nonhigh risk, or those who achieve MR after consolidation treatment. Moreover, parallel to evolution of not only induction but also consolidation regimens that have incorporated ATO into first-line treatment of APL, the significance of maintenance therapy may have been reduced even further.

The North American Intergroup study I0129/E2491 reported a superior 5-year DFS (61% vs 36%), with a reduction in relapse rate (22% vs 39%), proving clinical benefit with ATRA-based maintenance therapy.^{17,38} The APL93 trial similarly confirmed the beneficial effect of adding ATRA to maintenance therapy in a randomized study in which the regimen consisting of continuous low-dose 6-mercaptopurine (6-MP), methotrexate (MTX), and intermittent ATRA showed the lowest relapse rate (8%) at 2 years, compared with relapse for 6-MP plus MTX (13%), ATRA alone (21%) versus no maintenance (35%).²⁰ More importantly, this group recently updated the results of their previous study to indicate that the clinical benefit of maintenance therapy was mainly evident in high-risk patients whereas the low-risk and intermediate-risk patients experienced only marginal benefit.³⁹ With contrasting results, randomized trials by the GIMEMA⁴⁰ and Japanese Adult Leukemia Study Group (JALSG)⁴¹ have reported no difference in DFS with postconsolidation therapy, with follow-up of up to 12 years. However, the observations of the JALSG group trial may

not entirely be applicable, because ATRA was not included in maintenance therapy. Furthermore, data from the AIDA study appeared to suggest that patients who test molecularly negative after the consolidation therapy experience no real benefit from maintenance therapy.⁴²

These studies differed significantly in the treatment approach. Both the JALSG⁴¹ and the GIMEMA⁴⁰ groups administered a higher number of consolidation cycles with idarubicin as a choice of anthracycline therapy for induction and consolidation chemotherapy; in contrast, the EAPL^{20,39} and North American Intergroup^{17,38} trials administered only 2 consolidation courses with daunorubicin. Moreover, whereas studies by the GIMEMA and JALSG groups may have been confounded because all study patients tested negative for PML/RAR α at the end of consolidation, the North American Intergroup and EAPL studies did not examine the MR status at the end of consolidation, raising a question whether the benefit that was observed by the maintenance therapy in their study largely reflected the response of patients with residual disease after consolidation treatment.

Overall, the sum of reported studies points to discrepancies that suggest that the benefit of maintenance treatment may be dependent on preceding induction and consolidation therapy, as well as PML/RAR α molecular status after consolidation, which has clearly been shown to correlate with the relapse risk.^{43,44} Together with RT-PCR, which should be completed to document postconsolidation MR, subsequent molecular monitoring of patients can be performed based on the perceived risk of relapse. Furthermore, studies suggest that low-risk and intermediate-risk patients and those who achieve complete MR after consolidation may not benefit from the combination maintenance therapy. However, for high-risk patients, maintenance therapy for 1 to 2 years with intermittent ATRA and low-dose chemotherapy with 6-MP and MTX is recommended. Furthermore, molecular monitoring every 3 months for 2 years during maintenance for high-risk subgroups is also recommended, with the aim of monitoring and identifying potential molecular relapse. Because there are no prospective trial data in comparing 1 versus 2 years of maintenance therapy, we recommend continuation of maintenance therapy for 2 years unless toxicity develops. In those patients who develop cytopenias and have a negative molecular test with RT-PCR, a marrow analysis is recommended for evaluation of new cytogenetic anomalies that may represent therapy-related myelodysplastic syndrome (MDS) or AML.

MINIMAL RESIDUAL DISEASE MONITORING

Minimal residual disease (MRD) monitoring entails identification of the molecular product of the chimeric PML-RAR α transcript. The development of the real-time quantitative PCR (RQ-PCR) allowed more precise assessment of the kinetics of treatment response and relapse, setting foundation to MRD-directed therapy. Taking into account that frank relapse in APL can be complicated by a major risk of death because of hemorrhagic complications, and evidence that impending relapses can be reliably predicted by MRD monitoring with RT-PCR,^{45,46} there has been a growing interest in adopting MRD monitoring as a tool to guide and deliver preemptive therapy. Nevertheless, the optimal use of sequential MRD monitoring in treatment of APL remains controversial because of limited prospective data.

A prospective study by the PETHEMA group reported improved survival in patients salvaged with ATRA and anthracycline-based chemotherapy in molecular relapse compared with those who were treated only at frank hematologic relapse (historical control population).⁴⁶ However, OS of 44% at 2 years for the historical cohort patients was considerably lower than what is currently achieved with ATO-based regimens.⁴⁷ The UK NCRI prospective study⁴⁸ has similarly reported a benefit from MRD-directed preemptive therapy using ATO, showing the evidence for MRD monitoring being far superior to presenting WBC count as a therapy guide and the strongest predictor of relapse-free survival (RFS) with less toxicity and reduced rates of frank relapses. However, there remain many unanswered questions from the trial. Given that half of the trial patients (MRC AML15) received maintenance after consolidation treatment, the difference in kinetics of PML-RAR α transcripts and time from molecular to hematologic relapse among the group that did and did not receive maintenance therapy is unclear; furthermore, although the key aim of monitoring was to trigger preemptive therapy, more than half of the patients failed to have the salvage therapy initiated because of various technical reasons, questioning the large-scale practicality of this approach; the clinical outcome of patients in this trial reported in the 5-year RFS of 35% and OS of 41% remains less than optimal, implying that primary focus should be placed on improving the initial therapy in high-risk patients to prevent against, rather than detect, disease relapse.⁴⁹

The limited prospective data and the improved antileukemic efficacy of currently available standard treatments together question the true benefit of systematic molecular monitoring after consolidation therapy. As a result, the role of MRD monitoring as part of currently standard practice is changing, particularly for low-risk and intermediate-risk patients. The main reasons are the unanswered questions that pertain to the cumulative cost of serial testing, the implications of positive MRD screen, the chance of successful treatment at the time of MRD versus at the time of hematologic relapse as well as persistent anxiety potentially conferred by frequent testing.

