OncoTargets and Therapy

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REVIEW

Retinoic acid and arsenic trioxide in the treatment of acute promyelocytic leukemia: current perspectives

This article was published in the following Dove Press journal:
OncoTargets and Therapy
14 March 2017
Number of times this article has been viewed

Derek McCulloch
Christina Brown
Harry Iland

Institute of Hematology, Royal Prince Alfred Hospital, Camperdown, NSW, Australia

Abstract: Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia (AML) with a unique morphological appearance, associated coagulopathy and canonical balanced translocation of genetic material between chromosomes 15 and 17. APL was first described as a distinct subtype of AML in 1957 by Dr Leif Hillestad who recognized the pattern of an acute leukemia associated with fibrinolysis, hypofibrinogenemia and catastrophic hemorrhage. In the intervening years, the characteristic morphology of APL has been described fully with both classical hypergranular and variant microgranular forms. Both are characterized by a balanced translocation between the long arms of chromosomes 15 and 17, [t(15;17)(q24;q21)], giving rise to a unique fusion gene *PML-RARA* and an abnormal chimeric transcription factor (PML-RARA), which disrupts normal myeloid differentiation programs. The success of current treatments for APL is in marked contrast to the vast majority of patients with non-promyelocytic AML. The overall prognosis in non-promyelocytic AML is poor, and although there has been an improvement in overall survival in patients aged <60 years, only 30%–40% of younger patients are still alive 5 years after diagnosis. APL therapy has diverged from standard AML therapy through the empirical discovery of two agents that directly target the molecular basis of the disease. The evolution of treatment over the last 4 decades to include all-*trans* retinoic acid and arsenic trioxide, with chemotherapy limited to patients with high-risk disease, has led to complete remission in 90%–100% of patients in trials and rates of overall survival between 86% and 97%.

Keywords: acute promyelocytic leukemia, ATRA, arsenic trioxide

Background

The discovery of acute promyelocytic leukemia (APL) arose from early case reports of patients who presented with an acute leukemia and bleeding preponderance. Building on these published case reports, Dr Hillestad identified the common characteristics of this new and rapidly fatal disease.[1–5] A subsequent more detailed report on 20 patients treated at the Hôpital St Louis in Paris by Jean Bernard increased early understanding of this unique disease.[6] APL accounts for 3%–13% of acute myeloid leukemia (AML) based on data from UK and Swedish registries.[7,8] It has been reported that the incidence of APL is higher in populations originating from Central and South America, where APL may constitute 28% of AML cases.[9,10]

The characteristic morphology of APL has been described fully; first, the typical or hypergranular form of APL with characteristically abnormal promyelocytes exhibiting a densely granulated cytoplasm, Auer rods or Faggot cells (cells with bundles of Auer rods) and a nuclear membrane that is often reniform or bilobed.[11] A microgranular

Correspondence: Derek McCulloch
Institute of Haematology, Royal Prince Alfred Hospital, Missenden Road, Camperdown, NSW 2050, Australia
Email doctordexmcculloch@yahoo.co.uk

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Dovepress
http://dx.doi.org/10.2147/OTT.S100513

variant associated with a high white cell count (WCC) and predominantly bilobed nuclei was described later.[12] Both forms were found to be associated with a balanced translocation between the long arms of chromosomes 15 and 17, [t(15;17)(q24;q21)], giving rise to a unique fusion gene *PML-RARA*.[13,14] There are rarer cryptic and complex cytogenetic rearrangements that have been identified giving rise to a *PML-RARA* fusion; furthermore, variant gene fusion partners for the *RARA* gene not involving the *PML* locus have been described. The 2016 update of the WHO classification of myeloid neoplasms and myeloid malignancies specifically describes APL with *PML-RARA* to distinguish it from these other entities.[15,16] AML is recognized as a heterogenous disease, often with co-existing somatic mutations, contributing to its clonal evolution, relapse and poor overall survival (OS). In contrast, APL appears to be a less heterogeneous disease with a smaller portfolio of associated genetic mutations and thus a greater sensitivity to therapy. A recent mutational analysis of primary and relapse APL cases identified mutations in genes for Fms-like tyrosine kinase 3 (*FLT3*), Wilms tumor 1 (*WT1*) and *N-RAS* most commonly. However, mutations in genes recognized as recurring sites of genetic mutations in AML such as *DNMT3A*, *NPM1*, *IDH1/2*, *RUNX1*, *TP53*, *TET2* and *CEBPA* are absent or rarely present.[17]

The success of current treatments for APL is unparalleled and in marked contrast to the vast majority of patients with non-promyelocytic AML who can expect a 5-year OS of 30%–40%,[18–21] although it is accepted that patients diagnosed with AML with the so-called favorable cytogenetic rearrangements t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*, inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11* have a 5-year OS between 55% and 69%.[22–24] Similarly, patients with normal cytogenetics and concurrent mutations in the nucleophosmin-1 (*NPM1*) gene (without *FLT3* internal tandem duplications [ITDs]) or those possessing bi-allelic mutations of *CEBPA* can expect a 5-year OS between 50% and 70%.[25–34]

APL therapy has evolved through the empirical discovery of two agents that directly target the molecular foundation of the disease. The evolution of treatment over 4 decades to include all-*trans* retinoic acid (ATRA), arsenic trioxide (ATO) and chemotherapy in a variety of protocols has led to complete remission (CR) in 90%–100% of patients in trials and rates of OS between 86% and 97%.[35–42]

Chemotherapy era

The first therapeutic breakthrough in the treatment of APL was the introduction of anthracyclines. Prior to this, early case reports showed that only 6%–14% entered remission and the majority of patients died within 4 weeks.[43–45] In 1973, Bernard et al[46] reported in a review of 80 patients that daunorubicin as monotherapy increased CR rates from 13% to 55%. The effectiveness of anthracycline-based treatment was subsequently confirmed by European and North American researchers, including the use of an anthracycline as a single agent. These studies showed CR rates between 55% and 88%, with 35%–45% of patients entering a prolonged remission.[47–56] The effectiveness of anthracycline-based treatment appeared to be dose dependent, with higher doses of daunorubicin improving remission rates.[57] Thus, in the pre-ATRA era, patients diagnosed with APL typically underwent chemotherapy induction with an anthracycline and cytarabine, eg, the "7-3" regimen, similar to non-APL AML. However, unlike non-APL AML, there was no demonstrable benefit in APL when cytarabine was added to an anthracycline during induction therapy in APL.[48,50,58]

