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PRACTICE GUIDELINE

A Canadian consensus on the management of newly diagnosed and relapsed acute promyelocytic leukemia in adults

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ABSTRACT

The use of all-trans-retinoic acid (ATRA) and anthracyclines (with or without cytarabine) in the treatment of acute promyelocytic leukemia (APL) has dramatically changed the management and outcome of the disease over the past few decades. The addition of arsenic trioxide (ATO) in the relapsed setting—and, more recently, in reduced-chemotherapy or chemotherapy-free approaches in the first-line setting—continues to improve treatment outcomes by reducing some of the toxicities associated with anthracycline-based approaches. Despite those successes, a high rate of early death from complications of coagulopathy remains the primary cause of treatment failure before treatment begins. In addition to that pressing issue, clarity is needed about the use of ATO in the first-line setting and the role of hematopoietic stem-cell transplantation (HSCT) in the relapsed setting. The aim for the present consensus was to provide guidance to health care professionals about strategies to reduce the early death rate, information on the indications for HSCT and on the use of ATO in induction and consolidation in low-to-intermediate–risk and high-risk APL patients.

KEY WORDS

Acute promyelocytic leukemia, APL, management, supportive care, prophylaxis, infusions, arsenic trioxide, ATO, Trisenox, first-line treatment, transplantation, allogeneic transplantation, autologous transplantation

1. INTRODUCTION

Acute promyelocytic leukemia (APL) is a relatively rare form of leukemia, accounting for about 10%–15% of adults diagnosed with acute myeloid leukemia in the United States each year[1]. Cells from 92% of patients diagnosed with APL are characterized by a balanced reciprocal translocation between chromosomes 15 and 17, resulting in a fusion of the *PML* (promyelocytic leukemia) and *RARA* (retinoic acid receptor alpha) genes[2]. In most of the remaining APL cases, the variant translocations are characterized by fusions of *RARA* to other genes. Cases in which *RARA* translocations are lacking occur very rarely.

The *PML–RARA* translocation is not only a distinguishing feature of APL, it also drives the disease and is a key target for successful treatment. The presence of PML–RAR-α leads to a differentiation block at a retinoic acid–dependent stage of myeloid differentiation and also to increased self-renewal of cells at an earlier stage in differentiation. However, those defects can specifically be overcome by pharmacologic amounts of the retinoid all-trans retinoic acid (ATRA) and by arsenic trioxide (ATO), either alone or in combination[3].

Another distinguishing feature of APL is prominent coagulopathy, which is often found at presentation or shortly thereafter. Coagulopathy is associated with a high risk of hemorrhagic death, or thrombosis, or both[1]. Without early initiation of treatment, APL can be rapidly lethal. Even if definitive therapy is started early, mortality from hemorrhage (and thrombosis) occurs at a high rate during the first few days after presentation.

Since the recognition of APL as a distinct disease in 1957, several key developments have changed its prognosis from highly fatal to very curable[4]. Those developments include the discovery of the APL cell's heightened response to ATRA, to anthracyclines (with or without cytarabine) and to ATO, the adoption of risk-adapted treatments, and the recognition that immediate aggressive supportive care is required to reduce the incidence of early death from the complications of coagulopathy and thrombosis[3,5]. The use of ATRA in combination with anthracyclines (with or without cytarabine) as first-line treatment has made it possible to attain complete remission rates exceeding 90% and cure rates close to 80%[3]. In patients with low- and intermediate-risk disease, further improvements in outcome have recently been described with the use of non-chemotherapeutic approaches in

which the ATRA–ATO combination has resulted in a lower frequency of hematologic toxicities while still maintaining the high and durable response rates seen with conventional chemotherapy-based regimens[6]. Similar improvements in outcome have also been observed using reduced-chemotherapy ATO-containing approaches in high-risk APL[7].

Despite those successes, several unmet needs in APL treatment remain. The most significant challenge continues to be the high incidence of early death. In addition, although chemotherapy-based approaches have led to excellent response rates, they are associated with significant early hematologic toxicities and also with delayed long-term adverse effects, including cardiomyopathy and secondary malignancies such as therapy-related myelodysplasia and acute myeloid leukemia. In addition, for the small number of patients with relapsed APL, uncertainty remains about the best treatment options, especially the roles of autologous or allogeneic hematopoietic stem-cell transplantation (HSCT) in that setting. Finally, there is a need to improve outcomes in older patients, who might not be able to tolerate regimens based on conventional chemotherapy.

2. PURPOSE

The present review provides health care professionals with guidance about strategies to reduce the early death rate and information concerning the indications for HSCT and the use of ATO in induction and consolidation therapies for low-to-intermediate–risk and high-risk APL patients. The recommendations presented here were developed by a panel of APL experts from across Canada and focus on the treatment and management of adult patients with newly diagnosed and relapsed APL with the classical t(15;17) translocation.

3. METHODS

3.1 Identification and Selection of Studies

A systematic search of published papers in MEDLINE and of abstracts submitted to the annual meetings of the American Society of Hematology, the American Society of Clinical Oncology, and the European Hematology Association used these search terms: APL management, APL supportive, APL prophylaxis, APL infusion, ATO first-line treatment, arsenic trioxide APL, Trisenox APL, transplant, APL transplant, APL allogeneic, and APL autologous. Publications were excluded if they were published before January 2009, if they included treatment with ATO as a single agent in induction and consolidation, or if they examined the role of ATO in maintenance.