Rigorous sequential RQ-PCR monitoring has been found to be the strongest predictor of RFS in APL and, when coupled with preemptive therapy, represents a valid strategy toward reducing rates of clinical relapse.⁴⁸ Low-risk and intermediate-risk patients have a more favorable outcome with extremely low risk of relapse with currently available treatment protocols. Consequently, serious doubts can be raised about the usefulness of molecular monitoring in this group of patients if they are treated with contemporary strategies and followed with routine complete blood counts.⁵⁰ On the other hand, the high-risk patients carry a relapse risk of approximately 10%, which seems to suggest there may be a greater benefit for sequential MRD monitoring in this patient population^{48,51}; the optimal schedule for monitoring is still the subject for future research. Molecular monitoring may guide an appropriate salvage therapy for these patients based on the available evidence that suggests a higher relapse rate after a PCR-positive autologous hematopoietic stem cell transplantation (HSCT).⁵² In addition, a small subset of the high-risk patients may have the propensity for a central nervous system relapse. After achieving second morphologic remission, these patients are strongly recommended to receive intrathecal chemotherapy.⁵³ Allogeneic transplantation should be reserved for those patients who have evidence of persistent disease despite salvage therapy.

Keeping in mind the pace at which new effective therapeutic strategies are evolving with less residual disease to detect, MRD monitoring in APL may soon become less important for most patients.⁴⁸ Nevertheless, although still advised in the high-risk patients with APL, it is highly recommended that it be performed in reference laboratories with extensive expertise.

Role of HSCT

Those patients who experience persistence of disease after appropriate initial therapy or fail to achieve second molecular CR after salvage ATO at first relapse should be considered for allogeneic HSCT. Patients who relapse after initial therapy and achieve a second molecular CR after ATO salvage therapy do well with autologous HSCT. The choice between autologous versus allogeneic HSCT in second molecular CR was initially answered in a study that showed that for those patients with APL in second CR, autologous bone marrow transplantation (ABMT) with PML/RAR- α -negative marrow cells is likely to result in prolonged clinical and MRs. Conversely, patients who tested PCR-positive after reinduction required the use of alternative aggressive approaches, including unrelated allogeneic HSCT.⁵¹ This finding was also further investigated by the EAPL group, who showed an OS rate of 75% for patients with PCR-negative autologous HSCT, versus 52% for those who underwent allogeneic HSCT.⁵⁴ Differences in the survival were likely reflective of cumulatively higher treatment-related mortality for the allogeneic HSCT arm. Allogeneic and autologous stem cell transplantations (SCTs) were directly compared in the same retrospective study, which concluded that if performed in MR, ABMT is effective in patients who relapse after initial treatment with ATRA. At the same time, allogeneic SCT was found to be associated with high treatment-related mortality when performed after salvage with intensive chemotherapy.⁵⁴ Salvage with ATO instead, which has lower toxicity, promises to further improve the outcome of relapsing patients with APL.

INCREASING APL CURE RATES WITH EARLY DEATH REDUCTION

Since the first report of APL 50 years ago, rapid and unprecedented progress has been made in our understanding of the biology and therapeutic options available for APL, making its story epical in the chronicles of modern medicine. More recently, several studies have contributed to the optimization of the antileukemic efficacy of the current regimens for APL. Despite this and in the face of highly effective therapy, early death rates remain high,⁵⁵ and more efforts are need to reduce the early deaths in this highly curable disease.

Although infection is the principal cause of death in AML, hemorrhagic complications of the induction therapy are still often the primary cause of early death in APL.⁵⁶ Other associating factors significantly related to the severe bleeding and early death also include late diagnosis and delayed treatment initiation, in addition to increased WBC count.⁵⁶ Even although earlier multicenter cooperative studies report an approximate 5% to 10% early death rate within 1 month after the initiation of treatment,^{17,20,22–24} several population-based observational studies recently reported higher early death rates in unselected patients with APL,^{57,58} the largest of which involved a cohort of 1400 patients and reported a 17.3% early death rate despite use of ATRA (Fig. 2).⁵⁹ These results indicate that the availability and routine use of ATRA per se are not sufficient to eliminate the major cause of treatment failure in APL. They also further highlight the essence of educating a range of health care

providers across a wide spectrum of medical fields who may be the first to evaluate patients suspected of having APL with the knowledge necessary to approach them as a medical emergency that requires swift initiation of ATRA, aggressive supportive care to correct the coagulopathy, and transfer to experienced medical centers.

ATRA has been shown to rapidly improve biochemical parameters of the coagulopathy associated with APL, thereby reducing the severity of bleeding and the amount of blood products needed to maintain hemostatic stability.⁶⁰ ATRA should be started immediately on the first suspicion of the diagnosis. Although the real impact of ATRA in reducing the early death rate remains to be determined,^{17,20,61} it is the correct approach to presume a favorable risk/benefit ratio of its initiation, because the agent is unlikely to have any deleterious systemic effects should the final diagnostic assessment fail to confirm the diagnosis of APL. Much like with ATRA, supportive measures to reverse life-threatening coagulopathy including fresh frozen plasma, cryoprecipitate, fibrinogen and platelet transfusions to keep the fibrinogen concentration more than 100 to 150 mg/dL and platelet count more than 50,000/ μ L need to be instituted instantly. Posttransfusion values must be followed with the same vigilance, ensuring adequate repletion of all coagulation factors.⁶² Intense monitoring and aggressive correction of the same should be maintained during induction therapy for all patients suspected of having APL, irrespective of whether they may potentially be variant subtypes virtually resistant to the ATRA induction, until the disappearance of any clinical or laboratory signs of coagulopathy.

