How I Treat Acute Promyelocytic Leukemia

Reena Nair1, Vivek S. Radhakrishnan1

1Department of Clinical Haematology Oncology, Hematopoietic Cell Transplantation, Tata Medical Center, Kolkata, West Bengal, India

Address for correspondence Reena Nair, MD, Department of Clinical Haematology Oncology, Tata Medical Center, Newtown, Kolkata, West Bengal 700160, India (e-mail: reena.nair@tmckolkata.com).

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Introduction

Discoveries and interventions in cancer are rarely so disruptive and exceptional that they cause dramatic advances in our understanding of the underlying mechanisms of a disease and immediately impact changes in treatment which lead to instant cures. Acute promyelocytic leukemia (APL) is an example of one such a disease.

Traditionally APL comprised of 10% of acute myeloid leukemia (AML) patients, presenting with bleeding diathesis and early fatal hemorrhage in 8 to 47% cases, complete remission (CR) rate was 60 to 80% with conventional anthracycline and cytosine arabinoside for patients who survived the initial induction, and a 5-year disease-free survival (DFS) which ranged between 35 and 45%.1 Yet, patient after patient bled during induction and succumbed in the wards 30 years ago.

The treatment of patients with APL has changed significantly in the past three decades and is now considered as one of the most curable cancers.2 The high sensitivity of APL cells to anthracycline chemotherapy and the introduction of a targeted therapy like all-transretinoic acid (ATRA) therapy has led to the deintensification of therapy. The initial studies showed that omission of cytarabine was feasible in standard-risk patients.3 An important milestone was achieved when arsenic trioxide (ATO) demonstrated substantial activity in relapsed APL. Thereafter, ATO emerged as one of the most potent agents in this disease with most patients achieving molecular remissions, as assessed by polymerase chain reaction (PCR) testing.4 Several strategies involving the use of the most effective agents early on in the course of treatment include the following: the use of ATO after patients achieved complete remission with an initial ATRA plus ATO and gemtuzumab ozogamicin (GO).5-13

This article attempts to address the following aspects of APL management: the initial approach of patients with suspected APL, management strategies, and supportive care measures; and assessment of molecular response and management of relapsed disease. We also share some of our experiences.

Begin treatment at suspicion of the diagnosis: A clinical suspicion of APL accompanied by the presence of characteristic findings can lead to a diagnosis. The review of peripheral blood (PB) and/or bone marrow (BM) aspirate smears of the patient by an experienced hematopathologist or hematologist enables a presumptive diagnosis.14 The PB smear of a patient typically shows circulating promyelocytes and leukopenia (►Fig. 1A). Promyelocytes with abundant, irregular primary azurophilic granules and multiple auer rods are identified only in APL. The nucleus is bilobed or reniform in appearance. The promyelocytes are Myeloperoxidase positive (►Fig. 1B). A nuanced appreciation of the morphology of APL is critical, as this subset of AML warrants immediate treatment. APL can be therapy-related rarely, and its outcomes are similar to a de novo APL.15 Considering the observations of appropriate sampling, occurrence of concomitant marrow changes and, occasionally, an unusual clinical presentation in APL patients, we recommend a BM test at the time of diagnosis. However, institutional policy and management protocols must guide BM testing practice (diagnosis and response assessment) in each center.

Once a diagnosis is suspected, ATO and/or ATRA must be started to initiate induction therapy and mitigate the attendant coagulopathy, even if the confirmatory cytogenetics and molecular test results are awaited.16

Confirmation of the diagnosis: Several laboratory techniques can confirm diagnosis. Metaphase karyotyping is highly specific (►Fig. 2A) and can detect variant

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translocations. However, karyotyping is time consuming and is often unsuccessful in detecting cryptic cytogenetic or molecular rearrangements. Reverse-transcriptase PCR (RT-PCR) for the PML-Retinoic Acid Receptor alpha fusion transcript is now a routine confirmatory test for diagnosis and considered the “gold standard.” Fluorescence in situ hybridization (FISH; Fig. 2B) and the PML antibody methods are rapid tests to get a diagnosis in APL.

**Management**

In clinical practice, it is always advisable to hospitalize patients with APL, regardless of their risk status. This enables close monitoring, prompt initiation of therapy, and rigorous supportive care. Risk stratification in APL is based on white blood cell (WBC) and platelet counts. For the low- and intermediate-risk disease patients (WBC <10,000/mm³) with a significant coagulopathy, treatment should be initiated at suspicion of the diagnosis to ameliorate coagulopathy. If the WBC count increases rapidly or for the high-risk APL patient, the risk of differentiation syndrome can be reduced by initiating cytoreduction with the use of anthracyclines added to the induction therapy.