3.2 Formulation of Recommendations

After review and discussion of the evidence, the panel formulated recommendations with the aim of updating recommendations published in 2009 by the European LeukemiaNet (ELN)[8]. The panel considered both the level of evidence and the quality of the studies.

4. RECOMMENDATIONS

4.1 Question 1

How should patients with suspected APL be managed at first presentation?

Background: The high incidence of early death before and during induction treatment remains the most significant cause of treatment failure in APL[9,10]. Despite the use of ATRA therapy for almost two decades, early mortality has been reduced only modestly, as recently noted in a 2011 population-based study of the Surveillance, Epidemiology, and End Results database[11]. Contrary to reported incidence rates of early death from cooperative clinical trials (which are in the 5%–10% range)[11], recent population-based studies have shown those rates to be much higher, ranging from 17% (in a study of the Surveillance, Epidemiology, and End Results database) to 29% in a study of the Swedish Adult Acute Leukemia Registry[11–13]. Consistent with those findings, the results of a Canadian study by Paulson *et al.* in 2014 showed that the incidence of early death was 22%[14]. Factors contributing to the discrepancy between clinical trials and population-based studies might be a failure to refer patients with poor performance status (including those with cranial and pulmonary hemorrhage) to a leukemia centre in a timely manner and exclusion of such patients from clinical trials[15].

Overall, these recent studies identify a major unresolved issue in the management of an otherwise highly curable malignancy and should instruct health care providers to highlight the main cause of early death with an aim to identify treatment and management strategies that complement ATRA therapy. Given that early death occurs mainly as a result of complications from coagulopathy (bleeding and thrombosis)[11,16], which develops early and can progress rapidly, early consideration of the possibility of APL and the immediate initiation of treatment once APL is suspected (and before it is proven) is critical.

Current guidelines recommend that first-line treatment of potential complications be initiated immediately based on clinical presentation and the morphology of APL cells in an analysis of a peripheral blood smear or bone aspirate and before genetic confirmation[8,17]. Later genetic confirmation of *PML–RARA* is still mandatory, because a positive response to induction treatment with ATRA or ATO depends on the presence of the PML–RAR-α fusion protein[17].

The high risk of hemorrhagic early death in APL has prompted the authors of both the European and the North American guidelines to strongly recommend

implementation of three measures at the earliest suspicion of APL and before genetic confirmation[8,17]:

- Immediate ATRA therapy to help resolve the coagulopathy
- Aggressive replacement of cryoprecipitate, platelets, and fresh-frozen plasma
- Frequent, ongoing clinical monitoring of the patient

The ELN guidelines also highlight several factors associated with an increased likelihood of fatal hemorrhage: higher counts of white blood cells (WBCs) or peripheral blasts, abnormal levels of creatinine, poor performance status, active bleeding, hypofibrinogenemia (<100 mg/dL) or higher levels of fibrin degradation products or D-dimers in combination with an increase in prothrombin time or activated partial thromboplastin time[8]. Immediate ATRA treatment is critical because ATRA is known to rapidly reduce the biologic drivers of APL-associated coagulopathy, and therefore is likely to reduce the risk of early death from severe bleeding[8]. To accompany immediate ATRA therapy initiation, the recommendations call for aggressive and ongoing transfusions with fresh-frozen plasma, cryoprecipitate, and platelet concentrates to maintain fibrinogen levels above 1.5 g/L and platelet levels at 30–50×10^9/L[8,17]. The initial workup for coagulopathy should include, at a minimum, platelet count, prothrombin time, activated partial thromboplastin time, and fibrinogen level[8].

Patients presenting with a WBC count exceeding 10×10^9/L also have a higher risk of differentiation syndrome than do patients with a count of 10×10^9/L or fewer[8,17]. In a study by Kelaidi *et al.* examining high-risk patients in the APL 93 and APL 2000 trials, prophylactic dexamethasone was shown to reduce early induction deaths attributable to differentiation syndrome[18]. Based on that study, the ELN and U.S. National Comprehensive Cancer Network (NCCN) guidelines recommend considering prophylactic dexamethasone for patients with more than 10×10^9/L WBCs or those showing the first signs of differentiation syndrome[8,17]. The use of anticoagulant or antifibrinolytic therapy such as heparin or tranexamic acid to reduce the risk of bleeding is not recommended, and invasive procedures such as lumbar puncture and central venous catheterization are to be avoided before and during the early stages of remission induction because of the high risk of bleeding in APL[8].

Evidence: We identified only three studies that focused on supportive care (Table I). The study by Ikezoe *et al.*[21] examined the effects of recombinant human thrombomodulin on the clinical outcomes of patients with coagulopathy. Rescue from disseminated intravascular coagulation was shown to occur earlier in patients treated with recombinant human thrombomodulin than in historical control patients (log-rank $p = 0.019$). In the study by Barreto *et al.*[19], the effect of the prophylactic antifungal agent voriconazole on the incidence of differentiation syndrome in patients receiving ATRA plus chemotherapy was examined. A trend toward an increased incidence of differentiation syndrome in patients receiving voriconazole was observed, although the difference was not statistically significant because of the small sample size (hazard ratio: 1.96; 95% confidence interval: 0.65 to 5.94; $p = 0.23$). A study by Chang *et al.*[20] identified a higher WBC count (26.73 ± 6.18/μL vs. 13.03 ± 3.03/μL, $p = 0.026$) and prolonged prothrombin time (4.85 ± 0.70 s vs. 2.59 ± 0.28 s, $p = 0.002$) and activated partial thromboplastin time (3.98 ± 1.68 s vs. 0.96 ± 0.93 s, $p = 0.017$) as risk factors for bleeding in patients with APL.