Whereas genetic verification of the specific PML-RAR α fusion transcript is a prerequisite to definitive diagnosis of APL, fluorescence in situ hybridization and reverse RT-PCR (the turnaround time of which is 1 to 2 days) may not even be available at more decentralized health care centers. Immunostaining with anti-PML monoclonal antibodies performed on dry smears of bone marrow or even peripheral blood samples has been shown to have the sufficiently high sensitivity and specificity to establish a rapid diagnosis, which in this way is made in less than 4 hours.⁶³ This test may be of particular value in smaller centers lacking immediate access to sophisticated molecular diagnostics laboratories, and has further been shown in a large South American trial⁶⁴ to reduce early mortality by facilitating the rapid confirmation of the diagnosis. Nevertheless, even in the setting in which these tests are readily available, there should be no delay in initiation of ATRA if a sufficiently high index of suspicion is present. The immediate transfer of patients when stable to more experienced centers with a capacity to administer ATRA and provide aggressive repletion of the blood products may be beneficial.

IN SEARCH OF A CHEMOTHERAPY-FREE CURE FOR APL

Contemporary investigative efforts have influenced the therapeutic approach to the treatment of neoplastic processes, particularly hematologic malignancies in the direction of molecularly targeted therapies. In APL, it is in this spirit and on the weight of the breakthrough discoveries of agents such as ATRA and ATO that the adoption of novel treatment approaches devoid of conventional chemotherapy has begun. Although treatment of newly diagnosed APL with anthracycline-based regimens augmented with ATRA has been proved to be highly effective, eliminating the exposure of patients to cytotoxicity of

conventional DNA-disrupting chemotherapy has been the primary focus of recent studies. Reducing the potential for treatment-associated cardiomyopathy of anthracyclines, as well as infection risk associated with prolonged neutropenia, may further improve the overall outcome of patients with APL. Furthermore, although the risk of therapy-related MDS and AML is low in published series,^{65–67} removing this risk of therapy-related secondary malignancy may improve the outcome profile of patients with APL being treated with curative intent.

THE ROLE OF ATO

As a cytostatic agent, ATRA effectively induces complete differentiation of the promyelocyte clones, but it rarely gives rise to durable remissions when used as a single agent.⁶⁸ As a potent promoter of apoptosis^{69,70} ATO is not a direct activator of transcription or terminal differentiation, and, unlike ATRA, has been shown to be curative in APL, even as a single agent.

Recent insights into the molecular nature and the in vivo and in vitro dynamics of leukemic cells in APL have challenged the historical dogma that assumes the disappearance of the disease with the differentiation of APL leukemic clones. Current understanding suggests that the degradation of the chimeric product of translocation (PML-RAR α), initially considered to be a mere aftermath of differentiation therapy, plays a pivotal role in not only the loss of self-renewal capacity of APL clones but also the eradication of leukemic cancer stem cells (termed leukemia initiating cells) and ultimately stable disease remission.^{71–73}

ATRA functions by inducing proteasome-dependent degradation of RAR alpha moiety,⁷⁴ whereas ATO acts on the PML part of the fusion protein, resulting in rapid degradation of the PML-RAR α transcript.^{75,76} Given specific and divergent mechanisms of action of ATRA and ATO on the PML-RAR α protein, it is possible to hypothesize that combination of the 2 agents would degrade the fusion protein in synergy, leading to cooperative cure in APL. This hypothesis is what has been shown in murine models in which degradation of the fusion product leads to the disease clearance.^{52,77,78} Although data from clinical trials suggest that ATO does not seem to be sufficient for many patients as a single frontline therapy,^{79,80} the combination of ATRA and ATO leads to cure of many patients despite the absence of conventional chemotherapy.^{36,81–85}

In the clinical arena, ATO as a single agent has been shown to be equivalent to ATRA-based regimens with induction CRs of 85% to 86% in previously untreated patients with APL (Table 2).^{79,80} Nevertheless, the outcome of high-risk patients defined in this study with WBC count greater than 5000/ μ L at diagnosis (what would otherwise not be defined as high risk) in which patients were randomized to receive sequential ATO induction, 28-day consolidation, and a 6-month postconsolidation therapy was found to be inferior, with an EFS of 60% at 5 years, when compared with a similar subset of patients treated with ATRA-based chemotherapy.⁷⁹ The same outcome is evident when risk-stratifying patients by the conventional relapse risk grouping³⁵ with an EFS of less than 60% in high-risk patients.⁷⁹ In contrast, a study that followed shortly thereafter reported no difference in clinical outcome with the same ATO induction and consolidation therapy, irrespective of the presenting WBC

count.⁸⁰ For patients who presented with a WBC count greater than $50 \times 10^9/L$ (the value used to define hyperleukocytosis) and despite allowing the use of hydroxyurea, which was given to 73.6% of patients, and anthracyclines administered to 11% of patients, there was a higher early death rate of 13.9% to 14.7% because of hemorrhagic complications, suggesting that ATO as a single-agent frontline therapy may not be sufficient or appropriate for some patients with APL.

Building on the preclinical evidence of the synergistic effect of ATRA and ATO combination therapy,^{52,77,78} several rationally targeted studies have been launched for newly diagnosed patients with APL, with the aim to investigate the effect of this approach in the absence of significant exposure to conventional DNA-targeting chemotherapy. A randomized clinical trial from Shanghai in which patients were randomized to receive induction therapy with either ATRA, ATO, or the combination of the two,⁸¹ with subsequent consolidation and maintenance courses, resulted in the lowest rates of relapse, a faster CR rate, and a greater reduction in the number of PML-RAR α transcripts, without apparent greater toxicity compared with ATRA or ATO alone. The 7-year follow-up update on this report⁸² confirms the high efficacy and minimal toxicity of the combination treatment, with no difference in early death rates among the different treatment arms, and an overall early death rate of 6.5%. In a similar fashion, the study from the MD Anderson Cancer Center reported the combination ATRA and ATO treatment to be an effective regimen in previously untreated patients with APL with presenting WBC count less than $10 \times 10^9/L$, with a CR rate of 96% and few relapses even when eliminating conventional chemotherapy from consolidation course.⁸⁴ These investigators also reported, unlike investigators of a comparable study,⁸¹ that chemotherapy can be eliminated in consolidation, resulting in durable responses with few late relapses. Nevertheless, high-risk patients in this study who presented with WBC count $10 \times 10^9/L$ or greater achieved an inferior CR rate of 79% to 81% and a lower EFS (65% vs 90% at 2 years) because of early treatment failure from fatal hemorrhage and APL differentiation syndrome despite the addition of gemtuzumab ozogamicin (GO) or idarubicin during induction.⁸⁴

