Treatment of Acute Promyelocytic Leukemia in Adults

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ASSOCIATED CONTENT

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Abstract

The treatment of acute promyelocytic leukemia (APL) has evolved rapidly in the past two decades after the introduction of highly active drugs, including tretinoin (all-*trans*-retinoic acid) and arsenic trioxide. It is now possible to treat this disease without the use of traditional cytotoxic chemotherapy. Today's clinical guidelines include multiple regimens, some of which continue to use cytotoxic chemotherapy. This leaves the practicing oncologist with multiple treatment options when faced with a new case of APL. In an effort to standardize our approach to the treatment of newly diagnosed APL, we sought to develop a set of treatment recommendations at our institution. We identified eight major controversial issues in the treatment of APL. These controversial issues include the optimal dose and schedule of both all-*trans*-retinoic acid and arsenic trioxide, the optimal regimen for high-risk APL, the need for intrathecal prophylaxis, the use of prophylactic corticosteroids, and the need for maintenance therapy after consolidation. We reviewed the relevant literature and used the Delphi method among the coauthors to reach consensus for recommendations on the basis of the best available data and our own clinical experience. In this clinical review, we present our consensus recommendations, the reasoning behind them, and the grading of the evidence that supports them.

INTRODUCTION

Acute promyelocytic leukemia (APL) is an uncommon but highly curable leukemia with an incidence of 600 to 800 new cases per year in the United States.[1] The introduction of tretinoin (all-*trans*-retinoic acid; ATRA) in the 1980s revolutionized the treatment of APL. ATRA was added to various induction and consolidation regimens that contained conventional cytotoxic chemotherapy with remarkable improvement in both early and late outcomes. Treatment regimens have evolved rapidly over the past two decades with the emergence of arsenic trioxide (ATO). This paved the way for modern treatment regimens that abandoned conventional cytotoxic chemotherapy for a combination of ATRA and ATO alone. Today, a number of regimens have been developed through prospective clinical trials for the treatment of APL, and current clinical guidelines reflect these multiple options.[2,3] This presents the clinician with a number of choices, some of which have already been demonstrated in prospective studies to be suboptimal as a result, in part, of efficacy, toxicities, or cost. We sought to develop a set of treatment recommendations for newly diagnosed patients with APL at our institution. We identified eight major controversial issues in the treatment of APL. Through a process of literature review and examination of trial data (Table 1), we used the Delphi method among the coauthors to reach consensus

DOI: https://doi.org/10.1200/JOP.18.00328

Table 1. Summary of Major Acute Promyelocytic Leukemia Trials Considered for Our Consensus Recommendations