ATRA era

The concept of differentiation therapy arose from an improved understanding of cancer cell biology, such as the demonstration by Breitman et al[59] that ATRA and 13-*cis* retinoic acid could induce differentiation in the HL-60 myeloid leukemia cell line. ATRA was subsequently shown to induce differentiation of leukemic cells in culture more potently than 13-*cis* retinoic acid.[60,61] The PML-RARA fusion protein forms homodimers, recruits co-repressors and sequesters the normal RARA heterodimeric partner, retinoid X receptor-alpha. The complex binds to genes involved in myeloid differentiation, blocking their transcription. Retinoic acid in pharmacological doses binds to PML-RARA inducing a conformational change, allowing the dissociation of co-repressors and activating gene transcription and cellular differentiation.[62] Retinoic acid also induces PML-RARA degradation through recruitment of proteases (including caspases) and proteasomes; furthermore, this degradation pathway appears to be distinct to that required to induce differentiation.[63–68]

Following isolated case reports, Huang et al[69] published the successful treatment of APL with ATRA in 24 patients, with >90% CR and no exacerbation of coagulopathy or early death due to hemorrhage. The efficacy of ATRA was confirmed by Laurent Degos' group in Paris.[70,71] However, ATRA alone could not induce a prolonged remission as seen in the initial studies that demonstrated that despite maintenance therapy with ATRA or low-dose chemotherapy, the majority of patients relapsed within 6 months.[70,72,73]

Researchers also noted a clinical syndrome caused by ATRA-induced differentiation of leukemic cells. Differentiation syndrome (DS), as it became known, can manifest with unexplained fever, hypotension, weight gain (>5 kg), respiratory distress, pulmonary infiltrates, pleural and/or pericardial effusions and renal failure.[74,75] The pathogenesis of DS has not been well defined; the hypothesis derived from research in primary culture and using cell lines suggests a systemic inflammatory response driven by the release of pro-inflammatory cytokines, with endothelial damage, capillary leak and alterations in cellular adhesion molecule expression leading to tissue infiltration by leukemic cells and microcirculation occlusion.[76,77] The risk of DS is greatest in patients who present with or develop a raised white cell count (WCC) with treatment. Thus, regimens that include the myelotoxic effects of chemotherapy taken concurrently with ATRA help reduce the risk of rising WCC and DS. The standard accepted management once DS is recognized is treatment with corticosteroids, eg, dexamethasone 10 mg twice daily intravenously (IV) until resolution and for at least 3 days.[78] The use of prophylactic steroid therapy during induction shows a beneficial reduction in the incidence of DS, although no randomized studies have been reported.[38,39,79–81]

Intensive anthracycline-based chemotherapy in combination with ATRA demonstrated excellent results in early non-randomized and later randomized trials. The prospective randomized European APL91 trial that compared three cycles of chemotherapy with or without ATRA was stopped early due to the significant improvement in event-free survival (EFS) in the ATRA therapy cohort.[82,83] The EFS at 12 months in the ATRA-treated group was 79% compared to 50% in the chemotherapy-treated cohort (P=0.001), and after a 4-year follow-up, the EFS in the ATRA group was 63% compared to 17% in the chemotherapy-only cohort. The follow-up APL93 trial demonstrated a benefit to commencing chemotherapy simultaneously with ATRA as opposed to ATRA followed by sequential chemotherapy. The study also included a maintenance randomization and compared no maintenance, low-dose chemotherapy with 6-mercaptopurine (6-MP) and methotrexate, and ATRA 15 days every 3 months minus or plus low-dose chemotherapy. The rates of relapse at 2 years were 27%, 11%, 13% and 7.4%, respectively.[84]

Subsequently, ATRA in combination with chemotherapy was investigated by multiple groups with CR rates between 72% and 95%.[85–90] The Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) used an ATRA/idarubicin (AIDA) induction and added three cycles of consolidation containing idarubicin, cytarabine, etoposide, mitoxantrone and thioguanine. The resulting AIDA0493 protocol achieved a 95% CR rate, 2-year EFS of 79% and OS of 87%.[89,90] The Spanish Programa Espãnol de Tratamientos en Hematología (PETHEMA) LPA96 trial successfully demonstrated that removing all non-anthracycline drugs from the consolidation phase after an AIDA-based induction did not significantly affect patient outcomes with a CR rate of 89%, 2-year EFS of 79% and OS of 82%.[85] Similarly, the Australasian Leukaemia and Lymphoma Group (ALLG) APML3 trial used an AIDA induction backbone and an additional second cycle of idarubicin. The CR rate was 86%, and the importance of maintenance in this setting was shown by separate cohorts treated with or without maintenance, 4-year disease-free survival (DFS) 78.9% vs 46.9%, respectively.[91]

Since the combined data from the AIDA0493 and LPA096 trials had identified no benefit from the use of non-anthracycline drugs during consolidation, a joint analysis was undertaken that identified the WCC and platelet count as reliable predictors of relapse, after achievement of a CR. This heralded the era of risk-adapted therapy with the so-called Sanz criteria (Table 1).[92]

Subsequently, risk-stratified trials based on an AIDA induction backbone demonstrated a benefit of ATRA in consolidation for all patients (LPA99 trial) and cytarabine in consolidation for high-risk patients (LPA2005 and AIDA2000 trials).[37,93,94] In the LPA2005 trial, high-risk patient treatment with cytarabine reduced the 3-year relapse rate from 26% to 11% (P=0.03) when compared to the results from the LPA99 trial, with an overall CR rate for all patients of 92.5%.[37,94] Similarly, the AIDA2000 trial demonstrated that risk-adapted therapy in consolidation (ATRA for all patients, omission of non-anthracycline drugs for low/intermediate risk) resulted in all patients achieving better longer term outcomes. Low–intermediate risk patients suffered less toxicity and infection, while high-risk patients achieved a 6-year cumulative incidence of relapse (CIR) of 9.3% compared to 49.7% (P<0.001) in the previous AIDA0493 trial.[93]

The benefit of cytarabine in consolidation therapy for high-risk patients was also demonstrated by the French APL2000 trial, where a CR rate of 97.3% with a 7-year CIR of 7.1%, EFS of 82.2% and OS of 87.6% was achieved.

Table 1 Risk stratification in APL

Sanz risk category	WCC ($\times 10^9$/L)	Platelet count ($\times 10^9$/L)
Low	≤10	>40
Intermediate	≤10	≤40
High	>10	

Abbreviations: APL, acute promyelocytic leukemia; WCC, white cell count.