More recently, 124 patients with newly diagnosed APL were studied in the Australasian Leukemia and Lymphoma Group. These patients were treated with ATRA, ATO, and idarubicin during induction, followed by 2 courses of consolidation therapy with ATRA and ATO and 2-year postconsolidation therapy with ATRA, MTX, and 6-MP. After a median follow-up of 20 months, the 3-year OS and EFS rates were 93% and 87%, respectively.⁸⁵ The North American Intergroup randomized patients during induction to receive 2 cycles of consolidation of ATRA plus daunorubicin, either immediately after induction therapy or preceded by 2 25-day cycles of ATO plus ATRA.³⁶ Adding the ATO as an initial consolidation therapy significantly improved the 3-year DFS (90% vs 70%) and OS (86% vs 81%) irrespective of the risk stratification by presenting WBC count. With considerably reduced amount of anthracyclines coupled with a single cycle of ATO, a similar phase II study reported comparable outcomes with DFS 90% and OS 88% at a 2.7-year median follow-up (see Table 2).⁸⁶

Overall, although limited by the nonrandomized trial design, the body of evidence points toward a potential cooperative mechanism of disease suppression and elimination with

combination therapy with ATRA and ATO, raising the possibility of minimizing or perhaps even eliminating the use of conventional chemotherapy in the treatment of APL, particularly as it pertains to low-risk and intermediate-risk disease (commonly defined as those patients who present with WBC count $<10 \times 10^9/L$). Furthermore, according to the National Comprehensive Cancer Network Guidelines, ATRA and ATO represent an attractive alternative for older patients or patients otherwise unfit for conventional anthracycline therapy because of severe comorbidities of cardiovascular or other organ systems, secondary anthracycline-related APL, or women with previous breast cancer. Nevertheless, evidence suggests that in high-risk patients who present with increased WBC count, concomitant use of conventional chemotherapy such as anthracyclines remains critical to prevent rapid progression of leukocytosis and consequent APL differentiation syndrome. Ongoing randomized trials by several cooperative groups who will compare ATRA plus ATO with ATRA plus chemotherapy will shed further light into the safety of additional deintensification of APL therapy in high-risk patients without the compromise of cure rates.

TOWARD CURATIVE STRATEGIES IN APL

The introduction of the cytostatic, differentiating agent ATRA has transformed APL into one of the most curable subtypes of adult AML. Further institution of ATO to the therapeutic arsenal has brought forth the development of several frontline rationally targeted treatment protocols with the aim of limiting or eliminating exposure to traditional cytotoxic chemotherapy, reducing the treatment-associated complications and toxicities in most patients. Through risk-adapted approaches without the use of the cytotoxic chemotherapy, these questions are being tested in several multi-center trials.

In efforts to optimize the front-line therapies, colleagues in the GIMEMA group will compare ATRA plus ATO with minimal chemotherapy to control the WBC count during the induction to AIDA for intermediate-risk and high-risk patients (presenting WBC count $10 \times 10^9/L$ or less). The British NCRI (AML17 trial) with investigators from France will use the same randomization in all patients irrespective of the presenting WBC count. The role of maintenance therapy in high-risk patients who are induced and consolidated with ATO-containing regimens is to be answered through future prospective clinical trials.

An essential part of the strategy to further increase the cure rate and improve overall outcome of patients with APL are efforts focusing on successful implementation of strategies that will reduce early hemorrhagic deaths. This goal can be achieved through the education of a wide range of health care providers, who may be the first to encounter patients with APL in a variety of clinical settings that will prompt swift initiation of ATRA followed by aggressive blood product support and transfer to more equipped and specialized medical centers.

The ensuing decade will bring exciting answers and perhaps significant changes in the way we approach frontline treatment of patients with newly diagnosed APL. Soon, APL might be better individually tailored and rationally targeted with reduced exposure to conventional cytotoxic chemotherapy in most, if not all, patients as we learn more from data on the short-term and long-term safety and efficacy of ATRA and ATO-based nonchemotherapy

treatment protocols being investigated in ongoing clinical trials. Furthermore, novel formulations of the same targeted agents such as the oral formulation of ATO and an oral synthetic retinoid (Tamibarotene) designed to overcome ATRA resistance⁸⁷ may be promising new therapeutic options for patients with relapsed disease.