Recommendations: Owing to a lack of high-level evidence on supportive care in the medical literature, the panel made no changes or new recommendations beyond those made by the ELN. The panel strongly recommends prompt institution of supportive care measures as a critical strategy to reduce the early death rate in APL (Table II). A provisional diagnosis of APL (based on clinical presentation and morphology of the leukemic cells in a blood smear or bone marrow aspirate) is routinely available before genetic confirmation. Therefore, if a patient is suspected of having APL, ATRA should be started immediately. Based on laboratory tests, cryoprecipitate, fresh-frozen plasma, and platelets should be infused immediately, with the goal of maintaining fibrinogen levels above 1.5 g/L and platelets at 30×10^9/L. To consistently maintain those target levels, the panel recommends repeat monitoring at least every 6 hours, because daily monitoring can be inadequate in the presence of ongoing consumptive coagulopathy. Referral to a leukemia centre should occur promptly. Molecular genetic confirmation of the *PML–RARA* translocation should be obtained as quickly as possible to warrant initiation of full induction therapy (per the recommendations in response to question 2). The panel also recommends administering prophylactic steroids to all patients with high-risk disease[17].

4.2 Question 2

How should ATO be used in induction and consolidation for newly diagnosed APL patients?

Background: In combination with an anthracycline, and with or without cytarabine, ATRA has been the standard backbone in induction and consolidation treatment for newly diagnosed APL patients for more than a decade. Induction therapy using such a regimen yields a complete response (CR) rate in the 90%–95% range[3]. The role of ATO became clearer after several studies showed efficacy and safety for ATO with or without ATRA in the relapsed setting[22,23]

and, more recently, in first-line induction and consolidation[6,7,24–26]. In 1998, Soignet *et al.*[22] were the first to corroborate reports from China about the efficacy of ATO in treating APL by showing that ATO is highly efficacious at inducing remission in relapsed disease. Those results were confirmed in a larger multicentre trial in 2001 by the same group, who reported a CR rate of 85%, and 18-month overall survival (OS) and relapse-free survival rates of 66% and 56% respectively in relapsed APL[23]. Those studies formed the basis for the approval of ATO for the treatment of relapsed or refractory APL in Europe,

TABLE I Clinical trial data for supportive care treatments in acute promyelocytic leukemia (APL)

Reference	*Complication and treatment*	*Pts (n)*	*Median age (years)*	*Efficacy results and safety*
Barreto *et al.,* 2012[19] (APL patients at the Mayo Clinic during 2000–2011)				
	ATRA plus chemotherapy plus voriconazole	31	56 (range: 18–80)	Only body mass index differed between study arms [higher in patients receiving voriconazole (HR: 1.04; 95% CI: 1.001 to 1.078; p=0.0427)]. The overall incidence of DS was 35% (n=16), with patients receiving voriconazole being more likely to experience DS (HR: 2.31; 95% CI: 0.78 to 6.874; p=0.1308). After adjusting for body mass index, patients receiving voriconazole had a higher tendency to experience DS [especially severe DS (13 of 16 cases, 81%)]; however, because of small numbers, the trend was not statistically significant (HR: 1.96; 95% CI: 0.65 to 5.94; p=0.23). Admission to the intensive care unit was needed for management of severe DS in 7 patients (44%), 5 of whom had received voriconazole. Mean length of those stays was 4 days (range: 1–7 days), with no patients requiring intubation, but 29% receiving vasopressor support. No deaths were attributable to DS.
	ATRA plus chemotherapy (no fungal prophylaxis)	15		
Chang *et al.,* 2012[20]				
	Correlation of clinical bleeding events with lab coagulation profiles in APL	116	—	Overt DIC occurred in 77.6% of patients. In patients with bleeding, • WBC count was higher (p=0.026): 26.73±6.18/μL vs. 13.03±3.03/μL. • prothrombin time was prolonged (p=0.002): 4.85±0.70 s vs. 2.59±0.28 s. (Patients with a prothrombin time of 5 s or greater had a relative risk of 6.14 for bleeding.) • activated partial thromboplastin time was prolonged (p=0.017): 3.98±1.68 s vs. 0.96±0.93 s. Fibrinogen levels, platelet counts, and leukemia cell percentages were nonsignificantly different between bleeding and non-bleeding patients. Before initiation of ATRA, 7 patients experienced severe bleeding.
Ikezoe *et al.,* 2012[21]				
	DIC caused by APL; treated with rTM plus ATRA plus chemotherapy versus historical controls	9	—	Intracranial vascular incidents developed in 2 control patients. No bleeding-related mortality was noted in patients treated with rTM. Rescue from DIC occurred earlier in patients treated with rTM than in historical controls (log-rank p=0.019).
		8	—	

Pts = patients; ATRA = all-trans-retinoic acid; HR = hazard ratio; CI = confidence interval; DS = differentiation syndrome; DIC = disseminated intravascular coagulation; WBC = white blood cell; rTM = recombinant human thrombomodulin.

TABLE II Recommendations for supportive care in newly diagnosed or suspected acute promyelocytic leukemia (APL)

	Supportive care	*Implementation*	*Target*
1	Frequent, aggressive transfusions	Cryoprecipitate Platelets Fresh-frozen plasma	Fibrinogen levels should be greater than 1.5 g/L Platelet counts should be at least 30×10^9/L
2	Therapy with ATRA	Should be started immediately	Should be administered in divided doses Purpose is to treat coagulopathy and to initiate induction
3	Frequent monitoring	Immediate	Every 6 hours

ATRA = all-trans-retinoic acid.

the United States, and Canada. Several subsequent studies demonstrated similar results, with CR rates of 80%–100% and 2-year OS rates ranging from 56% to 82%[27–29].