ATO has emerged as one of the most active agents in APL treatment regimens. The mechanism of its action is based on the direct degradation of PML-RARα fusion transcripts. This leads to the transcription of RARα target genes which in turn causes the apparent differentiation and growth arrest of leukemia-initiating cells, either by apoptosis or by the loss of self-renewal ability. In addition, ATO appears to act in the mitochondria by the release cytochrome C which initiates caspase activation and promotes apoptosis. This action

<table>
<thead>
<tr>
<th>Therapy/study</th>
<th>Number</th>
<th>CR %</th>
<th>Postremission PCR (%)</th>
<th>Therapy</th>
<th>EFS (%)</th>
<th>OS (%)</th>
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<tbody>
<tr>
<td>ATRA</td>
<td></td>
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<td>Advani⁶</td>
<td>25</td>
<td>80</td>
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<td>ATRA/IDA</td>
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<td>No Ara-C</td>
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<td>ATO</td>
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<tr>
<td>Mathews et al⁶</td>
<td>72</td>
<td>86</td>
<td>76</td>
<td>ATO</td>
<td>74.8 at 3 years</td>
<td>86.1 at 3 years</td>
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<td>Ghavamzadeh et al⁷</td>
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<td>85.6</td>
<td>92</td>
<td>ATO</td>
<td>63.7 at 2 years</td>
<td>87.6 at 3 years</td>
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<td>ATO + ATRA</td>
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<tr>
<td>Hu²³</td>
<td>85</td>
<td>94.1</td>
<td>NR</td>
<td>ATRA + ATO</td>
<td>89.2 at 5 years</td>
<td>91 at 5 years</td>
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<td>Ravandi et al¹⁰</td>
<td>82</td>
<td>90</td>
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<td>ATRA + ATO</td>
<td>80 at 2 years</td>
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<tr>
<td>Dai et al²⁴</td>
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<td>93.3</td>
<td>ATRA + ATO</td>
<td>92.2 at 3 years</td>
<td>85 at 2 years</td>
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</table>

Abbreviations: Ara-C, Arabinoside Cytosine (Cytarabine); IDA, Idarubicin; APL, acute promyelocytic leukemia; ATO, arsenic trioxide; ATRA, all-trans-retinoic acid; CR, complete remission; EFS, event-free survival; NA, not available; OS, overall survival; PCR, polymerase chain reaction.
synergizes with retinoic acid action in effecting the loss of leukemia-initiating cells. A selected series of studies performed in the treatment of APL which used ATRA, ATO, and the two in combination with intensive chemotherapy, mild chemotherapy, and alone are listed in Table 1.

ATO plus ATRA combination is generally well tolerated, with fewer incidence of myelosuppression and significantly less infections. However, there are frequent increases in hepatic transaminases, and prolongations of the QTc interval. These side-effects are manageable with drug discontinuation for short periods and appropriate dose adjustments. Our practice is to start with single-agent ATO at the first suspicion of APL, use an anthracycline in patients with hyperleukocytosis, and add ATRA later on during induction, once the promyelocytes have cleared from the PB.

Supportive care: Aggressive supportive care is critical during the initial phase of induction. A complete blood count at least two times every day is recommended until coagulopathy resolves. The fibrinogen, prothrombin time, and partial thromboplastin time are monitored once a day. Platelet transfusions are recommended to maintain platelet counts above 30,000 to 50,000/µL. In the presence of coagulopathy or low fibrinogen levels, cryoprecipitate administration is recommended in the first 2 weeks of induction until the coagulopathy resolves or the fibrinogen levels remain above 150 mg/dL whichever is later. There is a risk of thrombosis at diagnosis and during treatment. A clear benefit from routine heparin use is yet to be demonstrated, except in the presence of a major deep vein thrombosis (DVT). In the setting of severe thromboses, unfractionated heparin may be used, with close monitoring and caution for the risk of bleeding. If a low-molecular-weight heparin (LMWH) is preferred, a platelet count adapted dosing of the LMWH is preferred (e.g., 70–80% of the recommended dose if, platelet count is 70,000/µL; 50%, if 50,000/µL; and stop, if <30,000/µL). Invasive procedures, such as lumbar puncture, central venous line insertions, bronchoscopy, and others, must be avoided in the initial phase of treatment, as long as coagulopathy is active.