REFERENCES

1. Tallman MS, Altman JK. Curative strategies in acute promyelocytic leukemia. *Hematology Am Soc Hematol Educ Program*. 2008;391–9. [PubMed: 19074116]
2. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the acute leukaemias. French-American-British (FAB) co-operative group. *Br J Haematol*. 1976; 33(4):451–8. [PubMed: 188440]
3. Rowley JD, Golomb HM, Dougherty C. 15/17 translocation, a consistent chromosomal change in acute promyelocytic leukaemia. *Lancet*. 1977; 1(8010):549–50. [PubMed: 65649]
4. Grignani F, Ferrucci PF, Testa U, et al. The acute promyelocytic leukemia-specific PML-RAR alpha fusion protein inhibits differentiation and promotes survival of myeloid precursor cells. *Cell*. 1993; 74(3):423–31. [PubMed: 8394219]
5. Hillestad LK. Acute promyelocytic leukemia. *Acta Med Scand*. 1957; 159:189–94. [PubMed: 13508085]
6. Guidez F, Ivins S, Zhu J, et al. Reduced retinoic acid-sensitivities of nuclear receptor corepressor binding to PML- and PLZF-RARalpha underlie molecular pathogenesis and treatment of acute promyelocytic leukemia. *Blood*. 1998; 91:2634. [PubMed: 9531570]
7. Melnick A, Licht JD. Deconstructing a disease: RARalpha, its fusion partners, and their roles in the pathogenesis of acute promyelocytic leukemia. *Blood*. 1999; 93:3167. [PubMed: 10233871]
8. Dong S, Tweardy DJ. Interactions of STAT5b-RARalpha, a novel acute promyelocytic leukemia fusion protein, with retinoic acid receptor and STAT3 signaling pathways. *Blood*. 2002; 99:2637. [PubMed: 11929748]
9. Gale RE, Hills R, Pizzey AR, et al. Relationship between FLT3 mutation status, biologic characteristics, and response to targeted therapy in acute promyelocytic leukemia. *Blood*. 2005; 106:3768–76. [PubMed: 16105978]
10. Barragán E, Montesinos P, Camos M, et al. Prognostic value of FLT3 mutations in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and anthracycline monochemotherapy. *Haematologica*. 2011; 96(10):1470–7. [PubMed: 21685470]
11. Tallman MS, Kwaan HC. Reassessing the hemostatic disorder associated with acute promyelocytic leukemia. *Blood*. 1992; 79(3):543–53. [PubMed: 1732003]
12. Cunningham I, Gee TS, Reich LM, et al. Acute promyelocytic leukemia: treatment results during a decade at Memorial Hospital. *Blood*. 1989; 73(5):1116–22. [PubMed: 2930837]
13. Fenaux P, Degos L. Treatment of acute promyelocytic leukemia with all-trans retinoic acid. *Leuk Res*. 1991; 15(8):655–7. [PubMed: 1895747]
14. Head DR, Kopecky KJ, Willman C, et al. Treatment outcome with chemotherapy in acute promyelocytic leukemia: the Southwest Oncology Group (SWOG) experience. *Leukemia*. 1994; 8(Suppl 2):S38–41. [PubMed: 7815835]
15. Degos L, Dombret H, Chomienne C, et al. All-trans-retinoic acid as a differentiating agent in the treatment of acute promyelocytic leukemia. *Blood*. 1995; 85(10):2643–53. [PubMed: 7742522]
16. Huang ME, Ye YC, Chen SR, et al. Use of all-trans retinoic acid in the treatment of acute promyelocytic leukemia. *Blood*. 1988; 72(2):567–72. [PubMed: 3165295]
17. Tallman MS, Andersen JW, Schiffer CA, et al. All-trans-retinoic acid in acute promyelocytic leukemia. *N Engl J Med*. 1997; 337(15):1021–8. [PubMed: 9321529]
18. Chen ZX, Xue YQ, Zhang R, et al. A clinical and experimental study on all-trans retinoic acid-treated acute promyelocytic leukemia patients. *Blood*. 1991; 78(6):1413–9. [PubMed: 1884013]
19. Castaigne S, Chomienne C, Daniel MT, et al. All-trans retinoic acid as a differentiation therapy for acute promyelocytic leukemia. I. Clinical results. *Blood*. 1990; 76(9):1704–9. [PubMed: 2224119]

20. Fenaux P, Chastang C, Chevret S, et al. A randomized comparison of all transretinoic acid (ATRA) followed by chemotherapy and ATRA plus chemotherapy and the role of maintenance therapy in newly diagnosed acute promyelocytic leukemia. The European APL Group. *Blood*. 1999; 94(4): 1192–200. [PubMed: 10438706]
21. 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. German AML Cooperative Group. *Leukemia*. 2000; 14(8):1362–70. [PubMed: 10942230]
22. 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. Gruppo Italiano-Malattie Ematologiche Maligne dell'Adulto and Associazione Italiana di Ematologia ed Oncologia Pediatrica Cooperative Groups. *Blood*. 1997; 90(3):1014–21. [PubMed: 9242531]
23. Asou N, Adachi K, Tamura J, et al. Analysis of prognostic factors in newly diagnosed acute promyelocytic leukemia treated with all-trans retinoic acid and chemotherapy. Japan Adult Leukemia Study Group. *J Clin Oncol*. 1998; 16(1):78–85. [PubMed: 9440726]
24. Sanz MA, Martin G, Rayon C, et al. A modified AIDA protocol with anthracycline-based consolidation results in high antileukemic efficacy and reduced toxicity in newly diagnosed PML/RARalpha-positive acute promyelocytic leukemia. PETHEMA group. *Blood*. 1999; 94(9):3015–21. [PubMed: 10556184]
25. Berman E, Little C, Kher U, et al. Prognostic analysis of patients with acute promyelocytic leukemia [abstract]. *Blood*. 1991; 78:43a.
26. Avvisati G, Lo Coco F, Diverio D, et al. AIDA (all-trans retinoic acid 1 idarubicin) in newly diagnosed acute promyelocytic leukemia: a Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) pilot study. *Blood*. 1996; 88(4):1390–8. [PubMed: 8695858]
27. Burnett AK, Hills RK, Grimwade D, et al. Idarubicin and ATRA is as effective as MRC chemotherapy in patients with acute promyelocytic leukaemia with lower toxicity and resource usage: preliminary results of the MRC AML15 Trial. *ASH Annual Meeting Abstracts*. 2007; 110(11):589.
28. Ades L, Chevret S, Raffoux E, et al. Is cytarabine useful in the treatment of acute promyelocytic leukemia? Results of a randomized trial from the European Acute Promyelocytic Leukemia Group. *J Clin Oncol*. 2006; 24(36):5703–10. [PubMed: 17116939]
29. Ades L, Raffoux E, Chevret S, et al. Is AraC required in the treatment of standard risk APL? Long term results of a randomized trial (APL 2000) from the French Belgian Swiss APL Group. *ASH Annual Meeting Abstracts*. 2010; 116(21):13.
30. O'Donnell MR, Abboud CN, Altman J, et al. Acute myeloid leukemia. *J Natl Compr Canc Netw*. 2011; 9(3):280–317. [PubMed: 21393440]
31. Sanz MA, Montesinos P, Rayon C, et al. Risk-adapted treatment of acute promyelocytic leukemia based on all-trans retinoic acid and anthracycline with addition of cytarabine in consolidation therapy for high-risk patients: further improvements in treatment outcome. *Blood*. 2010; 115(25): 5137–46. [PubMed: 20393132]
32. Lo-Coco F, Avvisati G, Vignetti M, et al. Front-line treatment of acute promyelocytic leukemia with AIDA induction followed by risk-adapted consolidation for adults younger than 61 years: results of the AIDA-2000 trial of the GIMEMA Group. *Blood*. 2010; 116(17):3171–9. [PubMed: 20644121]
33. Sanz MA, Martin G, Gonzalez M, et al. Risk-adapted treatment of acute promyelocytic leukemia with all-trans-retinoic acid and anthracycline monotherapy: a multicenter study by the PETHEMA group. *Blood*. 2004; 103(4):1237–43. [PubMed: 14576047]
34. Sanz MA, Vellenga E, Rayon C, et al. All-trans retinoic acid and anthracycline monotherapy for the treatment of elderly patients with acute promyelocytic leukemia. *Blood*. 2004; 104(12): 3490–3. [PubMed: 15292063]
35. Sanz MA, Lo Coco F, Martin G, et al. Definition of relapse risk and role of nonanthracycline drugs for consolidation in patients with acute promyelocytic leukemia: a joint study of the PETHEMA and GIMEMA cooperative groups. *Blood*. 2000; 96(4):1247–53. [PubMed: 10942364]