Overall, ATO has been shown to be well tolerated, with most patients experiencing only mild toxic effects. In some patients, ATO is associated with differentiation syndrome and QTc prolongation, both of which are effectively counteracted when specific preventive measures are implemented[30]. The published studies also show that hematologic toxicity with ATO is lower than it is with chemotherapeutic regimens for re-induction of remission[3].

Currently, APL treatment is based on risk stratification by WBC count[17]. Patients with a count of 10×10^9/L or less are classified as low risk (platelets > 40×10^9/L) or intermediate risk (platelets $\leq 40\times10^9$/L) for relapse, and patients with a count exceeding 10×10^9/L are considered at high risk of relapse.

In 2009 and 2011 respectively, the ELN and the NCCN recommended 1 cycle of ATRA plus anthracycline-based chemotherapy (idarubicin alone, or daunorubicin plus cytarabine) as the standard first-line induction treatment for newly diagnosed patients with low-to-intermediate–risk and high-risk APL[8,17]. In 2013, the NCCN guidelines were updated to include ATO plus ATRA (without chemotherapy) as an option for first-line induction and consolidation treatment in newly diagnosed patients with low-to-intermediate–risk APL[17]. Consolidation treatment after induction has been more controversial and varied. However, the ELN recommends ATRA plus 2–3 cycles of anthracycline-based chemotherapy as the standard approach for consolidation therapy, and at least 1 dose of cytarabine is recommended in high-risk patients less than 60 years of age[8]. For consolidation in high-risk patients, the NCCN recommends three options: ATO in combination with ATRA and daunorubicin, daunorubicin plus cytarabine with 5 doses of intrathecal chemotherapy, or ATRA in combination with idarubicin, cytarabine, and mitoxantrone. For low-to-intermediate–risk patients, the NCCN recommends four options: ATO plus ATRA, ATRA in combination with idarubicin and mitoxantrone, daunorubicin plus cytarabine, and ATO in combination with ATRA and daunorubicin.

Evidence: Our literature search revealed nine studies that examined the efficacy and safety of ATO in combination with chemotherapy in first-line treatment, and another five studies that examined the efficacy and safety of the chemotherapy-free approach of ATO plus ATRA in first-line treatment of newly diagnosed APL patients (Table III).

ATO Plus ATRA Plus Chemotherapy: Nine studies investigated the role of ATO in combination with ATRA and chemotherapy regimens (idarubicin–cytarabine–daunorubicin) in induction, or consolidation, or both (Table III). Rates of CR ranged from 84.7% to 97%, and rates of disease-free survival ranged from 72% (median follow-up: 16.5 months) to 97.4% at 5 years[7,24,25,31–36]. The OS rates ranged from 86% at 3 years to 91.7% at 5 years[7,24,25,31–36]. One study that combined ATO, ATRA, and idarubicin in induction and ATO and ATRA in consolidation demonstrated equally favourable outcomes in 2-year OS rates, regardless of Sanz risk category[7]. The reported early death rates ranged from 5.9% to 11.3%[31,34,36]. Differentiation syndrome was reported at frequencies ranging from 1.1% to 18%[31,34], and one study reported transient QTc prolongation in 20% of patients[34].

ATO Plus ATRA: One phase III randomized clinical trial compared the efficacy and safety of ATO plus ATRA with those of ATRA plus chemotherapy in newly diagnosed patients with low-to-intermediate–risk APL (Table III)[6]. Patients at low or intermediate risk received either ATO plus ATRA (n = 77) for induction and consolidation, or ATRA plus idarubicin for induction (n = 79), followed by 3 cycles of ATRA plus chemotherapy for consolidation, and low-dose chemotherapy plus ATRA for maintenance. Rates of CR in the ATO plus ATRA group and the ATRA plus chemotherapy group were 100% and 95% respectively (p = 0.12). The 2-year event-free survival (EFS) rates were 97.1% in the ATO plus ATRA group and 86% in the ATRA plus chemotherapy group (p = 0.02, Table III).

TABLE III Clinical trial data for first-line arsenic trioxide (ATO) treatments in acute promyelocytic leukemia (APL)

Regimen type	*Reference*	*Study*		*Treatment phases*	*Pts* (n)	*Median age (years)*	*Risk (%)*	*Response (%)*	*Survival (%)*			*CIR (%)*	*Safety and other efficacy*
		Type	*Arm or arms*						*Event-free*	*Disease-free*	*Overall*		
ATO plus ATRA, plus chemotherapy													
	Hu *et al.,* 2009[31]												
	—		ATRA plus ATO induction plus chemotherapy consolidation	Induction: ATRA plus ATO daily until CR Consolidation: 3 courses of daunorubicin plus cytarabine Maintenance: 5 cycles of sequential ATRA, ATO, and low-dose chemotherapy	85	—	—	CR: 94.1 Median time to CR: 27 days Median follow-up of patients in CR: 70 months	5-Year: 89.2±3.4	5-Year RFS in CR: 94.8±2.5	All 5-year: 91.7±3.0 5-Year reached CR: 97.4±1.8	—	Early deaths (within 15 days of induction): 5 pts (intracranial hemorrhage: 3 pts; retinoic acid syndrome: 1 pt; disseminated intravascular coagulation: 1 pt)
	Gore *et al.,* 2010[25]												
	Phase II		ATO consolidation	Induction: ATRA plus daunorubicin Consolidation: cytarabine plus daunorubicin plus ATO Maintenance: Risk-stratified therapies; all received ATRA	45	50 (range: 19–70)	Sanz risk class: Low, 36 Intermediate, 29 High, 32	Induction: CR, 91.1; MR, 34 of 40 pts Consolidation: MR, 36 of 37 pts	3-Year: 76±7	3-Year: 88.7±6	3-Year: 88±5	—	Median follow-up: 2.7 years During induction, 4 pts died
	Powell *et al.,* 2010[24]												
	Phase III		No ATO consolidation	Induction: ATRA, cytarabine, and daunorubicin Consolidation: 2 courses of ATRA plus daunorubicin	237	—	—	90	3-Year: 63	3-Year: 70	3-Year: 81	—	—
			With ATO consolidation	Induction: ATRA, cytarabine, and daunorubicin Consolidation: 2 courses of ATRA plus daunorubicin plus ATO	244	—	—	90	3-Year: 80 (p<0.0001)	3-Year: 90 (p<0.0001)	3-Year: 86 (p=0.059)	—	—