The results in high-risk patients were comparable to those in low–intermediate risk patients who achieved a 7-year CIR of 12.9%.[95] A joint review of the results from the APL2000 and LPA99 trials confirmed a greater benefit for low–intermediate risk patients on an ATRA-idarubicin-based protocol and better survival for high-risk patients with more intense anthracycline and cytarabine consolidation.[96] It was proposed that because the AIDA protocol contained a higher cumulative dose of anthracycline or drugs with anthracycline equivalency, it generated better responses in lower risk patients.[97] In contrast, the UK MRC AML15 trial found no benefit to the inclusion of chemotherapy other than anthracyclines in the treatment of 285 patients who unsurprisingly experienced more toxicity and required an average of 19 more days in hospital.[98]

The result of this progressive improvement in the understanding of patients' risk and response was the European LeukaemiaNet recommendations for the management of APL. The expert panel advised induction based on an anthracycline/ATRA combination; a standard approach to consolidation should involve two to three cycles of anthracycline-based chemotherapy, intermediate- or high-dose cytarabine should be included in those younger patients with a WCC $>10\times10^9$/L and that maintenance therapy should be used in patients treated with protocols in which maintenance has been shown to be of benefit.[78]

The success achieved through treatment with ATRA-anthracycline-based protocols is unparalleled in other AML, but concern regarding the long-term risk of anthracycline and other chemotherapy exposure remains. Secondary cytogenetic abnormalities such as therapy-related myelodysplasia/AML have a reported incidence between 0.97% and 6.5% in French and Italian patient groups, respectively, and 2.2% at 6 years in all patients treated in the LPA96, LPA99 and LPA2005 trials who achieved CR.[99–105] Anthracycline-related cardiotoxicity is also a concern[106,107] as research has shown that patients treated on AIDA-based protocols developed subclinical but detectable diastolic dysfunction and regional wall motion abnormalities.[106] Recognized common acute side effects associated with ATRA therapy include fever, rash, headache and pseudotumor cerebri; the latter occurs more commonly in adolescents/children and may prompt dose reduction or cessation of ATRA in severe cases.[108] Long-term toxicity secondary to ATRA therapy has not been seen but requires ongoing review.

The arsenic era

Arsenic in various forms has been in use for >2000 years, by both Hippocrates in ancient Greece and in traditional Chinese medicine.[109,110] Thomas Fowler's eponymous solution of ATO was used as a tonic for the treatment of a variety of ailments and was also used to treat leukemia in the late 19th and early 20th centuries.[111,112]

In 1973, researchers in Harbin province developed a solution of ATO and mercury chloride named "Ailing I" also known as "Ai-Lin I", which they used to treat patients with acute and chronic leukemia. The successful treatment of patients with APL was reported initially in Chinese journals and was followed by a landmark publication in 1997, when researchers from Harbin and Shanghai described CR rates of 90% in patients with APL who had relapsed after ATRA and chemotherapy treatment and were treated with ATO as a single agent.[113] The proposed mechanism of action for ATO was the dose-dependent induction of apoptosis or differentiation.[114]

Subsequent research has shown that arsenic's therapeutic efficacy is due to its effect on the PML moiety of the PML-RARA fusion protein. The normal PML protein is of fundamental importance for the formation of so-called nuclear bodies (NBs), which allow recruitment and interaction of proteins through the posttranslational modifications of sumoylation and ubiquitination.[115] NBs are disrupted in APL with consequent loss of their tumor-suppressive activity. Arsenic binds to the PML component of PML-RARA through two cysteine residues in the B2 domain of PML protein, inducing their oxidation, leading to disulfide bond formation.[116,117] The subsequent reformation of PML-containing NBs allows sumoylation of the PML/PML-RARA protein, concomitant recruitment of a SUMO-dependent ubiquitin ligase (RNF4) and polyubiquitination. The final step is the degradation of the PML moiety and its associated RARA partner by the proteasome.[118,119] Additionally, arsenic induces the degradation of PML/PML-RARA through the production of reactive oxygen species (ROS) that also produces oxidation of PML and formation of NBs. Since anthracyclines can also stimulate the production of ROS, there may a contributory role of anthracyclines in PML-RARA degradation.[120] Thus, in combination ATRA and ATO target the degradation of PML-RARA through distinct interactions with the RARA or PML moieties, respectively. The result is a synergistic destruction of the fusion protein and eradication of leukemia-initiating cells (LICs).[121,122]

The efficacy of ATO in the relapse setting was confirmed in a pilot study in New York, where 11 of 12 extensively pretreated patients achieved a CR. A subsequent multicenter study of 40 patients in first or second relapse utilized ATO for induction, consolidation and maintenance therapy. The CR rate was 85%, and the 18-month OS and relapse-free

survival (RFS) were 66% and 56%, respectively.[123,124] As the treatment of APL using ATRA-anthracycline-based protocols improved, ATO was shown to be an efficacious salvage treatment for relapse patients by numerous groups.[125–130]

The first successful trial of ATO in the treatment of newly diagnosed APL by Shen et al demonstrated that induction with ATO alone could induce CR in 90% of patients, whereas 95% of patients treated with ATRA alone or ATRA plus ATO achieved CR. There was a significantly shorter time to CR for patients treated with ATO/ATRA vs ATRA alone (25.5 vs 40.5 days, P=0.0003).[131] The protocol described by Shen et al contained moderately intensive consolidation therapy with three cycles of chemotherapy.[131] Longer term follow-up shows a 5-year DFS for the ATO/ATRA cohort of 94.8% and OS of 91.7%.[132] Another Chinese study reported on 90 patients also induced with either ATRA or ATO/ATRA who achieved CR rates of 90% vs 93%, respectively (P=0.56). The cohort of ATRA-induced patients was subsequently split and treated with traditional or ATO-containing consolidation/maintenance regimens. Replacing four of 10 cycles of chemotherapy in consolidation/maintenance with ATO increased the 3-year RFS from 72.4% to 92.9% (P=0.048). A similar RFS rate of 92.6% was achieved in ATO/ATRA-induced patients, who also received ATO-containing consolidation/maintenance.[133]

The benefits of ATO use in consolidation were borne out by results of the North American Leukemia Intergroup C9710 study, where 90% of patients achieved a CR after ATRA and chemotherapy, and were then randomized to either receive additional ATO consolidation (two cycles of 0.15 mg/kg/day for 5 days for 5 weeks) or progress to a common ATRA/daunorubicin consolidation. The addition of ATO increased the 3-year EFS from 63% to 80% (P<0.0001) and 3-year DFS for all patients from 70% to 90% (P<0.0001). Crucially, consolidation with ATO significantly improved DFS for both low–intermediate (P<0.001) and high-risk patients (P<0.0001) compared to those not receiving ATO consolidation. Furthermore, there was no statistically significant difference between the 3-year DFS achieved using ATO consolidation in low–intermediate and high-risk cohorts (P=0.24).[36]