36. Powell BL, Moser B, Stock W, et al. Arsenic trioxide improves event-free and overall survival for adults with acute promyelocytic leukemia: North American Leukemia Intergroup Study C9710. *Blood*. 2010; 116(19):3751–7. [PubMed: 20705755]
37. Flanagan SA, Meckling KA. All- trans-retinoic acid increases cytotoxicity of 1-beta-D-arabinofuranosylcytosine in NB4 cells. *Cancer Chemother Pharmacol*. 2003; 51(5):363–75. [PubMed: 12736759]
38. Tallman MS, Andersen JW, Schiffer CA, et al. All-trans retinoic acid in acute promyelocytic leukemia: long-term outcome and prognostic factor analysis from the North American Intergroup protocol. *Blood*. 2002; 100(13):4298–302. [PubMed: 12393590]
39. Ades L, Guerri A, Raffoux E, et al. Very long-term outcome of acute promyelocytic leukemia after treatment with all-trans retinoic acid and chemotherapy: the European APL Group experience. *Blood*. 2010; 115(9):1690–6. [PubMed: 20018913]
40. Avvisati G, Lo-Coco F, Paoloni FP, et al. AIDA 0493 protocol for newly diagnosed acute promyelocytic leukemia: very long-term results and role of maintenance. *Blood*. 2011; 117(18):4716–25. [PubMed: 21385856]
41. Asou N, Kishimoto Y, Kiyoi H, et al. A randomized study with or without intensified maintenance chemotherapy in patients with acute promyelocytic leukemia who have become negative for PML-RARalpha transcript after consolidation therapy: the Japan Adult Leukemia Study Group (JALSG) APL97 study. *Blood*. 2007; 110(1):59–66. [PubMed: 17374742]
42. Avvisati G, Petti MC, Lo Coco F, et al. AIDA: the Italian way of treating acute promyelocytic leukemia (APL), final act. *Blood*. 2003; 102(Suppl 1) [abstract 487].
43. Lo Coco F, Diverio D, Falini B, et al. Genetic diagnosis and molecular monitoring in the management of acute promyelocytic leukemia. *Blood*. 1999; 94(1):12–22. [PubMed: 10381493]
44. 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(10):1959–73. [PubMed: 12357347]
45. Lo Coco F, Diverio D, Avvisati G, et al. Therapy of molecular relapse in acute promyelocytic leukemia. *Blood*. 1999; 94(7):2225–9. [PubMed: 10498592]
46. Esteve J, Escoda L, Martin G, et al. Outcome of patients with acute promyelocytic leukemia failing to front-line treatment with all-trans retinoic acid and anthracycline-based chemotherapy (PETHEMA protocols LPA96 and LPA99): benefit of an early intervention. *Leukemia*. 2007; 21(3):446–52. [PubMed: 17205057]
47. Thirugnanam R, George B, Chendamarai E, et al. Comparison of clinical outcomes of patients with relapsed acute promyelocytic leukemia induced with arsenic trioxide and consolidated with either an autologous stem cell transplant or an arsenic trioxide-based regimen. *Biol Blood Marrow Transplant*. 2009; 15(11):1479–84. [PubMed: 19822309]
48. Grimwade D, Jovanovic JV, Hills RK, et al. Prospective minimal residual disease monitoring to predict relapse of acute promyelocytic leukemia and to direct preemptive arsenic trioxide therapy. *J Clin Oncol*. 2009; 27(22):3650–8. [PubMed: 19506161]
49. Park JH, Tallman MS. Managing acute promyelocytic leukemia without conventional chemotherapy: is it possible? *Expert Rev Hematol*. 2011; 4(4):427–36. [PubMed: 21801134]
50. Grimwade D, Tallman MS. Should minimal residual disease monitoring be the standard of care for all patients with acute promyelocytic leukemia? *Leuk Res*. 2011; 35(1):3–7. [PubMed: 20674017]
51. Meloni G, Diverio D, Vignetti M, et al. Autologous bone marrow transplantation for acute promyelocytic leukemia in second remission: prognostic relevance of pre-transplant minimal residual disease assessment by reverse-transcription polymerase chain reaction of the PML/RAR alpha fusion gene. *Blood*. 1997; 90(3):1321–5. [PubMed: 9242568]
52. Lallemand-Breitenbach V, Guillemain MC, Janin A, et al. Retinoic acid and arsenic synergize to eradicate leukemic cells in a mouse model of acute promyelocytic leukemia. *J Exp Med*. 1999; 189(7):1043–52. [PubMed: 10190895]
53. de Botton S, Sanz MA, Chevret S, et al. Extramedullary relapse in acute promyelocytic leukemia treated with all-trans retinoic acid and chemotherapy. *Leukemia*. 2006; 20:35–41. [PubMed: 16307026]