TABLE III Continued

Regimen type	Reference	Study		Treatment phases	Pts (n)	Median age (years)	Risk (%)	Response (%)	Survival (%)			CIR (%)	Safety and other efficacy
		Type	Arm or arms						Event-free	Disease-free	Overall		
ATO plus ATRA, plus chemotherapy (continued)													
	Liu *et al.*, 2011[32]												
	Single-centre 1988–2009	ATRA with or without ATO, plus chemotherapy		ATRA or ATO (or both) with anthracycline-based induction; after 3 courses of consolidation chemotherapy pts (*n*=279) received 2 years of maintenance	340	—	—	CR: 84.7	—	5-Year RFS: 83.7±2.6	5-Year: 89.0±2.4	—	Median follow-up: 49 months (range: 6–255 months) During induction, 50 pts died
	Huang *et al.*, 2012[33]												
	—	ATO consolidation		ATO daily, two 21-day courses	139	42 (range: 18–65)	—	CR: 91.2	5-Year: 75 (p<0.001)	—	5-Year: 83 (p=0.002)	—	WHO grade 3/4 adverse events (low: 74.82%; high: 25.18%; p≤0.001): neutropenia, 1.4%; infection, 0.7%; nausea/vomiting, 27.3%
		High-dose cytarabine		High-dose cytarabine (2 courses) plus daunorubicin plus cytarabine (2 courses)	132	37 (range: 17–65)	—		5-Year: 54	—	5-Year: 71	—	WHO grade 3/4 adverse events (low: 77.27%; high: 22.73%): neutropenia, 94.7%; infection, 87.1%; nausea/vomiting, 58.3%
	Iland *et al.*, 2012[7]												
	Phase II	ATRA plus idarubicin plus ATO		Induction: ATRA plus idarubicin plus ATO, plus prednisone and hemostatic support Consolidation 1 and 2: ATRA plus ATO Maintenance: ATRA plus methotrexate plus 6-mercaptopurine	124	44 (range: 3–78)	Low: 26 Intermediate: 54 High: 20	hCR: 95	2-Year failure-free survival: 88.1	2-Year: 97.5	2-Year: 93.2	2-Year freedom from relapse: 97.5	—

TABLE III Continued

Regimen type	Reference	Study: Type	Study: Arm or arms	Treatment phases	Pts (n)	Median age (years)	Risk (%)	Response (%)	Survival (%): Event-free	Survival (%): Disease-free	Survival (%): Overall	CIR (%)	Safety and other efficacy
ATO plus ATRA, plus chemotherapy (continued)													
	Menon *et al.*, 2012[34]												
	—		ATO plus ATRA plus daunorubicin	Phase 1: ATO Phase 2: ATRA plus daunorubicin Phase 3: ATRA	106	30	Sanz risk class: I: 16 II: 39 III: 45	After phase I: CyR: 71; MR: 66.6 After phase II: MR: 96	—	RFS: 72	86.2	8.4	Median follow-up: 16.5 months Safety: early death, 11.3% differentiation syndrome, 18%; transient QT prolongation, 20%; grade II peripheral neuropathy, 5%
	Ades *et al.*, 2013[35]												
	Phase III	A1	(standard)	Induction: ATRA until CR, plus idarubicin, plus cytarabine First consolidation: same chemotherapy course Second consolidation: idarubicin plus cytarabine Maintenance: intermittent ATRA and continuous 6-mercaptopurine plus methotrexate	117	<70	WBCs: $<10\times10^9$/L	CR: 97	2-Year: 95.5 (p=NS)	—	2-Year: 96.6 (p=NS)	2-Year: 4 pts	Median duration in days (A1 vs. A2 vs. A3) of neutropenia: first consolidation, 24 vs. 24 vs. 17; second consolidation, 23 vs. 19 vs. 13; of thrombocytopenia: first consolidation, 25 vs. 23 vs. 20; second consolidation,
			A2	Same as A1, but cytarabine replaced by ATO in both consolidation courses	118				2-Year: 96.5	—	96.5	2-Year: 0 pts	27 vs. 18 vs. 18; of hospitalization: first consolidation,
			A3	Same as A1, but cytarabine replaced by ATRA in both consolidation courses	117				2-Year: 95.6	—	97.4	2-Year: 5 pts	32 vs. 32 vs. 18; second consolidation, 29 vs. 30 vs. 15