Trial (reference)	Risk Groups (No. of patients)	Induction	Consolidation	Maintenance	Prophy-lactic Corticosteroids	DFS, %	OS, %
Lo-Coco et al[4,5]; APL0406	Low (112)	ATRA + ATO *v*	ATRA + ATO *v*	None for ATRA/ATO group	Yes	ATRA+ ATO: 97	ATRA + ATO: 99
	Intermediate (147)	ATRA + IDA	ATRA + IDA + MITZ	ATRA + MTX + 6MP for ATRA/CHT group		ATRA + CHT: 82 (4 years)	ATRA + CHT: 93 (4 years)
Abaza et al[6,7]; MD Anderson	Low (133)	ATRA + ATO + (GO/ IDA for high risk)	ATRA + ATO	None	Yes	Low risk: 99	Low risk: 89
	High (54)					High risk: 89 (5 years)	High risk: 86 (5 years)
Illand et al[8]; APML4	Low (33) Intermediate (67) High (23)	ATRA + ATO + IDA	ATRA + ATO	ATRA + MTX + 6MP	Yes	Low/intermediate risk: 96 High risk: 95 (5 years)	Low/intermediate risk: 96 High risk: 87 (5 years)
Burnett et al[9]; AML17	Low (177)	ATRA + ATO + (GO for high risk) *v*	ATRA + ATO *v*	None	No	ATRA + ATO: 98	ATRA + ATO: 93
	High (56)	ATRA + IDA	ATRA + IDA + MITZ			ATRA + IDA: 70 (4 years)	ATRA + IDA: 89 (4 years)
Lancet et al[10]; SWOG/ Alliance/ECOG S0535	High (73)	ATRA + ATO + GO	ATRA + ATO + DNR + GO	ATRA + 6MP + MTX	No	93 (3 years)	88 (3 years)
Powell et al[11]; C9710	Low (136)	ATRA +	ATRA + DNR + ATO *v*	ATRA *v*	No	ATRA + DNR + ATO consolidation arm: 90	ATRA + DNR + ATO consolidation arm: 86
	Intermediate (232)	AraC + DNR	ATRA + DNR	ATRA + 6MP + MTX		ATRA + DNR consolidation arm: 70 (3 years)	ATRA + DNR consolidation arm: 81 (3 years)
	High (113)						
Coutre et al[12]; SWOG/ CALGB/ECOG S0521	Low (38)	ATRA +	ATO and ATRA + DNR	ATRA + 6-MP + MTX *v* None if RT-PCR is negative	No	No maintenance: 96 (3 years)	91 (3 years)
	Intermediate (67)	AraC + DNR					

Abbreviations: 6MP, 6-mercaptopurine; AraC, cytarabine; ATO, arsenic trioxide; ATRA, all-*trans*-retinoic acid; CHT, chemotherapy; DFS, disease-free survival; DNR, daunorubicin; IDA, idarubicin; MITZ, mitoxantrone; MTX, methotrexate; OS, overall survival; RT-PCR, reverse-transcription polymerase chain reaction.

for recommendations on the basis of the best available data and our own clinical experience. Here, we present our deliberations leading to our consensus recommendations along with some of the alternatives used by others (Table 2).

A BRIEF NOTE ON THE ACUTE MANAGEMENT OF APL

APL is highly curable, but a substantial percentage of patients die within the first month of diagnosis. Data from the Swedish Adult Acute Leukemia Registry show an early death rate of 29%, mostly as a result of bleeding, with 35% of these patients dying before ever receiving ATRA.[14] Prompt administration of ATRA at the first suspicion of APL is of utmost importance, and the clinician should not delay ATRA therapy pending cytogenetic or molecular confirmation of the diagnosis. ATRA has minimal toxicity and can be discontinued if the diagnosis of APL is later abandoned. Conversely, delaying the administration of ATRA can lead to serious complications, such as fatal hemorrhage and disseminated intravascular coagulation. Other supportive measures include maintaining the platelet count greater than 30,000/μL, the internationalized normalized ratio for prothrombin time at less than 1.5, and fibrinogen greater than 100 to 150 mg/dL through blood product transfusions. Minimizing unnecessary procedures, such as central venous catheters, lumbar puncture, and leukapheresis, is also recommended. We regularly administer intravenous vitamin K to our patients to overcome the deficit produced by disseminated intravascular coagulation, prolonged antibiotic therapy, and often poor nutritional status while receiving remission induction therapy.

OPTIMAL AGENTS TO TREAT LOW- AND INTERMEDIATE-RISK APL

The Sanz risk score uses WBC count and platelet count to categorize patients into three risk groups—low, intermediate, and high.[15] This particular score was developed by the Italian Adult Haematological Diseases Group (GIMEMA) and the Spanish Program for the Study and Treatment of Hematological Malignancies (PETHEMA) group and correlates with relapse-free survival (RFS). Low- and intermediate-risk APL are often considered together and are defined by a WBC count of less than 10,000/μL.[15] High-risk APL has a WBC count greater than 10,000/μL.