54. de Botton S, Fawaz A, Chevret S, et al. Autologous and allogeneic stem-cell transplantation as salvage treatment of acute promyelocytic leukemia initially treated with all-trans-retinoic acid: a retrospective analysis of the European acute promyelocytic leukemia group. *J Clin Oncol*. 2005; 23:120–6. [PubMed: 15534358]
55. de la Serna J, Montesinos P, Vellenga E, et al. Causes and prognostic factors of remission induction failure in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and idarubicin. *Blood*. 2008; 111(7):3395–402. [PubMed: 18195095]
56. Breccia M, Latagliata R, Cannella L, et al. Early hemorrhagic death before starting therapy in acute promyelocytic leukemia: association with high WBC count, late diagnosis and delayed treatment initiation. *Haematologica*. 2010; 95(5):853–4. [PubMed: 20015875]
57. Alizadeh AA, McClellan JS, Gotlib JR, et al. Early mortality in acute promyelocytic leukemia may be higher than previously reported. *Blood*. 2009; 114:1015.
58. Micol J, Raffoux E, Boissel N, et al. Do early events excluding patients with acute promyelocytic leukemia (APL) from trial enrollment modify treatment result evaluation? Real-life management of 100 patients referred to the University Hospital Saint-Louis between 2000 and 2010. *Blood (ASH Annual Meeting Abstracts)*. 2010; 116 Abstract 1083.
59. Park JH, Qiao B, Panageas KS, et al. Early death rate in acute promyelocytic leukemia remains high despite all-trans retinoic acid. *Blood*. 2011; 118(5):1248–54. [PubMed: 21653939]
60. Di Bona E, Avvisati G, Castaman G, et al. Early haemorrhagic morbidity and mortality during remission induction with or without all-trans retinoic acid in acute promyelocytic leukaemia. *Br J Haematol*. 2000; 108(4):689–95. [PubMed: 10792270]
61. Visani G, Gugliotta L, Tosi P, et al. All-trans retinoic acid significantly reduces the incidence of early hemorrhagic death during induction therapy of acute promyelocytic leukemia. *Eur J Haematol*. 2000; 64(3):139–44. [PubMed: 10997878]
62. Sanz MA, Grimwade D, Tallman MS, et al. Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. *Blood*. 2009; 113(9):1875–91. [PubMed: 18812465]
63. Dimov ND, Medeiros LJ, Kantarjian HM, et al. Rapid and reliable confirmation of acute promyelocytic leukemia by immunofluorescence staining with an antipromyelocytic leukemia antibody. *Cancer*. 2010; 116(2):369–76. [PubMed: 19950129]
64. Rego EM, Kim H, Ruiz-Arguelles GJ, et al. Improving the treatment outcome of acute promyelocytic leukemia in developing countries through international cooperative network. Report on the International Consortium on Acute Promyelocytic Leukemia Study Group. *ASH Annual Meeting Abstracts*. 2009; 114(6)
65. Andersen MK, Pedersen-Bjergaard J. Therapy-related MDS and AML in acute promyelocytic leukemia. *Blood*. 2002; 100(5):1928–9. [author reply: 1929]. [PubMed: 12211197]
66. Garcia-Manero G, Kantarjian HM, Kornblau S, et al. Therapy-related myelodysplastic syndrome or acute myelogenous leukemia in patients with acute promyelocytic leukemia (APL). *Leukemia*. 2002; 16(9):1888. [PubMed: 12200720]
67. Latagliata R, Petti MC, Fenu S, et al. Therapy-related myelodysplastic syndrome-acute myelogenous leukemia in patients treated for acute promyelocytic leukemia: an emerging problem. *Blood*. 2002; 99(3):822–4. [PubMed: 11806982]
68. Hu J, Shen ZX, Sun GL, et al. Long-term survival and prognostic study in acute promyelocytic leukemia treated with all-trans-retinoic acid, chemotherapy, and As₂O₃: an experience of 120 patients at a single institution. *Int J Hematol*. 1999; 70(4):248–60. [PubMed: 10643151]
69. Shen ZX, Chen GQ, Ni JH, et al. Use of arsenic trioxide (As₂O₃) in the treatment of acute promyelocytic leukemia (APL): II. Clinical efficacy and pharmacokinetics in relapsed patients. *Blood*. 1997; 89:3354–60. [PubMed: 9129042]
70. Soignet SL, Maslak P, Wang ZG, et al. Complete remission after treatment of acute promyelocytic leukemia with arsenic trioxide. *N Engl J Med*. 1998; 339:1341–8. [PubMed: 9801394]
71. Nasr R, Guillemain MC, Ferhi O, et al. Eradication of acute promyelocytic leukemia-initiating cells through PML-RARA degradation. *Nat Med*. 2008; 14(12):1333–42. [PubMed: 19029980]
72. Licht JD. Acute promyelocytic leukemia—weapons of mass differentiation. *N Engl J Med*. 2009; 360(9):928–30. [PubMed: 19246367]