TABLE III Continued

Regimen type	Reference	Study		Treatment phases	Pts (n)	Median age (years)	Risk (%)	Response (%)	Survival (%)			CIR (%)	Safety and other efficacy
		Type	Arm or arms						Event-free	Disease-free	Overall		
ATO plus ATRA, plus chemotherapy (continued)													
	Lou *et al.*, 2013[36]												
	Retro-spec-tive	ATO plus ATRA induction and maintenance, plus chemotherapy consolidation		ATO plus ATRA induction, 3 courses of consolidation chemotherapy, and 2-year sequential maintenance with ATO and ATRA	137	—	(A) Low or intermediate: 92 pts (B) High: 45 pts	CR: 93.4	—	5-year RFS: A: 98.7 vs. B: 87.9 (p=0.016)	5-Year: A: 98.9 vs. B: 97.4 (p=0.53)	4	Median follow-up: 35 months Early death: 9 pts (6.6%)
ATO plus ATRA, chemotherapy-free													
	Dai *et al.*, 2009[37]												
	—	ATRA plus ATO		ATRA plus ATO for induction and consolidation	90	—	—	CR: 93.3 Time to CR: 31 days	—	3-Year RFS: 92.9±3.2	—	—	High incidence of hepatotoxicity during remission induction
		ATRA-based		ATRA-based induction	72			Time to CR: 39 days	—	3-Year RFS: 72.4±7.6	—	—	—
	Arora *et al.*, 2010[38]												
	—	ATRA plus ATO		Induction: ATRA plus ATO until hCR Consolidation: ATRA for 6 weeks plus ATO 5 days per week (all patients had 3 consolidation therapies, each after a gap of 1 month) Maintenance: ATRA, 6-mercaptopurine, and methotrexate for 2 years	25	33 (range: 13–48)	—	hCR: 92 Median time to hCR: 35 days (range: 15–49 days)	—	—	—	—	Coagulopathy: 22 (85%) ATRA syndrome: 9 (36%) QTc prolongation: 2 During therapy, 4 pts died (2 during induction, 1 after successful induction, 1 during maintenance) Median follow-up (remaining 18 pts): 17 months (range: 3–57 months)

TABLE III Continued

Regimen type	Reference	Study		Treatment phases	Pts (n)	Median age (years)	Risk (%)	Response (%)	Survival (%)			CIR (%)	Safety and other efficacy
		Type	Arm or arms						Event-free	Disease-free	Overall		
ATO plus ATRA, chemotherapy-free (continued)													
	Ravandi *et al.*, 2010[39]												
		Phase II	ATRA plus ATO with or without GO	ATRA plus ATO beginning on day 10 (cohort 1, *n*=47) or on day 1 (cohort 2, *n*=57) of ATRA; if high-risk, pts were given GO on day 1 in both cohorts	104	46 (range: 14–81)	Low: 70 High: 30	CR: 98	5-Year: 86 Median follow-up: 115 weeks (range: 4–397 weeks)	—	5-Year: 88	5	94 Pts still alive
	Pei *et al.*, 2012[40]												
		—	ATRA plus ATO	ATRA plus ATO induction and consolidation	73	—	—	CR: 94.5 Time to CR: 27 days (range: 21–43 days)	—	—	—	—	Median follow-up: 52 months (range: 35–74 months) Early death: 4 pts (5.5%)
	Lo-Coco *et al.*, 2013[6]												
		Phase III	Arm A: ATRA plus ATO	ATO plus ATRA until CR, then ATO 5 days per week, 4 weeks on, 4 weeks off, for a total of 4 courses and ATRA 2 weeks on, 2 weeks off for a total of 7 courses	75	44.6 (range: 19.1–70.2)	WBCS: $\leq 10\times10^9$/L	CR: 100 (p=0.12)	2-Year: 97 Difference: 11 95% CI: 2 to 22 Noninferior: p<0.001 Superior: p=0.02	2-Year: 97 (p=0.11)	2-Year: 99 (p=0.02)	2-Year: 1 (p= 0.24)	Median follow-up: 34.4 months Grade 3/4 neutropenia for more than 15 days was significantly more frequent in arm A than in arm B Episodes of fever or infection: 26 pts (p<0.001) Grade 3/4 hepatic toxicity: 63% (p<0.001) differentiation syndrome: 19% (p=0.62) Leukocytosis: 47% (p=0.007) QTc prolongation: 16% (p<0.001)

TABLE III Continued

Regimen type	*Reference*	*Study*		*Treatment phases*	*Pts* (n)	*Median age (years)*	*Risk (%)*	*Response (%)*	*Survival (%)*			*CIR (%)*	*Safety and other efficacy*
		Type	*Arm or arms*						*Event-free*	*Disease-free*	*Overall*		
ATO plus ATRA, chemotherapy-free (continued)													
			Arm B: ATRA plus idarubicin	Standard ATRA, plus idarubicin induction followed by 3 cycles of anthracycline-based plus ATRA consolidation and low-dose chemotherapy and ATRA for maintenance	79	46.6 (range: 18.7–70.2)	WBCS: $\leq 10\times10^9$/L	CR: 95	2-Year: 86	2-Year: 90	2-Year: 91	2 Year: 6	Episodes of fever or infection: 59 Grade 3/4 hepatic toxicity: 6% Differentiation syndrome: 16% Leukocytosis: 24% QTc prolongation: 0%

Pts = patients; CIR = cumulative incidence of relapse; ATRA = all-trans retinoic acid; CR = complete response; RFS = relapse-free survival; WHO = World Health Organization; HCR = hematologic complete response; CYR = cytogenetic remission; MR = molecular response; WBCS = white blood cells; NS = nonsignificant; CI = confidence interval; GO = gemtuzumab ozogamicin.