The APL0406 trial (ClinicalTrials.gov identifier: NCT00482833) by the GIMEMA, German Austrian AML Study Group (AMLSG), and the Study Alliance Leukemia (SAL) group was a landmark trial that compared ATRA and ATO with standard ATRA and chemotherapy using the AIDA (ATRA and idarubicin) regimen in front-line therapy for the treatment of low- and intermediate-risk APL.[4] This was a multicenter, randomized, prospective noninferiority trial. Final results of this trial with a 50-month median follow-up were published in 2017 and demonstrated improvements in event-free survival (EFS), cumulative incidence of relapse, and overall survival (OS) in the ATRA/ATO arm compared with the ATRA/chemotherapy arm.[5] The UK AML 17 trial (ClinicalTrials.gov identifier: NCT00052299) reported similar results for patients who were treated with ATRA/ATO, showing lower relapse rates and no difference in OS at 4 years compared with ATRA/chemotherapy.[9] On the basis of these results, our standard approach to our patients with low- and intermediate-risk APL is to treat with ATRA and ATO without the use of cytotoxic chemotherapy.

OPTIMAL DOSE OF ATRA IN INDUCTION AND CONSOLIDATION

Studies that have investigated the treatment of APL in adults have mostly used ATRA at a total per-day dose of 45 mg/m^2, usually administered in two divided doses. A lower dose of ATRA, 25 mg/m^2, has been used in the pediatric population. This lower dose is thought to decrease the incidence of intracranial hypertension.[16,17] Use of a lower dose of ATRA is supported by pharmacokinetic studies in adults. In 1990, Castaigne et al[18] treated 30 adult patients with 25 mg/m^2 per day of ATRA alone. Ten of 12 patients treated for newly diagnosed APL achieved a complete remission. Pharmacokinetic studies were performed in five patients. Peak plasma concentrations and the mean area under the concentration-time curve were not lower than levels obtained with the 45 mg/m^2 dose.[18] One adult study by Shen et al[19] used the 25-mg/m^2 dose in 39 patients, which resulted in a high rate of complete remission (≥ 90%). Although reducing the risk for intracranial hypertension remains an important consideration, the experience in adult randomized clinical trials is almost exclusively with the higher dose of ATRA. We recommend using the standard adult dose of 45 mg/m^2 per day, although we are comfortable reducing the dose to 25 mg/m^2 per day for patients who develop severe headache or pseudotumor cerebri.

OPTIMAL SCHEDULE FOR ATRA IN CONSOLIDATION

The APL0406 study administered ATRA for 2 weeks every 4 weeks for a total of seven cycles—28 weeks—in

Table 2. Major Controversial Issues in the Treatment of APL With Our Recommendations to Address Those Issues and Alternative Regimens Reported in the Literature