APL differentiation syndrome: For a physician treating APL, differentiation is an important cardiorespiratory distress syndrome requiring a high index of suspicion, close observation, and anticipation. Symptoms include cough and shortness of breath, while signs are typically those of weight gain, effusions (pleural and/or pericardial), and lung infiltrates. The clinical features can mimic fluid overload accompanied by pleural effusions or pneumonia. An important differential diagnosis is diffuse alveolar hemorrhage as distinguishing between the two can sometimes become difficult. A vigilant approach and instituting dexamethasone (10-mg twice daily), at the earliest symptom or sign of this condition, should be followed. It is the best to avoid the practice of waiting for imaging abnormalities to develop, before instituting fluid restriction and steroids. ATO or ATRA may have to be withheld based on the severity of the syndrome and resumed on resolution of all signs and symptoms. Resumption of therapy may require steroid cover as the syndrome may recur. The role of prophylactic steroid use in APL induction therapy to reduce the risk of differentiation syndrome was suggested by the findings of a nonrandomized study and has been used in some published protocols thereafter. The administration of steroids to neutropenic patients may predispose them to infection, caution is advised thereof. In patients presenting with high leucocyte counts (>30,000/µL), prophylactic corticosteroids (dexamethasone or methyl prednisolone or prednisolone) should be considered if there are no significant medical contraindications, but the data to support this approach is limited.

Dose and duration: ATO is given in the dose of 10 mg (0.15 mg/kg), as a 3 to 4 hours infusion daily for 6 to 8 weeks during induction. ATRA at 45 mg/m² can be safely added once the peripheral smear shows no promyelocytes. This strategy has helped us reduce the induction mortality from APL syndrome from 40% in our initial series to less than 10%. If the PB shows morphological remission with normalization of the three lineages, and the marrow is in remission, induction therapy is stopped at 6 to 8 weeks. Early molecular studies are not advised in APL, as the time to remission is around 1.5 months. Molecular tests to confirm durable remission are done after consolidation and can be considered after induction in a trial setting.

Monitoring of unique adverse events: In patients with risk factors for cardiac arrhythmias, previous episodes of QTc prolongation and those with symptoms like dizziness and syncope, receiving ATO, must undergo strict monitoring for electrocardiogram (ECG) changes. If an event like syncope, tachycardia or arrhythmia occurs or if QTc interval value becomes longer than 500 ms, the patient may be hospitalized for ECG and electrolyte monitoring. After stopping ATO, other drugs which are known to prolong QTc interval must be withheld if feasible. Once QTc returns to 460 ms or lesser and electrolytes are stable, one can consider resumption of ATO at 50% doses and escalate it to the full dose with close monitoring. QTc determination and gender differences must be remembered in this background.

Case: A 19-year-old patient presented with bleeding gums, nose, and widespread petechiae and bruising for 15 days. Her PB smear showed pancytopenia with abundance of promyelocytes. She was diagnosed as low-risk APL with t(15;17). She was admitted and started on therapy with ATRA for 90 days along with three courses of daunomycin, 45 mg/m² for 3 days in every 28 days.

Therapeutic Options

1. Non–high-risk group patients (WBC count <10,000/µL): ATRA plus ATO has been established as the new standard of care in APL patients without high-risk features, based on the results of two pivotal phase-3 clinical studies that compared the safety and efficacy of this combination against the previous standard of care which used ATRA plus chemotherapy. Survival outcomes, both event-free survival (EFS) and overall survival (OS), using the ATRA plus ATO combination demonstrated noninferiority and a potential superiority in an Italian German study. A recent update from the study group reported on
long-term outcomes of the strategy. At a median follow-up of 41 months, the benefit of the combination of ATRA plus ATO increased over time translating into improved EFS and OS outcomes and lower cumulative relapse incidence. The National Cancer Research Institute (NCRI) United Kingdom (UK) cooperative group conducted a similar study which tested ATRA plus chemotherapy against ATRA plus ATO in APL patients, irrespective of the WBC count. The results of this study were updated recently and demonstrate a higher EFS and lower cumulative incidence of relapse rates in patients receiving ATRA plus ATO. The OS outcomes between the two arms, however, were not statistically different. This lack of difference in the OS rates could potentially be due to the study recommended practice of “preemptive treatment” with ATO, in patients developing molecular relapse on serial minimal residual disease (MRD) monitoring. MRD monitoring of patients demonstrated a high compliance rate in this study. The long-term results of a single institution nonrandomized study suggest that ATRA plus ATO combination induces sustained responses even in patients with WBC counts >10,000/µL. Based on the strengths of these studies, the combination of ATRA plus ATO, without chemotherapy, can be considered as the new standard of care in the setting of non–high-risk APL.