Patients in the ATO plus ATRA group experienced more QTc prolongation (16% vs. 0%, $p < 0.001$), more hepatic toxicity (63% vs. 6%, $p < 0.001$), and more hyperleukocytosis (47% vs. 24%, $p = 0.007$).

Four other studies examined the efficacy and safety of ATO plus ATRA as induction and consolidation therapy (Table III). The CR rate ranged from 92% to 98%[37–40], with an early death rate of 5.5% reported in one study[40] and an 8% induction failure rate because of death reported in another[38]. The 5-year OS rates ranged from 83% to 98.9%[33,36,39,41]. One study reported a 3-year disease-free survival rate of 92.9%[37], and one study reported a 5-year EFS rate of 86%[39].

Recommendations: The panel recommends ATO plus ATRA as induction and consolidation treatment for untreated, low-to-intermediate–risk APL patients. This recommendation is based on the results of the randomized phase III study by Lo-Coco *et al.*[6], which showed that this combination was noninferior to the AIDA regimen (ATRA plus idarubicin). The study also showed that ATO plus ATRA was associated with less hematologic toxicity and infection[6]. For high-risk patients, the panel recommends induction with combination chemotherapy consisting of idarubicin, ATRA, and ATO, followed by consolidation with ATO and ATRA, as used in the phase II study reported by Iland *et al.*[7].

4.3 Question 3

What is the role of HSCT in the treatment of relapsed APL?

Background: Although some evidence suggests that treatment intensification with HSCT can improve patient outcomes after ATO-induced second remission[42], the best consolidation treatment in that setting remains unknown[8]. The selection of the best treatment option (HSCT or chemotherapy) in second CR after ATO—and also the choice between allogeneic and autologous HSCT—depends on several factors, including molecular status at second complete response, duration of first remission, age, and donor availability[8]. Compared with allogeneic HSCT, autologous HSCT is associated with a lower risk of transplantation-related morbidity and mortality and might be an appropriate treatment choice for patients with a second remission who do not have minimal residual disease detectable by polymerase chain reaction (PCR) at the time of collection of hematopoietic stem cells. Compared with autologous HSCT, allogeneic HSCT is associated with a greater risk of transplantation-related death. However, because allogeneic HSCT has a strong anti-leukemic effect, it could be considered for patients who have failed to achieve a second molecular remission or for those with a very short first CR duration.

For patients with relapsed APL, the NCCN guidelines recommend ATO plus ATRA for induction of remission or for patients who fail to achieve molecular remission

after completion of consolidation treatment after relapse[17]. After a morphologic remission, patients should be evaluated for *PML–RARA* status by PCR and treated with one of the following options:

- Autologous HSCT (if PCR-negative)
- Further courses of ATO (if PCR-negative and not suitable for HSCT)
- Allogeneic HSCT (if PCR-positive)
- Enrolment in a clinical trial

For patients who fail to reach a morphologic remission, the NCCN recommends allogeneic HSCT or enrolment in a suitable clinical trial. Recommendations by the ELN are consistent with those of the NCCN[8].

Evidence: Nine studies examined the role of HSCT in consolidation treatment of APL patients after first relapse (Table IV). Six of the studies examined the role of autologous or allogeneic HSCT after remission induction with chemotherapy, cytarabine, or ATO, with or without ATRA. Yanada *et al.* reported a 5-year OS rate of 77% in patients receiving autologous HSCT after a median follow-up of 4.9 years[43]. In their respective studies, Yanada *et al.,* Shepard *et al.*[47], and Ferrara *et al.*[48] reported relapse rates of 8.5%, 25%, and 23% in patients treated with autologous HSCT. A study by Thirugnanam *et al.*[49] showed a higher 5-year EFS rate in patients treated with autologous HSCT than in those receiving only ATO with or without ATRA (83.33% vs. 34.45%, $p = 0.001$). Ramadan *et al.*[46] examined the role of allogeneic HSCT in second remission and beyond, reporting a 4-year OS rate of 62% when HSCT was performed in the second CR and 31% in patients transplanted beyond the second CR ($p = 0.05$). A study by Linker *et al.* showed a 5-year disease-free survival rate of 67% after a median follow-up of 8.2 years in patients receiving two-step autologous HSCT[50].

Three studies compared clinical outcomes in patients treated with autologous or allogeneic HSCT and in those who did not receive HSCT. The Fujita *et al.*[44] study compared outcomes in patients receiving autologous HSCT, allogeneic HSCT, and no HSCT. The 5-year OS and EFS rates were 83.3% and 41.7% respectively in the autologous-HSCT group, 76.2% and 71.1% in the allogeneic-HSCT group, and 77.4% and 50.7% in the non-HSCT group. In a retrospective study, Pemmaraju *et al.*[45] demonstrated 7-year OS rates of 85.7%, 49.4%, and 40% in patients treated with autologous HSCT, allogeneic HSCT, and chemotherapy respectively ($p = 0.48$). In a study by Holter Chakrabarty *et al.,* the 5-year OS rate was higher for patients who received autologous HSCT than for those who underwent allogeneic HSCT (75% vs. 54%, $p = 0.002$)[51]. The same study also showed a numerically higher 5-year disease-free survival rate for patients who underwent autologous transplantation (63% vs. 50%, $p = 0.10$).