Subsequently, three groups of researchers attempted to investigate whether ATO as monotherapy or in combination with minimal doses of chemotherapy could successfully treat patients diagnosed with APL. Two independent groups based in Tehran and Vellore reported the results of trials employing ATO as a monotherapy during induction, consolidation and maintenance, with chemotherapy only given in the event of leukocytosis or DS. The overall CR rate achieved was 86% in both trials with DFS in the Indian cohort of 87% at 3 years vs 63.7% in the Iranian cohort at 2 years.[134,135] The poorer outcomes from the Tehran study were likely due to lower ATO exposure in the initial Iranian regimen, and despite adding additional consolidation cycles to their schedule after 2006, Iranian patients received less ATO within the first 6 months compared to the Vellore patients. Follow-up results at 5 years showed a DFS and an OS for the Vellore vs Tehran cohorts of 80% vs 67% and 74% vs 64%, respectively.[136,137] Patients defined by the Vellore study criteria as good risk (WCC $<5\times10^9$/L, platelets $>20\times10^9$/L) had an EFS of 90% and OS of 100% compared to 60% and 63% in higher risk patients. Thus, ATO has impressive activity as a single agent but in higher risk patients, there still appeared a need for additional therapy. Furthermore, in combination with ATO, ATRA has been proposed to increase the expression of aquaglyceroporin 9, which facilitates increased ATO uptake.[138]

The combination of ATRA, ATO and gemtuzumab ozogamicin for high-risk patients or those with rising WCCs was trialed by researchers at the M.D. Anderson Cancer Center. Gemtuzumab ozogamicin is a humanized anti-CD33 monoclonal antibody covalently conjugated with a cytotoxic anti-tumor agent calicheamicin. Over 6 years, 82 patients were treated with a CR rate of 90% and a 3-year estimated OS of 85%.[35,139] The trial was small but demonstrated the potential benefits of the regimen, and the OS rates are similar to those of the LPA99 and C9710 trial of the same period without the use of traditional chemotherapeutic drugs or maintenance.[36,94] However, high-risk patients and those aged >60 years still had poorer outcomes with OS rates of 69% and 73%, respectively.

The ALLG APML4 trial rationalized the treatment of newly diagnosed patients to therapy with a combination of ATRA and ATO in combination with idarubicin in lower cumulative doses than those used in AIDA-based protocols. The aim of induction with ATRA, ATO and an anthracycline was to achieve the shortest time to remission and reduce the risks of hyperleukocytosis and DS. Aggressive hemostatic support and prophylactic prednisolone were included to reduce the rate of bleeding, DS and early death. The trial included consolidation therapy with ATRA/ATO and a 2-year maintenance regimen of ATRA, 6-MP and methotrexate proven to be of benefit in some previous studies.[84,91] The early death rate was lower than in the APML3 trial, but not significantly so (3.2% vs 7.1%, P=0.29), while achieving a CR rate of 95% and a 2-year DFS of 97.5%.[38] After a median follow-up of 4.2 years, there was a significant improvement in 5-year OS (94%, P=0.02; Figure 1), DFS (95%, P=0.001; Figure 2) and EFS

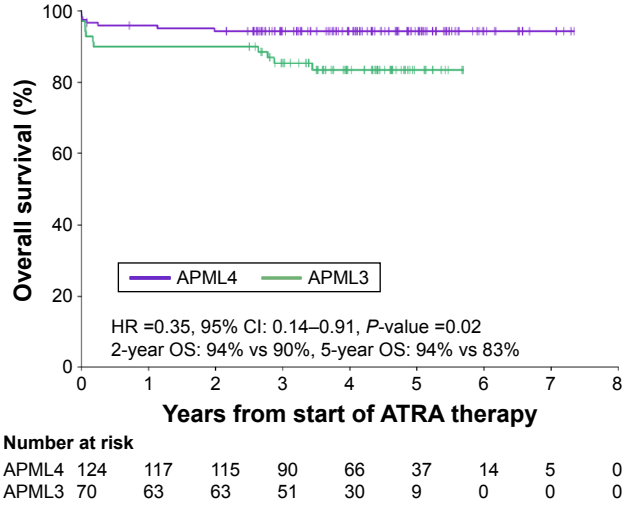

Figure 1 Comparison of OS in the ALLG APML4 and ALLG APML3 trials.
Note: Figure was provided courtesy of H Iland (APML4 principal investigator) from the Australasian Leukaemia and Lymphoma Group APML4 Statistical Report (June 2013) by Collins M, Di Iulio J, and Beresford J (unpublished).
Abbreviations: OS, overall survival; ALLG, Australasian Leukaemia and Lymphoma Group; HR, hazard ratio; CI, confidence interval; ATRA, all *trans*-retinoic acid.

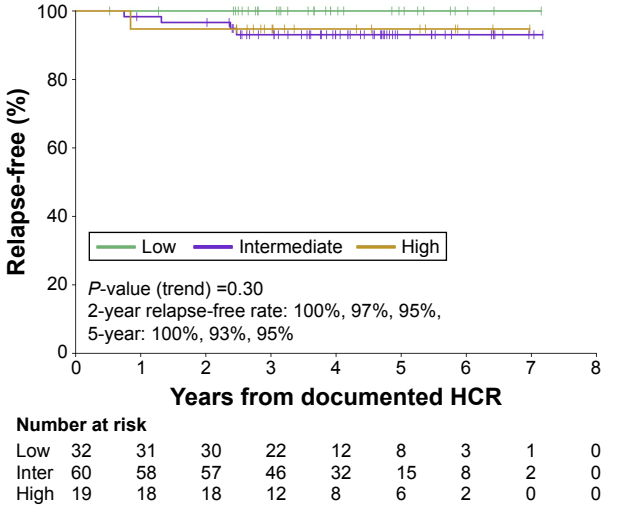

Figure 3 Estimated Kaplan–Meier curve for freedom from relapse from documented hematological CR in the APML4 trial, stratified by Sanz risk category.
Note: Figure was provided courtesy of H Iland (APML4 principal investigator) from the Australasian Leukaemia and Lymphoma Group APML4 Statistical Report (June 2013) by Collins M, Di Iulio J, and Beresford J (unpublished).
Abbreviations: CR, complete remission; HCR, hematological complete remission.