Mathews et al administered an ATO monotherapy regimen and reported a CR rate of 86% and a cumulative long-term relapse incidence of 18%, with a 5-year OS of approximately 74.2%. Low-risk patients of APL managed with this ATO monotherapy regimen had a 5–year OS of 100%. This study has successfully advocated the use of ATO monotherapy for all APL patients and is presently one of the most cost-effective regimens for a significant proportion of our patients.

2. **High-risk group patients (WBC count >10,000/μL)**: ATRA plus ATO with the addition of cytoreductive chemotherapy, and ATRA plus chemotherapy are the recommended therapeutic options in the high-risk APL patients. Neither regimens have been demonstrated superior from each other in prospective randomized controlled trials (RCT). One RCT compared ATRA plus ATO against ATRA plus chemotherapy and did not find any significant difference in outcomes between the treatments.

In this study, however, a single dose of GO (6 mg/m²) was added in high-risk APL patients receiving the ATRA plus ATO regimen.

The Australasian Leukemia and Lymphoma Group (ALLG) employed an interesting strategy in the high-risk group which included an ATRA plus ATO–based regimen followed by a 1-year maintenance therapy. In comparison to a historical cohort of ATRA plus chemotherapy combination, despite a 50% reduction in idarubicin dosing, the outcomes confirmed significantly improved results both in the low-risk and high-risk group patients. Further, there were no significant differences in outcomes between the two risk categories.

In a single-center experience from our group, 131 consecutive patients were treated with sequential ATO followed by ATRA with anthracyclines. At a median follow-up of 60 months, the outcomes are promising with 84.81% patients alive and an EFS of 77.82%. The EFS in the Sanz low-risk group was better (85%) than the intermediate- and high-risk combined cohort (76%), with 100% of the low-risk group patients alive at last follow-up compared with 82% in the latter group. In the long-term, survival outcomes were comparable to the published real-world data.

**Case:** Patient achieved complete hematological remission after the initial induction of ATRA and daunomycin, which was followed by two consolidation ATO on alternate month. She received 560 mg of ATO as a cumulative dose and was advised follow-up at 3 monthly for the first year.

### Assessment of Disease Response and Monitoring

The preferred method for molecular response monitoring in APL is Real time Quantitative-PCR. The inherent advantages of RQ-PCR over qualitative RT-PCR are the following: fewer false-negative tests as poor-quality samples are identified efficiently, response kinetics is captured effectively, and the platform is less prone to contamination. To address appropriateness of samples for MRD testing, a longitudinal study used the RQ-PCR platform to compare BM and PB samples for PML/RARα monitoring and reported that molecular relapses were detected earlier in the BM samples versus PB samples. Though this and other data suggest BM as the ideal sample for MRD monitoring, PB sample continues to be a pragmatic, comfortable and reasonable alternative for the patient. It is possible that by allowing for more frequent monitoring of PB than BM, the sensitivity of detection of relapse between the two options will potentially be similar over time.

There is no data regarding a precise recommendation for the intervals between visits for long-term follow-up of patients who have an MRD-negative status. It may be reasonable to consider performing complete blood counts once in 3 months in the first year after diagnosis, at 6-month intervals during the next 2 years and less frequently thereafter.

### Role of Maintenance

The role of a maintenance therapy phase in APL is being debated and may not have any impact in the management of non–high-risk APL, based on the good outcomes reported from the ATRA plus ATO approaches without maintenance therapy. No benefit was found in the AIDA 0493 study in patients who were in molecular remission (PCR negative) and received maintenance therapy postconsolidation. In the high-risk APL patients, there may be a potential role for maintenance therapy in those who have received the ATRA plus chemotherapy regimens, while in the ATRA plus ATO combination regimens, its omission is being investigated currently. Having stated that, any maintenance approach should follow evidence-based institutional protocol, institutional experience, and practices thereof.
Strategies for Management of Molecular and Hematological Relapse

With the advent of molecular monitoring, molecular relapse and the much rarer scenario of molecular persistence post-consolidation are highly predictive of imminent loss of hematological remission. Additional treatment is immediately indicated in patients who harbor persistent molecular disease or develop molecular relapse, and this may include hematopoietic cell transplantation (HCT) where appropriate and feasible. The salvage treatment used will depend on the nature of upfront therapy received. In patients relapsing post-ATRA plus chemotherapy regimens, an ATRA plus ATO approach can achieve a new molecular remission. ATRA plus chemotherapy is an option that we can explore in patients who have relapsed an ATRA plus ATO frontline therapy. The recommendation from the European Leukemia Net expert panel is to promptly start preemptive therapy in patients with molecular relapse and prevent a hematological relapse. In patients who develop a late relapse (after 2 years in CR), switching to an alternative regimen as compared with the frontline regimen used may not be warranted. However, a regimen with lesser side effects may be chosen.