Treatment Question	Grade*	Consensus Recommendation	Alternative
A: Optimal dose of ATRA to be used in induction and consolidation?	1B	45 mg/m^2/d in divided doses	25 mg/m^2/d
B: Optimal schedule of ATRA in consolidation?	1C	45 mg/m^2 7 days on and 7 days off for a total of 28 weeks	45 mg/m^2/d for 2 weeks every 4 weeks for a total of seven cycles (28 weeks total)
C: Dose and schedule of ATO?	1A	Induction: 0.15 mg/kg/d until remission for a maximum of 60 days Consolidation (four cycles, 8 weeks each): Weeks 1-4: 0.15 mg/kg/d, 5 days per week	Induction: Week 1: 0.3 mg/kg (days 1-5) Weeks 2-8: 0.25 mg/kg twice per week Consolidation (four cycles): Week 1: 0.3 mg/kg (days 1-5) Weeks 2-4: 0.25 mg/kg twice per week
D: Treatment of patients with low- and intermediate-risk APL (WBC $<$ 10,000/μL)	1A	Induction: ATRA 45 mg/m^2/d + ATO 0.15 mg/kg/d until remission for a maximum of 60 days Consolidation: Weeks 1-4: ATO 0.15 mg/kg/d, 5 days per week (four cycles, 8 weeks each) ATRA: 45 mg/m^2 7 days on and 7 days off for a total of 28 weeks	Induction: ATRA 45 mg/m^2/d + ATO 0.15 mg/kg/d until remission for a maximum of 60 days Consolidation: Weeks 1-4: ATO 0.15 mg/kg/d, 5 days per week (four cycles, 8 weeks each) ATRA: 45 mg/m^2/d for 2 weeks every 4 weeks for a total of seven cycles (28 weeks total)
E: Treatment of patients with high-risk APL (WBC $>$ 10,000/μL)	1B	Induction: ATRA 45 mg/m^2/d + ATO 0.15 mg/kg/d until clinical remission + one dose of GO on day 1 If GO is not available, administer one dose of idarubicin 12 mg/m^2 on day 1 for patients without cardiac dysfunction For patients with cardiac dysfunction, start hydroxyurea (2-3 g/d) on day 1 Consolidation (four cycles, 8 weeks each): Weeks 1-4: ATO 0.15 mg/kg/d, 5 days per week; ATRA 45 mg/m^2 for 7 days on and 7 days off for a total of 28 weeks	Induction: ATRA 45 mg/m^2/d until clinical remission + daunorubicin 50 mg/m^2 $\times$ 4 days + cytarabine 200 mg/m^2 $\times$ 7 days Consolidation: ATO 0.15 mg/kg/d $\times$ 5 days for 5 weeks $\times$ 2 cycles Then, ATRA 45 mg/m^2 $\times$ 7 days + daunorubicin 50 mg/m^2 $\times$ 3 days for two cycles[2] *or* Induction: ATRA 45 mg/m^2/d until clinical remission + idarubicin 12 mg/m^2 on days 2, 4, 6, 8 Consolidation: ATRA 45 mg/m^2 $\times$ 15 days + idarubicin 5 mg/m^2 and cytarabine 1 g/m^2 $\times$ 4 days $\times$ one cycle Then, ATRA $\times$ 15 days + mitoxantrone 10 mg/m^2/d $\times$ 5 days $\times$ one cycle Then, ATRA $\times$ 15 days + idarubicin 12 mg/m^2 $\times$ one dose + cytarabine 150 mg/m^2 every 8 hours $\times$ 4 days $\times$ one cycle[2] *or* Induction: ATRA 45 mg/m^2 (days 1-36) + Age-adjusted idarubicin 6-12 mg/m^2 on days 2, 4, 6, 8 + ATO 0.15 mg/kg (days 9-36 as 2-hour intravenous infusion) Consolidation: ATRA 45 mg/m^2 $\times$ 28 days + ATO 0.15 mg/kg/d $\times$ 28 days $\times$ one cycle

(continued on following page)

Table 2. Major Controversial Issues in the Treatment of APL With Our Recommendations to Address Those Issues and Alternative Regimens Reported in the Literature (continued)

Treatment Question	Grade*	Consensus Recommendation	Alternative
			Then, ATRA 45 mg/m^2 × 7 days every 2 weeks × 3 + ATO 0.15 mg/kg/d × 5 days for 5 weeks × one cycle[2]
F: CNS prophylaxis	1C	No CNS prophylaxis for any risk group when ATRA/ATO is used	Prophylactic intrathecal chemotherapy for high risk patients in remission
G: Corticosteroids for prophylaxis and/or treatment of differentiation syndrome	1C	No prophylaxis with corticosteroids Dexamethasone 10 mg twice per day at the first signs or symptoms of differentiation syndrome	Prednisone 0.5 mg/kg until the end of induction for prophylaxis *or* Methylprednisolone 50 mg/d for 5 days during induction for prophylaxis *or* Prednisone 1 mg/kg/d as prophylaxis
H: The need for maintenance therapy	1B	Bone marrow examination with molecular studies required at the end of consolidation No maintenance therapy administered if in molecular remission by RT-PCR	Single agent ATRA ATRA 45 mg/m^2 orally for 7 days repeated every other week for 1 year *or* ATRA 45 mg/m^2 for 15 days every 3 months