(90%, *P*=0.02) when compared to APML3.[41] In addition, high-risk patients in the APML4 trial appeared to benefit as the freedom from relapse was not significantly different between risk groups (Figure 3). Furthermore, in high-risk patients, the 5-year CIR was only 5%, as compared to 11% at 3 years for the LPA2005 protocol, 9% at 6 years for AIDA2000 and 9.5% at 5 years for APL2000.[37,80,93,96]

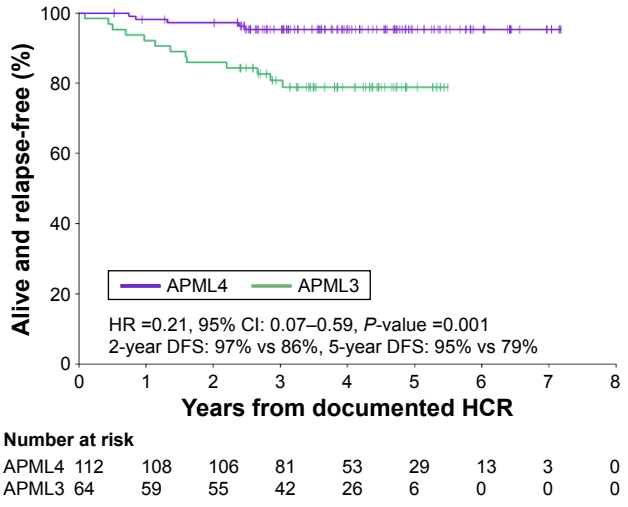

Figure 2 Comparison of DFS in the ALLG APML4 and ALLG APML3 trials.
Note: Figure was provided courtesy of H Iland (APML4 principal investigator) from the Australasian Leukaemia and Lymphoma Group APML4 Statistical Report (June 2013) by Collins M, Di Iulio J, and Beresford J (unpublished).
Abbreviations: DFS, disease-free survival; ALLG, Australasian Leukaemia and Lymphoma Group; HR, hazard ratio; CI, confidence interval; HCR, hematological complete remission.

These benefits were achieved without the addition of further moderate–high-dose chemotherapy during induction and/or consolidation, as utilized in the PETHEMA, GIMEMA and APL group trials and led to the incorporation of the APML4 protocol into the Canadian APL management guidelines and the National Comprehensive Cancer Network guidelines for high-risk APL.[140,141] Therefore, ATO + ATRA appeared to be an efficacious therapy for induction and consolidation in newly diagnosed APL, but randomized trials focusing on low/intermediate-risk vs high-risk APL were lacking.

The APL0406 trial, a prospective, randomized, Phase III, multicenter study of low–intermediate risk patients by the GIMEMA, German–Austrian Acute Myeloid Leukemia Study and Study Alliance Leukemia groups tested whether ATO and ATRA induction and consolidation without maintenance therapy was non-inferior to the established AIDA2000 protocol. The impressive results included ATO/ATRA-treated patients achieving rates of CR, 2-year OS and 2-year EFS of 100%, 99% and 97%, respectively, compared to 95% (*P*=0.12), 91% (*P*=0.02) and 86% in the AIDA arm (*P*<0.001 for non-inferiority and *P*=0.02 for superiority).[39] The most recently published follow-up data showed that the 50-month EFS, OS and CIR were 97.3%, 99.2% and 1.9% in the ATO/ATRA cohort vs 80% (*P*<0.01), 92.6% (*P*=0.0073) and 13.9% (*P*=0.0013) in the AIDA cohort, respectively.[142] This study has helped define the current "Gold-Standard" treatment for low–intermediate risk APL.[140,141]

In the case of high-risk APL patients, the TUD-APOLLO-064 (NCT02688140) trial may clarify management by comparing an AIDA2000-based high-risk treatment arm (minus etoposide and thioguanine) with an APL0406-based treatment with two additional doses of idarubicin during induction.

The UK National Cancer Research Institute (NCRI) AML17 trial randomized newly diagnosed APL patients to treatment with either AIDA induction and consolidation or ATRA combined with ATO given in a similar overall dose to that used in APL0406 but where more drug is given in the first week of the induction and consolidation cycles then less frequently in subsequent weeks. Fifty-seven high-risk patients were included (30 in the ATO/ATRA cohort), and gemtuzumab ozogamicin was also given to 28 of the 30 high-risk patients. The other two received additional idarubicin. The primary outcome of quality of life did not differ significantly between cohorts, but ATRA/ATO patients required less supportive care in the first two cycles of therapy as compared to the AIDA cohort.[40] In terms of secondary outcomes, CR was achieved in 89% of the AIDA cohort vs 94% for ATRA/ATO (P=0.18). In comparison between the ATRA/ATO and AIDA patients, there was significant improvement in 4-year EFS, 91% vs 70% (P=0.002), cumulative incidence of morphological relapse 1% vs 18% (P=0.0007), cumulative incidence of molecular relapse 0% vs 27% ($P<0.0001$) but not OS 93% vs 89% (P=0.25). The incidence of death in remission was very low 2% vs 1% in both ATRA/ATO and AIDA cohorts, respectively. There was a trend toward significant improvement in the 4-year EFS for high-risk patients treated with ATRA/ATO vs AIDA (87% vs 64%), but this did not reach significance (P=0.07).

Table 2 provides a comparison of the most recent trials utilizing ATO in low–intermediate and high-risk APL.

Arsenic side effects

ATO can induce myelosuppression, hepatic dysfunction, gastrointestinal disturbance, hyperleukocytosis and DS.[76,114,134,135,143] However, the most significant side effect requiring close monitoring is QT interval prolongation and the development of cardiac arrhythmia such as *torsade de pointes*. Electrocardiographic monitoring on a regular and frequent basis (twice weekly in our institution), measurement and replacement of electrolytes, especially potassium and magnesium, with the concurrent cessation of other drugs that can prolong the QT interval are recommended. Prolongation of the QT corrected for heart rate to >500 ms should prompt cessation of ATO. Long-term rates of secondary malignancies have not been extensively studied, but one short medium-term study found no increase in the incidence of secondary neoplasms in patients treated with ATRA-ATO.[144] Furthermore, no concerns regarding secondary malignancy were seen in long-term follow-up of a subset of the Shanghai cohort published recently.[145]