Recent studies have demonstrated that in patients with relapsed disease who achieve a second molecular remission, autologous HCT may be considered as the first choice for a consolidation approach. This approach has been questioned in a recent NCRI UK report, especially in patients who achieve a molecular remission with ATRA plus ATO salvage. This may be truly so in patients who do not have CNS disease at relapse and have received a full course of consolidation with ATO. Relapsed patients who fail to achieve a second molecular remission with an appropriate salvage regimen, must be considered for an allogeneic HCT. In patients in whom allogeneic transplantation is not possible, additional courses of ATO consolidation may be considered. New and repurposed drugs considered in this setting include GO and bortezomib.

**Case:** Patient was under 3 monthly follow-up. During her second follow-up, she revealed her pregnancy and the desire to continue the same despite all explanations regarding the teratogenic effects of ATRA and ATO. She delivered a healthy male child and in subsequent follow-ups 2 years later came back to announce her second pregnancy 25 months after completion of her ATO dose and delivered a healthy female baby.

In our report, among 43 patients with APL treated with ATO, 6 of them subsequently went on to successfully conceive a child. These patients had received cumulative ATO doses ranging from 280 to 1,330 mg. These six patients did not need additional reproductive technologies or infertility treatments and conceived within a range of 6 months to 7 years from ATO completion. Based on these findings, Stein and Tallman concluded that some patients exposed to curative doses of ATO for the treatment of APL can conceive and carry a pregnancy to term. Efforts such as that from Gupta and colleagues should be a precursor to larger scale, prospective, correlative studies of fertility and pregnancy outcomes in trials using ATO plus ATRA without chemotherapy, in induction and consolidation treatment of APL.

**Summary**

In our initial audit of 19 patients, ATRA was provided on compassionate grounds to be used in patients who were not eligible for anthracycline-based therapy. Unlike induction with daunorubicin and cytarabine, when most patients succumbed to hemorrhage or sepsis, ATRA alone resulted in responses in 72% patients but these responses were not durable and most patients relapsed at a median of 8 months.
nancy outcomes were reported. A rare toxicity reported for child-bearing potential after the use of ATO and the preg-
current practice is outlined in Fig. 3C at 5 years (patients and 85% OS for intermediate- and high-risk patients
ful in reducing the initial mortality to ATRA syndrome. The change in strategy was adapted using ATO induction fol-
results and reduce the early treatment mortality, a

Abbreviations: APL, acute promyelocytic leukemia; ARDS, acute respiratory distress syndrome; ATO, arsenic trioxide; ATRA, all-trans retinoic acid; MRD, minimal residual disease; PCR, polymerase chain reaction.

(range: 1–28 months – Fig. 3A). In the subsequent audit of 25 patients, ATRA was followed by intensive chemotherapy and the 3-year survival improved to 42% (– Fig. 3B).28 However, both ATRA syndrome, as well as consolidation chemotherapy resulted in a high treatment-related mortality.27 To improve the results and reduce the early treatment mortality, a change in strategy was adapted using ATO induction followed by ATRA, along with anthracycline, as consolidation and ATRA maintenance thereafter. This strategy was successful in reducing the initial mortality to ATRA syndrome. The recent report published suggests 100% survival for low-risk patients and 85% OS for intermediate- and high-risk patients at 5 years (– Fig. 3C).29 Patients on follow-up were evaluated for child-bearing potential after the use of ATO and the pregnancy outcomes were reported.44 A rare toxicity reported for the first time in literature was avascular necrosis of the femur in a patient on ATRA along with chemotherapy and has been subsequently confirmed by other authors.46 Our current practice is outlined in Table 2.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Our current practice</th>
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<tr>
<td>Induction therapy for APL is chemotherapy-free using ATO followed by ATRA once peripheral blood clears of promyelocytes</td>
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<tr>
<td>Single dose of anthracycline, only to mitigate hyperleukocytosis, in the initial phase of induction</td>
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<tr>
<td>ATO/ATRA is stopped for impending ARDS temporarily, along with steroid use, for ±3 days</td>
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<tr>
<td>Postremission induction ATRA/ATO consolidation ± maintenance according to MRD (PCR) status</td>
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