Abbreviations: APL, acute promyelocytic leukemia; ATO, arsenic trioxide; ATRA, all-*trans*-retinoic acid; GO, gemtuzumab ozogamicin.
*Grade of recommendation and quality of evidence as used in UpToDate.[13]

postremission consolidation.[4] A similar schedule was used in the UK AML 17 study and the MD Anderson group.[9,20] The North American Intergroup Protocol C9710 study used a unique schedule of ATRA in consolidation.[11] In this particular study, ATRA was administered on an alternate week schedule: 7 days on, followed by 7 days off. The rationale behind this schedule was the observation that ATRA induces its own catabolism. Pharmacokinetic studies show that ATRA plasma concentration levels decrease with continued administration of the drug. This effect is observed as early as within the first 7 days.[21] Active metabolites of ATRA induce CYP26A1, which, in turn, converts these same metabolites into inactive forms.[22] Of importance, this catabolic enzyme activity declines to baseline within 7 days of discontinuing ATRA, restoring optimal plasma levels to be achieved when ATRA is restarted. This schedule was also used during consolidation in the Australian APML4 trial.[8] On the basis of these observations, we recommend the alternate week schedule used in the C9710 study for ATRA during consolidation for a total of 28 weeks; however, administering ATRA for 2 weeks every 4 weeks is an established alternative.

OPTIMAL DOSE AND SCHEDULE FOR ATO IN CONSOLIDATION

We identified two schedules that are used for the administration of ATO. The first schedule was used in the APL0406 and the APML4 study and by the MD Anderson group and consists of ATO 0.15 mg/kg/d as a 2-hour intravenous infusion during induction until remission is achieved, typically 5 to 6 weeks. ATO can be discontinued if there are no leukemic cells observed in the marrow at that point. In consolidation, ATO has most often been administered for four cycles, with a cycle length of 8 weeks. The drug is typically administered during weeks 1 to 4 at 0.15 mg/kg/d for 5 days per week.[4,8,20]

The UK AML 17 study used a different dose schedule for ATO in induction and consolidation. This schedule specified daily loading doses of 0.3 mg/kg for 5 days during the first week of each course, but became less intensive during weeks 2 to 4 with more convenient outpatient twice per week dosing using 0.25 mg/kg each day.[9] Patients received five courses in total, including induction and consolidation. It is unclear if neuropathy is any different between the lower dose or the intermittent schedules. We use the first regimen, which

delivers a total dose of 21 mg/kg of ATO. As the second regimen reduces the number of outpatient visits in weeks 2 to 4 to twice per week, it could be an attractive alternative for patients who are unable to return to the clinic 5 days per week.

Of note, obesity is a risk factor for the development of APL.[23] ATO dosing used in clinical trials is weight based and this can lead to high doses of ATO administered to obese patients. In a phase I and II study of ATO in patients with relapsed APL, three of 10 patients died suddenly during treatment—all three were obese.[24] Shen and colleagues[25] demonstrated that, in 20 patients with relapsed APL, there was no difference in OS or RFS in patients who were treated with low-dose ATO (0.08 mg/kg) compared with standard-dose ATO (0.15 mg/kg). To our knowledge, no other clinical trials have used this lower dosing regimen so far. A phase I trial in pediatric patients used ideal body weight instead of actual body weight in patients with a body mass index more than 30 kg/m.[26] ATO concentrations were lower in these patients, but these obese patients still seemed to have a higher frequency of toxicities. As a result of a lack of sufficient data, we continue to treat our obese patients with ATO on the basis of actual body weight. We watch closely for toxicities, including prolongation of the QT interval on electrocardiogram, liver function test abnormalities, GI symptoms (nausea, vomiting, or abdominal pain), and neuropathy. We hold ATRA and ATO if liver enzymes elevate to greater than 5× the upper limit of normal.[4] We restart ATO and ATRA at one-half the previous dose as soon as liver function tests decline to less than 4× the upper limit of normal. If liver enzymes continue to normalize, we increase to the initial dose after 7 days.