Oral vs IV arsenic

Oral formulations of ATO have been used to consolidate CR in newly diagnosed or relapsed adult and pediatric patients.[146–149] Recent trials into the use of oral tetra-arsenic tetra-sulfide (As_4S_4) also known as Realgar, in a formulation with Indigo naturalis, *Salvia miltiorrhiza* and *radix pseudostellariae* (RIF), have shown apparent equivalency to intravenous ATO in the treatment of APL. APL07, a multicenter, randomized trial of 242 patients, found that in the primary outcome of 2-year DFS, ATRA-RIF induction was non-inferior to ATRA-ATO with subsequent common chemotherapy consolidation, 98.1% vs 95.5% (non-inferior $P<0.001$). The CR rates were similar, 99.1% vs 97.2% (P=0.62) and 3-year OS of 99.1% vs 96.6% (P=0.18).[150] On longer term follow-up of 231 patients, the 7-year CIR, EFS and OS rates in the RIF vs ATO cohorts were not significantly different, and there was no significant difference in the CIR, EFS or OS between the high-risk and non-high-risk group.[151] Thus, Realgar-based therapy appears to be as efficacious as the ATO form. Researchers have proposed that while arsenic is known to target PML and induce its degradation via ubiquitination,[114] the active agents in Indigo naturalis and *S. miltiorrhiza* (indirubin and tanshinone II, respectively) facilitate the uptake of arsenic into leukemic cells in a manner similar to ATRA.[138,152] The ALLG APML5 trial (ACTRN12616001022459p) will soon begin recruiting to investigate the bioavailability and performance of a novel oral ATO formulation vs IV ATO in combination with ATRA in consolidation.

The role of maintenance

The relative contribution of maintenance therapy is controversial with evidence from the ATRA-chemotherapy era for and against its use.[153–156] However, a recent Cochrane meta-analysis could not identify a benefit from maintenance for OS despite an improvement in DFS.[157] Recent trials incorporating ATO have more clearly demonstrated the success achieved without maintenance in non-high-risk patients. The APL0406 trial demonstrated non-inferiority of ATRA-ATO without maintenance over ATRA-Ida with maintenance in non-high-risk patients.[39,142] In addition, non-high-risk patients treated

Table 2 Results of recent ATO-inclusive trials

Risk category	Protocol (published trial analysis period)	Median follow-up (years)	No	Age restriction (years)	CR	ED	CIR	Death in CR	DFS	EFS	OS	Therapy-related neoplasm
Low-intermediate risk	**APL0406**[142] ATRA-ATO (4-yr)	3.4	127	18–71	100%	0%	1.9%	0.8%	ns	97.3%	99.2%	0
	APL0406 ATRA-Ida (4-yr)	3.4	132	18–71	97%	3%	13.9%	3.7%	ns	80%	92.6%	2
	UK AML17[40] ATRA-ATO ± GO (4-yr)	2.5	86	≥16	94% (all risk groups)	4%	1%[a,c] 0%[b,c]	2%[c]	97%[a] 98%[b]	92%	95%[d]	0
	UK-AML17 ATRA-Ida (4-yr)	2.5	92	≥16	89% (all risk groups)	6%	18%[a] 27%[b]	1%[c]	78%[a] 70%[b]	71%	90%[c]	1-risk group ns
	MD Anderson[139] ATRA/ATO ± GO (3-yr)	1.9	56	ns	95%	3.6%	0%	4% of all patients	ns	89%[e]	89%[e]	ns
	North American Intergroup C9710[36] No ATO in Consolidation (3-yr)	2.4	144	≥15	93%–94%	4%	ns	ns	77%[e]	71%[e]	ns	ns
	North American Intergroup C9710 ATO in consolidation (3-yr)	2.4	189	≥15	93%–94%	4%	ns	ns	90%[e]	84%[e]	ns	ns
	APML4[41] ATRA-ATO-Ida (5-yr)	4.2	101	>1	96%	2%	5%	0%	96%	92%	96%	ns
High-risk	**UK AML17**[40] ATRA-ATO (4-yr)	2.5	30	≥16	ns	ns	ns	2%[c]	ns	87%[f]	87%[d]	ns
	UK AML17 ATRA-Ida (4-yr)	2.5	27	≥16	ns	ns	ns	1%[c]	ns	64%[f]	84%[d]	ns
	MD Anderson[139] ATRA/ATO ± GO (3-yr)	1.9	26	ns	81%	19%	11%	4% of all patients	ns	65%[e]	75%[e]	ns
	North American Intergroup C9710[36] No ATO (3-yr)	2.4	58	≥15	71%	20%	ns	ns	46%[e]	39%[e]	ns	ns
	North American Intergroup C9710 ATO consolidation (3-yr)	2.4	55	≥15	71%	20%	ns	ns	87%[e]	64%[e]	ns	ns
	APML4[41] ATRA-ATO-Ida (5-yr)	4.2	23	>1	88%	8.7%	5%	0%	95%	83%	87%	ns

Notes: [a]Morphological, [b]molecular, [c]difference between high and low-intermediate risk not given, [d]no significant difference in OS between ATRA-ATO and ATRA/Ida therapy within risk groups, [e]estimated from published survival curves (data not given), [f]no significant difference in EFS between ATRA-ATO and ATRA/Ida in high-risk patients. The year given in parentheses is the time-point at which the survival endpoints were analyzed.

Abbreviations: ATO, arsenic trioxide; CR, complete remission; CIR, cumulative incidence of relapse; DFS, disease-free survival; ED, early death; EFS, event-free survival; OS, overall survival; ATRA, all *trans*-retinoic acid; ns, not specified; Ida, idarubicin; GO, gemtuzumab ozogamicin.

with ATRA-ATO in the UK AML17 trial achieved a 4-year OS of 95% with an overall 4-year cumulative incidence of morphological relapse of 1% in the ATRA-ATO arm despite no maintenance therapy.[40] In the APML4 trial,[38,41] the lack of significant difference in the freedom from relapse between high- and non-high-risk patients appears to be the result of the ATRA-ATO-Ida induction and prolonged ATRA-ATO consolidation, not a historical maintenance regimen. In the era of oral ATRA-arsenic therapy, it may be that prolonged oral consolidation or maintenance therapy will prove useful in high-risk patients in combination with less chemotherapy intensive regimens.