73. Ablain J, de Thé H. Revisiting the differentiation paradigm in acute promyelocytic leukemia. *Blood*. 2011; 117(22):5795–802. [PubMed: 21444912]
74. Zhu J, Gianni M, Kopf E, et al. Retinoic acid induces proteasome-dependent degradation of retinoic acid receptor alpha (RARalpha) and oncogenic RARalpha fusion proteins. *Proc Natl Acad Sci U S A*. 1999; 96(26):14807–12. [PubMed: 10611294]
75. Shao W, Fanelli M, Ferrara FF, et al. Arsenic trioxide as an inducer of apoptosis and loss of PML/RAR alpha protein in acute promyelocytic leukemia cells. *J Natl Cancer Inst*. 1998; 90(2): 124–33. [PubMed: 9450572]
76. Chen GQ, Shi XG, Tang W, et al. Use of arsenic trioxide (As₂O₃) in the treatment of acute promyelocytic leukemia (APL): I. As₂O₃ exerts dose-dependent dual effects on APL cells. *Blood*. 1997; 89(9):3345–53. [PubMed: 9129041]
77. Zheng PZ, Wang KK, Zhang QY, et al. Systems analysis of transcriptome and proteome in retinoic acid/arsenic trioxide-induced cell differentiation/apoptosis of promyelocytic leukemia. *Proc Natl Acad Sci U S A*. 2005; 102(21):7653–8. [PubMed: 15894607]
78. Gianni M, Koken MH, Chelbi-Alix MK, et al. Combined arsenic and retinoic acid treatment enhances differentiation and apoptosis in arsenic-resistant NB4 cells. *Blood*. 1998; 91(11):4300–10. [PubMed: 9596679]
79. Mathews V, George B, Chendamarai E, et al. Single-agent arsenic trioxide in the treatment of newly diagnosed acute promyelocytic leukemia: long-term follow-up data. *J Clin Oncol*. 2010; 28(24):3866–71. [PubMed: 20644086]
80. Ghavamzadeh A, Alimoghaddam K, Rostami S, et al. Phase II study of single-agent arsenic trioxide for the front-line therapy of acute promyelocytic leukemia. *J Clin Oncol*. 2011; 29(20): 2753–7. [PubMed: 21646615]
81. Shen ZX, Shi ZZ, Fang J, et al. All-trans retinoic acid/As₂O₃ combination yields a high quality remission and survival in newly diagnosed acute promyelocytic leukemia. *Proc Natl Acad Sci U S A*. 2004; 101(15):5328–35. [PubMed: 15044693]
82. Hu J, Liu YF, Wu CF, et al. Long-term efficacy and safety of all-trans retinoic acid/ arsenic trioxide-based therapy in newly diagnosed acute promyelocytic leukemia. *Proc Natl Acad Sci U S A*. 2009; 106(9):3342–7. [PubMed: 19225113]
83. Estey E, Garcia-Manero G, Ferrajoli A, et al. Use of all-trans retinoic acid plus arsenic trioxide as an alternative to chemotherapy in untreated acute promyelocytic leukemia. *Blood*. 2006; 107(9): 3469–73. [PubMed: 16373661]
84. Ravandi F, Estey EH, Cortes JE, et al. Phase II study of all-trans retinoic acid (ATRA), arsenic trioxide (ATO), with or without gemtuzumab ozogamicin (GO) for the frontline therapy of patients with acute promyelocytic leukemia (APL). *Blood (ASH Annual Meeting Abstracts)*. 2010; 116 Abstract 1080.
85. Iland H, Frank F, Supple S, et al. Interim analysis of the APML4 trial incorporating all-trans retinoic acid (ATRA), idarubicin, and intravenous arsenic trioxide (ATO) as initial therapy in acute promyelocytic leukaemia (APL): an Australasian Leukaemia and Lymphoma Group (ALLG) study. *International Oral Arsenic Union & 38th Annual Scientific Meeting Hong Kong Society of Haematology*. 2010;16. [abstract 6].
86. Gore SD, Gojo I, Sekeres MA, et al. Single cycle of arsenic trioxide-based consolidation chemotherapy spares anthracycline exposure in the primary management of acute promyelocytic leukemia. *J Clin Oncol*. 2010; 28(6):1047–53. [PubMed: 20085935]
87. Di Veroli A, Ramadan SM, Divona M, et al. Molecular remission in advanced acute promyelocytic leukaemia after treatment with the oral synthetic retinoid Tamibarotene. *Br J Haematol*. 2010; 151(1):99–101. [PubMed: 20618325]

Fig. 1.
(A-C) Current DFS after initial treatment of APL.

Fig. 2.
Survival functions by diagnosis time periods.

Table 1

Outcome of major contemporary trials in APL

Groups (References)	Year	N	CR (%)	D(E)FS (%)	Therapy
EAPL group ²⁹	1999	99	92%	84	ATRA + DA
GIMEMA ²²	1997	240	95	79	ATRA + IDA
North American study ¹⁷	1997	172	72	75	ATRA-based induction/maintenance
PETHEMA ²⁴	1999	123	89	92	ATRA + IDA (Ara-C, etoposide in consolidation)
GAMLCG ²¹	2000	51	92	88	HiDAC + ATRA

Abbreviations: DA, daunorubicin; D(E)FS, disease (event)-free survival; GAMLCG, The German Acute Myeloid Leukemia Cooperative Group; HiDAC, high dose Ara-C; IDA, idarubicin; N, number.

Table 2

ATO-based treatment and outcomes in APL

Groups (References)	N	Median Age, Years (Ranges)	Follow-up (mo)	Outcomes (%)
Mathews et al ⁷⁹	72	28 (3–75)	60	ED: 13.9 CR: 86.1 5-y DFS: 80 5-y OS: 74.2
Ghavamzadeh et al ⁸⁰	197	29 (11–71)	38	ED: 14.7 CR: 85.8 5-y DFS: 66.7 5-y OS: 64.4
Shanghai Institute of Hematology ⁸¹	61	30.5 (14–74)	18	ED: 5 CR: 95 Median DFS: 13 mo
		39.5 (15–69)		ED: 10 CR: 90 Median DFS: 16 mo
		34 (14–62)		ED: 4.8 CR: 95.2 Median DFS: 20 mo
Shanghai Institute of Hematology ⁸²	85	N/A	70	ED: 5.9 CR: 94.1 5-y EFS: 89.2 5-y OS: 91.7
MDACC ⁸⁴	82	47 (14–81)	25	ED: 8.5 CR: 92 3-yr OS: 85
ALLG ⁸⁵	124	44 (3–78)	20	ED: 3 CR: 97 3-y EFS: 87 3-y OS: 93
North American Intergroup C9710 ³⁶	481	N/A (15–79)	54	ED: 8 CR: 90 3-y DFS: 70–90 3-y OS: 81–86
Gore et al ⁸⁶	45	50 (19–70)	32	ED: 8.9 CR: 91.1 3-y DFS: 88.7 3-y EFS: 76 3-y OS: 88

Abbreviations: ALLG, Australasian Leukemia and Lymphoma Group; CR, complete remission; ED, early death; MDACC, MD Anderson Cancer Center; N, number of patients; N/A, not available.