Experience with ATO in renal failure is limited as trials generally exclude these patients. No dose adjustments are needed for creatinine clearance of 30 mL/min or more. Administration of ATO to a few patients with severe renal dysfunction has been reported with good outcomes. ATO was administered to this group at 36% to 40% dose reductions on the basis of measured ATO serum levels.[27]

ATO has the propensity to prolong the corrected QT (QTc) interval, placing the patient at risk for dangerous arrhythmias; therefore, we recommend obtaining a baseline ECG before initiation of therapy, along with monitoring serum electrolytes daily and QTc interval at least weekly during induction. For QTc prolongation greater than 450 milliseconds, we withhold any medication known to prolong the QTc interval and fully replete electrolytes intravenously. If there were no improvement or for QTc greater than 500 milliseconds, we discontinue ATO. After QTc normalizes, we resume ATO with a 50% dose reduction, then gradually re-escalate the dose in the absence of QTc prolongation.

TREATMENT OF PATIENTS WITH HIGH-RISK APL

Whereas ATRA and ATO are now the standard of care for the treatment of lower-risk APL, optimal treatment of high-risk APL remains a debated issue. These patients present with WBC counts greater than 10,000/μL and have a higher incidence of complications during remission induction. The landmark GIMEMA APL0406 trial set the stage for the omission of cytotoxic chemotherapy in low- and intermediate-risk patients but excluded patients with high-risk APL. Patients with high-risk APL present a unique set of challenges: A high WBC count at presentation may rise rapidly after the initiation of ATRA, increasing the risk of complications as a result of differentiation syndrome, hypoxemia, disseminated intravascular coagulation, and intracranial hemorrhage. ATRA and ATO alone are insufficient for the treatment of high-risk APL, and there seems to be a benefit from substantial cytoreduction early during induction. Cytotoxic chemotherapy with idarubicin was added to a combination of corticosteroids, ATRA, and ATO to treat 23 high-risk patients in the Australian APML4 study. The 5-year DFS was 95% and OS 87% for these patients with high-risk APL. This trial also used additional chemotherapy during maintenance.[8]

MD Anderson Cancer Center developed a regimen using gemtuzumab ozogamicin (GO), an anti-CD33 monoclonal antibody conjugated to the anthracycline antibiotic calicheamicin.[6] GO 9 mg/m^2 was administered on day 1 in induction for high-risk patients. Their patients also received ATRA 45 mg/m^2 and ATO 0.15 mg/kg/d until clinical remission. They continued ATRA and ATO during consolidation but did not administer maintenance therapy. When GO was unavailable, the MD Anderson trial allowed for one dose of idarubicin at 12 mg/m^2. The 5-year EFS, DFS, and OS for 54 high-risk patients were 81%, 89%, and 86%, respectively.[7] A similar regimen was also used in 28 patients with high-risk APL in the UK AML17 trial; however, GO was used at 6 mg/m^2 instead of 9 mg/m^2. OS and EFS were not significantly different at 4 years between the different risk groups in this study.[9] GO 9 mg/m^2 was also used in the Southwest Oncology Group (SWOG/Alliance) Eastern Cooperative Oncology Group ECOG-S0535 study (ClinicalTrials.gov

identifier: NCT00551460) that enrolled 73 patients with high-risk APL. This trial used daunorubicin later during consolidation. The 3-year OS was 88% and 3-year RFS 93%.[10]

On the basis of these data, we recommend treating high-risk APL with ATRA 45 mg/m^2 and ATO 0.15 mg/kg/d until clinical remission and administering one dose of GO 6 mg/m^2 on day 1 or shortly thereafter. An alternative would be to divide the GO dose into doses of 3 mg/m^2 administered on days 1, 4, and 7 of induction, using the schedule pioneered by the French ALFA group when treating acute myeloid leukemia in older patients.[28]