FLT3 mutation

Mutations within *FLT3*, either ITDs or tyrosine kinase domain mutations, are present in 12%–38% and 2%–20% of cases of APL, respectively.[158,159]

The effects of *FLT3* mutations on patient outcomes are inconsistent and appear dependent on the treatment regimen.[38,91,132,159–161] A meta-analysis by Beitinjaneh et al of patients treated predominantly with ATRA and chemotherapy identified lower rates of DFS and OS in patients with a *FLT3*-ITD. The risk ratio for 3-year DFS and OS in *FLT3*-ITD compared to wild type was 1.477, P=0.042 and 1.42, P=0.03, respectively.[159] Possession of a *FLT3* mutation also appeared to increase the risk of induction death in adults and children.[158,162] The addition of ATO to therapy appears to overcome the deleterious impact of a *FLT3* mutation. The negative effect of *FLT3* mutation on OS found in the ALLG APML3 trial was absent after the addition of ATO in induction and consolidation in the follow-up APML4 trial.[38,91] Similarly, in the APL0406 trial cohort of low–intermediate risk patients, the presence of a *FLT3* mutation was not associated with a poorer EFS when treated with ATO/ATRA. However, there was a trend toward a poorer EFS when treated without ATO in combination with ATRA.[163]

In addition to *FLT3* mutations, other pretreatment parameters associated with inferior prognosis include short PML-RARA isoforms (associated with bcr3 breakpoints) and increased expression of CD2, CD34 and CD56.[164] However, their relevance in the era of arsenic-based therapy has not been confirmed.

Early deaths

The unparalleled rates of survival in patients achieving a CR through current treatment protocols only help to highlight the continuing problem of early deaths. In contemporary trial publications from tertiary centers, the early death rates are <10%.[36,37,93,132,165] However, this is likely to underestimate the true rate as the trial data are vulnerable to various forms of selection bias, eg, failure to include diagnosed patients who succumb prior to therapy, restriction according to age or performance status or those who were never appropriately diagnosed in the first instance.[93,166,167] Retrospective analysis of patient outcomes outside the confines of a trial and population data identifies the rate of early death as between 17% and 29%.[8,165,167–169]

Coagulopathy and catastrophic bleeding, particularly within the brain and lungs, are the most common causes of early demise.[8,167,169–171] There is a pathological activation of both pro-coagulant and fibrinolytic pathways in APL, and the contributions of tissue factor (TF), cancer procoagulant, Annexin II, plasminogen and thrombin activatable fibrinolytic inhibitor (TAFI) have been reviewed by both Breen et al[172] and Kwaan and Cull.[173] The pathological disturbance in the fibrinolytic pathway largely driven by increased Annexin II expression on abnormal promyelocytes is reversed by ATRA-induced differentiation.[174] However, pro-apoptotic treatment with chemotherapy and/or ATO will increase the levels of pro-coagulants, such as TF and cellular/membrane phospholipids. Therefore, treatment with ATRA should be started at the earliest suspicion of APL after clinical and morphological assessment, while awaiting confirmatory molecular or cytogenetic testing, and should be combined with aggressive hemostatic support programs using platelets and appropriate plasma components.[78] Recent reports detailed the use of a recombinant form of the thrombin inhibitor, thrombomodulin, in the treatment of APL-associated coagulopathy.[175–177] The thrombin–thrombomodulin complex in association with plasmin activates TAFI, and thereby inhibits fibrinolysis.[178]

The simplest and most powerful intervention shown to reduce the early death rate is education to both improve early identification of patients with APL and advocate for urgent initiation of therapy in a manner analogous to the emphasis on timely treatment of patients with acute coronary syndromes. Programs in developing countries to improve the treatment of patients using education, international collaboration, support and specific committees tasked with improving drug access and early initiation have driven dramatic improvements in patient survival.[179]

Pediatric patients

There is an increased incidence of the microgranular variant (M3v) of APL in children, with associated leukocytosis and greater risk of coagulopathy and/or DS.[180] The treatment of children with APL has mirrored the developments made in

adult therapy, and currently accepted protocols are based on research by the APL, GIMEMA, PETHEMA and German–Austrian–Swiss groups. Combinations of ATRA and chemotherapy help to achieve CR and 5-year OS rates between 92%–95% and 87%–90%, respectively.[181–185] Protocol modifications in the pediatric population include the reduction of ATRA dose to 25 mg/m^2, which helps to reduce the severity of side effects including headaches and pseudotumor cerebri, while achieving similar results to 45 mg/m^2.[78,184–187] Independent studies by German and Japanese investigators using ATRA throughout induction, consolidation and maintenance and utilizing anthracycline and high-dose cytarabine in consolidation have shown similar OS rates. Creutzig et al[188] reported an OS of 89% at 5 years for pediatric patients in consecutive AML–Berlin/Frankfurt/Muenster trials. Imaizumi et al[189] reported that patients in the AML99-M3 study achieved an OS of 91% at 7 years.

ATO used as monotherapy for induction, consolidation and maintenance treatment of 11 children with microgranular APL in Vellore induced a CR in 91% with 30-month OS of 91% and RFS of 81%.[190] Similarly, researchers in China treated 19 children (including seven high-risk patients) with single-agent ATO for induction of remission and 3 years post-remission therapy. The CR, 5-year OS and EFS rates were 89.5%, 83.9% and 72.7%, respectively.[191] Another single-center analysis compared ATRA vs ATRA-ATO induction with the use of ATRA in consolidation for all children and an additional 28-day cycle of ATO in consolidation for the experimental arm. All children also received extensive consolidation chemotherapy. There was a significant

Table 3 Commonly employed current treatment regimens in APL, stratified by risk category