If GO were unavailable, we recommend one dose of idarubicin 12 mg/m^2 for patients without cardiac dysfunction. For patients with cardiac dysfunction, an alternative would be hydroxyurea—2 to 3 g per day—starting on day 1. Major toxicities of these agents are listed in Table 3. Once high-risk patients are in remission, we use ATRA and ATO without cytotoxic chemotherapy for postremission consolidation with the same schedule used in low- and intermediate-risk patients as detailed above.

CNS PROPHYLAXIS

CNS involvement is rare in APL. Relapse in this site was previously associated with a high WBC count at presentation and with CNS hemorrhage.[29] This prompted the incorporation of prophylactic intrathecal chemotherapy in the postremission treatment of high-risk patients in some protocols. Of importance, randomized prospective data examining the value of prophylactic intrathecal chemotherapy are not available. In addition, regimens that incorporate prophylactic therapy belong to the pre-ATO era when ATRA and chemotherapy alone were used for the treatment of APL. ATO is known to cross the blood-brain barrier and has CNS penetration at therapeutically meaningful levels—CSF concentration at 20% to 50% of plasma concentration.[30,31] Prophylactic intrathecal chemotherapy was not used in trials that incorporated ATRA and ATO, including the Australian APML4 trial, the UK AML17 trial, the MD Anderson protocol, and the Intergroup S0535 trial. These trials included high-risk patients and reported low rates of CNS relapse.[7-10] On this basis, we do not use prophylactic intrathecal chemotherapy in the treatment of APL for any risk groups.

MANAGEMENT OF INCREASING LEUKOCYTOSIS DURING INDUCTION IN LOW- AND INTERMEDIATE-RISK APL

GO has been administered as a single dose of 6 or 9 mg/m^2 when WBC count rises to greater than 30,000/μL during induction in low- and intermediate-risk patients.[20] Alternatively, hydroxyurea could be administered when WBC count rises to greater than 10,000/μL, starting with a dose of 500 mg every 6 hours.[4] Our experience is mainly using hydroxyurea in this setting.

Table 3. Common Toxicities Associated With Therapeutic Agents Used in the Treatment of Acute Promyelocytic Leukemia

Therapeutic Agent	Major Toxicity
Tretinoin (all-*trans*-retinoic acid)	Differentiation syndrome Cytokine release syndrome Transaminitis Pseudotumor cerebri Hypertriglyceridemia Xeroderma and cheilitis
Arsenic trioxide	QT prolongation Arrhythmias Differentiation syndrome Hepatotoxicity Electrolyte abnormalities Nausea/vomiting Peripheral neuropathy
Idarubicin	Myelosuppression Cardiotoxicity (cardiomyopathy) Arrhythmias Nausea/vomiting Mucositis Transaminitis Alopecia Skin rash
Gemtuzumab ozogamicin	Myelosuppression Hepatotoxicity Veno-occlusive disease (sinusoidal obstruction syndrome) Infusion reactions (fever, chills, hypotension, hypoxia)
Hydroxyurea	Myelosuppression Cutaneous vasculitis; ulceration
Dexamethasone	Hyperglycemia Hypertension Psychiatric disturbances Insomnia Peptic ulcer Immunosuppression