Protocol	Induction	Consolidation	Maintenance
Low-intermediate risk			
APL0406[39]	ATRA 45 mg/m^2/d PO + ATO 0.15 mg/kg/d IV until CR (max 60 days)	ATRA 45 mg/m^2/d PO for 14 days then rest for 14 days ×7 cycles + ATO 0.15 mg/kg/d IV for 5 days per week for 4 weeks then rest for 4 weeks ×4 cycles	Nil
LPA2005[37]	ATRA 45 mg/m^2/d PO[c] + ATO 0.15 mg/kg/d IV until CR (max 60 days)	1. ATRA 45 mg/m^2/d PO d1–15 + Idarubicin 5^{low}/7^{int} mg/m^2/d d1–4 2. ATRA 45 mg/m^2/d PO d1–15 + MTZ 10 mg/m^2/d d1–3 3. ATRA 45 mg/m^2/d PO d1–15 + Idarubicin 12 mg/m^2/d d1^{low} or d1–2^{int}	ATRA 45 mg/m^2/day PO d1–15 every 90 days MTX 15 mg/m^2/wk IM d15–90 6-MP 50 mg/m^2/wk PO d15–90 for 2 years
High risk			
APML4[38]	ATRA 45 mg/m^2/day PO d1–36 ATO 0.15 mg/kg/day IV d9–36 Idarubicin 6–12 mg/m^2 d2, 4, 6, 8[a,b]	1. ATRA 45 mg/m^2/d PO days 1–28 + ATO 0.15 mg/kg/d IV d1–28 2. ATRA 45 mg/m^2/d PO d1–7, 15–21 and 29–35 + ATO 0.15 mg/kg/d IV for 5 days per week for 5 weeks	ATRA 45 mg/m^2/day PO d1–14 every 90 days MTX 5–15 mg/m^2/wk PO d15–90 6-MP 50–90 mg/m^2/wk PO d15–90 ×8 cycles
Study C9710[36]	ATRA 45 mg/m^2/d PO until CR (max 90 days) + Cytarabine 200 mg/m^2 d3–9 + DNR 50 mg/m^2 d3–6	1. ATO 0.15 mg/kg/d IV for 5 days per week for 5 weeks ×2 cycles 2. ATRA mg/m^2/d PO days 1–7 + DNR 50 mg/m^2 d1–3 ×2 cycles	ATRA mg/m^2/d PO days 1–7 repeated on alternate weeks MTX 20 mg/m^2/wk PO 6-MP 60 mg/m^2/d PO for 1 year
APL2000[96]	ATRA 45 mg/m^2/d PO until CR + Cytarabine 200 mg/m^2 d1–7 + DNR 60 mg/m^2 d1–3	1. DNR 60 mg/m^2/d d1–3 + Cytarabine 200 mg/m^2/d d1–7 2. DNR 45 mg/m^2/d d1–3 + Cytarabine 2 g/m^2/12 h d1–5 (50 years) or Cytarabine 1.5 g/m^2/12 h d1–5 (50–60 years) + 5 doses of MTX 15 mg/Cytarabine 50 mg given IT	ATRA 45 mg/m^2/day PO d1–15 every 90 days MTX 15 mg/m^2/wk PO d15–90 6-MP 50 mg/m^2/wk PO d15–90 for 2 years
LPA2005[37]	ATRA 45 mg/m^2/d PO[c] until CR + Idarubicin 12 mg/m^2/d d2, 4, 6, 8[d]	1. ATRA 45 mg/m^2/d PO d1–15 + Idarubicin 5 mg/m^2/d d1–4 + Cytarabine 1 g/m^2/d d1–4[e] 2. ATRA 45 mg/m^2/d PO + MTZ 10 mg/m^2/d d1–5 3. ATRA 45 mg/m^2/d PO + Idarubicin 12 mg/m^2/d d1 + Cytarabine 150 mg/m^2/8h d1–4	ATRA 45 mg/m^2/day PO d1–15 every 90 days MTX 15 mg/m^2/wk IM d15–90 6-MP 50 mg/m^2/wk PO d15–90 for 2 years

Notes: [a]Age adjusted; 1–60 years, 12 mg/m^2; 61–70 years, 9 mg/m^2; >70 years, 6 mg/m^2. [b]Prednisolone 1 mg/kg/day PO on d1–10 or until WCC <1×10^9/L. [c]ATRA 25 mg/m^2/d if ≤20 years. [d]If >70 years Idarubicin 12 mg/m^2 d8 omitted. [e]If >60 years no Cytarabine given in consolidation and Idarubicin dose as per intermediate risk patients described in LPA2005 low-int risk protocol.

Abbreviations: Low, low risk patients; Int, intermediate risk patients; MTX, Methotrexate; 6-MP, Mercaptopurine; DNR, Daunorubicin; MTZ, Mitoxantrone; IT, intrathecal; IM, intramuscular; IV, intravenous; PO, per os (orally).

improvement in survival with the inclusion of ATO with a 6.25-year EFS, DFS and OS for ATRA vs ATRA-ATO of 70.4% vs 92.5% (P=0.021), 76.4% vs 97.1% (P=0.012) and 70.4% vs 95.3% (P=0.007), respectively.[192]

Therefore, progress has been made toward the introduction of ATRA-arsenic in the pediatric population, but risk-adapted trials to investigate rationalized chemotherapy are lacking. The Children's Oncology Group Phase III, multicenter AAML0631 and AAML1331 trials (NCT00866918 and NCT02339740) are currently underway and aim to investigate risk-adapted and arsenic-based strategies in children.

Pregnancy

The management of pregnant patients with APL has been discussed in the European LeukemiaNet recommendations and most recently and succinctly by Milojkovic and Apperley.[78,193] In summary, the management of APL in the first trimester rests on the decision on whether an elective termination is chosen as this will allow the initiation of standard ATRA-chemotherapy or ATRA-ATO-based therapy that is otherwise contraindicated. Should the patient elect to continue the pregnancy, then ATRA is excluded in the first trimester because of the risk of fetal malformations.[193] Arsenic therapy is not possible at any time in pregnancy due to its embryotoxicity.[194,195] Treatment with daunorubicin is recommended, given its lower capacity to transfer across the placenta, lower solubility in lipids compared to idarubicin and shorter half-life. However, there remains an increased risk of abortion, premature labor, neonatal neutropenia and low birth weight.[194] Treatment after the second trimester can include the use of ATRA in combination with daunorubicin or as monotherapy, although there is an associated risk of ATRA resistance, short remission and DS in newly diagnosed patients.[71–73,196] Similarly, treatment with daunorubicin alone in newly diagnosed patients carries the risk of the exacerbation of the APL-associated coagulopathy and hemorrhage. Combination daunorubicin-ATRA therapy would logically achieve the best outcomes for the patient (and indirectly the fetus) but close monitoring of the potentially toxic side effects is essential including cardiac toxicity associated with ATRA.[78,197,198] In all patients, there is a need for comprehensive multi-disciplinary care involving an obstetrician, a fetal medicine specialist and a hematologist.

Conclusion

The paradigm of differentiation therapy constructed on the discovery and success with ATRA has evolved with the introduction of ATO and the recognition of the synergistic destruction of the PML-RARA protein. The serendipitous discovery of two agents that directly target the *PML-RARA* mutation that drives disease has led to unparalleled success in patient cure, through better eradication of LICs. The benefits of risk-adapted therapy with ATRA-chemotherapy and now ATRA-ATO without chemotherapy have been established for low–intermediate risk patients. Recent research appears to show that in high-risk patients, ATRA-ATO may overcome the increased relapse risk provided they are combined with rationally reduced use of chemotherapy or gemtuzumab ozogamicin, and randomized controlled trials are underway that will hopefully confirm this. Maintenance therapy appears dispensable in low-risk patients treated with ATRA-ATO, but this has not been defined in the high-risk cohort. There is significant progress to be made in the early death rate, particularly in developing countries, and the increasing availability of oral ATRA therapy may facilitate this. Examples of currently recommended treatment regimens for APL are summarized in Table 3.

Disclosure

The authors report no conflicts of interest in this work.

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