PROPHYLACTIC USE OF CORTICOSTEROIDS

Differentiation and cytokine release syndrome remains an important cause of morbidity and mortality during remission

induction treatment of APL. One approach to diminish differentiation syndrome is to use corticosteroids as prophylaxis during induction. The GIMEMA APL0406 study administered a prophylactic dose of prednisone 0.5 mg/kg/d until the end of induction.[4] MD Anderson Cancer Center included methylprednisolone 50 mg/d for 5 days, followed by a rapid taper during induction.[20] The Australian APML4 study administered prednisone at 1 mg/kg/d during induction as well.[8] So far, there are no randomized clinical trials that have addressed the prophylactic use of corticosteroids. The Intergroup C9710 study did not use prophylactic corticosteroids but recommended that dexamethasone 10 mg twice per week be started promptly for typical symptoms of fever, erythematous rash, tachypnea, weight gain, and leukocytosis.[11] The UK AML 17 and S0535 studies also did not use prophylactic corticosteroids.[9,10] Dexamethasone was recommended for the treatment of cytokine release (differentiation) syndrome. The argument against the prophylactic use of corticosteroids in all patients with APL emphasizes the additional risks of hyperglycemia, gastritis and intestinal bleeding, pancreatitis, immune suppression, and antipyretic effects in neutropenic patients.

On the basis of our clinical experience, we recommend against the use of prophylactic corticosteroids and instead recommend the prompt administration of intravenous dexamethasone 10 mg every 12 hours at the first signs or symptoms of differentiation syndrome. These features include fever, tachycardia, tachypnea, hypoxia, erythematous rash, fluid retention, pulmonary infiltrates, and pleural and pericardial effusions. We continue ATRA and ATO unless the patient becomes clinically unstable.

THE NEED FOR MAINTENANCE THERAPY

The APL0406, UK AML 17, and MD Anderson Cancer Center protocols did not use maintenance therapy for patients in molecular remission at the end of consolidation.[4,9,20] The latter two studies included high-risk patients. Long-term follow-up of the GIMEMA AIDA 0493 study (ClinicalTrials.gov identifier: NCT01064557) did not demonstrate a benefit in 12-year DFS from maintenance therapy; however, this study did demonstrate a lower DFS in the high-risk group regardless of maintenance therapy.[32] The SWOG/ECOG/Cancer and Leukemia Group B (CALGB) S0521 trial (ClinicalTrials.gov identifier: NCT00492856) randomly assigned 105 patients with APL who achieved molecular remission either to maintenance or no maintenance, and after 36 months there had been no relapses in either arm.[12] On the basis of these data, we recommend against maintenance therapy if the patient achieves a complete molecular remission by reverse-transcription polymerase chain reaction (RT-PCR) at the end of consolidation. This recommendation is strongest for lower-risk patients. Other experts may continue to opt for maintenance therapy for high-risk patients.

Long-term follow-up is an important aspect of care for survivors of APL. Clinical trials have used frequent bone marrow biopsies at 3-month intervals to monitor survivors for molecular relapse; however, frequent bone marrow biopsies can be expensive, uncomfortable, and impractical. Monitoring for molecular relapse in the peripheral blood via RT-PCR of the *PML-RARA* fusion transcript is a reasonable alternative. Peripheral blood molecular assays closely correlate with bone marrow assays.[33] A median delay of approximately 1 month was observed when comparing peripheral blood minimal residual disease assays with bone marrow samples.[34] The clinical significance of this delay remains unclear but could be overcome with testing peripheral blood at shorter intervals than bone marrow. After an initial negative result, we recommend monitoring peripheral blood *PML-RARA* transcript levels by RT-PCR every 3 months for 2 years after the completion of consolidation. If the *PML-RARA* transcript level becomes positive at any time in the peripheral blood, a bone marrow biopsy should then follow to confirm molecular or morphologic relapse.

Assessment for therapy-related toxicities is also an important part of long-term monitoring for these patients (Table 3). The main toxicities of prolonged ATRA and ATO therapy include pseudotumor cerebri, photophobia, and neuropathy. Anthracyclines carry the risk of cardiomyopathy and secondary leukemia. Therapy-related myeloid neoplasms that lack the t(15;17) have been reported as second malignancies in patients with previously treated APL.[35] JOP

Authors' Disclosures of Potential Conflicts of Interest
Disclosures provided by the authors are available with this article at jop.ascopubs.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Treatment of Acute Promyelocytic Leukemia in Adults

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