Recommendations: The panel recommends consolidation treatment options consistent with those stated in the NCCN guideline: autologous HSCT for patients who achieve molecular remission after ATO-induced second CR, with allogeneic HSCT reserved for patients with persistent disease by molecular monitoring (PCR-positive). Patients who achieve PCR-positive remissions, but who are not suitable for HSCT, should be treated with up to 6 cycles of ATO for consolidation treatment. The panel recommends consideration of allogeneic HSCT or enrolment in clinical trials for patients who do not achieve remission.

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6. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to declare.

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TABLE IV Clinical trial data for hematopoietic stem-cell transplantation (HSCT) in acute promyelocytic leukemia (APL)

Reference	*Study*		*Treatment description*	*Pts* (n)	*Median age*	*Risk* (%)	*Response* (%)	*Survival* (%)			CIR (%)	*Safety and other efficacy*
	Type	*Arm or arms*						*Event-free*	*Disease-free*	*Overall*		
Yanada *et al.*, 2013[43]												
	Phase II	ATO induction plus auto-HSCT	ATO induction and consolidation, peripheral blood stem cell harvest after high-dose cytarabine, and auto-HSCT	35	46 (range: 20–64)	—	CR: 81 after induction	5-Year: 65	—	5-Year: 77	3 Pts	Median follow-up: 4.9 years Transplant-related mortality: 0%
Fujita *et al.*, 2013[44]												
	Retro-spec-tive	Auto-HSCT	Auto-HSCT after CR2[a]	6	44 (range: 27–60)	—	—	5-Year: 41.7	—	5-Year: 83.3	5-Year: 58.3	Transplant-related mortality: 0%
		Allo-HSCT	Allo-HSCT after CR2[a]	21	36 (range: 22–59)	—	—	5-Year: 71.1	—	5-Year: 76.2	5-year: 9.8	Transplant-related mortality: 19%
		Non-HSCT	Various regimens after CR2[a]	30	53 (range: 16–72)	—	—	5-Year: 45.4	—	5-Year: 75.3	5-Year: 51.0	Among older patients (age ≥40 years), 5-year overall survival was significantly better in the non-HSCT group than in the HSCT group (78.0% vs. 40.5%, p=0.04)
Pemmaraju *et al.*, 2013[45]												
	Retro-spec-tive	Auto-HSCT	Retrospective analysis of outcomes for pts with relapsed APL treated at one institution during 1980–2010; 3 patients received both auto- and allo-HSCT	10	36 (range: 13–50)	—	CR: 100 at time of HSCT	7-Year: 68.6 (p=0.45)	—	7-Year: 85.7 (p=0.48)	—	Median follow-up: 74 months (range: 26–135 months) 1-Year transplant-related mortality: 10%
		Allo-HSCT		17	31 (range: 16–58)	—	CR: 71 at time of HSCT	7-Year: 40.6	—	7-Year: 49.4	—	Median follow-up: 118 months (range: 28–284 months) 1-Year transplant-related mortality: 29%
		Chemotherapy		16	44 (range: 24–79)	—	—	—	—	7-Year: 40	—	Median follow-up: 122 months (range: 32–216 months)

TABLE IV Continued

Reference	Study		Treatment description	Pts (n)	Median age (years)	Risk (%)	Response (%)	Survival (%)			CIR (%)	Safety and other efficacy
	Type	Arm or arms						Event-free	Disease-free	Overall		
Ramadan *et al.*, 2012[46]												
—	Allo-HSCT		Allo-HSCT for pts in CR2 (n=15) or CR3+ (n=16)	31	39		—	—	—	4-Year for CR2 vs. CR3+: 62 vs. 31 (p=0.05)	4-Year for CR2 vs. CR3+: 32 vs. 44 (p=0.37)	Median follow-up: 55 months (range: 4–100 months) 4-Year overall survival (RT-PCR-negative vs. -positive): 64% vs. 27% (p=0.03) 4-Year CIR (RT-PCR-negative vs. -positive): 30% vs. 47% (p=0.30) Transplant-related mortality: 19.6%
Shepard *et al.*, 2011[47]												
—	ATO, then auto-HSCT		ATO re-induction after relapse from CR1 [single-agent ATO (n=15), ATO plus intrathecal therapy (n=2), ATO plus chemotherapy (n=4)] followed by auto-HSCT for pts with relapsed APL	21	31 (range: 1–54)	WBCs >10× 10^9/L (n=4); Platelets <40× 10^9/L (n=13)	CR2 after ATO: 95	—	Median: 4 years (range: 0.34–10.8)	—	25 relapsed; median time to relapse: 384 days (range: 126–513 days)	All first-line induction had ATRA, 85% received maintenance after consolidation in CR1. Safety of ATO: differentiation syndrome (n=3); prolonged QTc (n=3); grade 3 infection (n=2); grade 2 or 3 transaminitis (n=2) Safety of auto-HSCT: grade 3 mucositis (n=4)
Ferrara *et al.*, 2010[48]												
—	Auto-HSCT		Auto-HSCT after second MR; no maintenance or consolidation therapy given after auto-HSCT	13	39 (range: 18–69)	—	—	—	—	—	11 pts still alive: 10 in MR; 1 in CR3	Median follow-up: 25 months 2 Pts relapsed after auto-HSCT and died in refractory disease; 1 pt relapsed, but achieved CR3 and was awaiting allo-HSCT
Thirugnanam *et al.*, 2009[49]												
Single-centre	Auto-HSCT		After MR2 with ATO-based therapy, pts opted to undergo auto-HSCT	14	For all 37 pts: 34 (range:	Median duration of CR1: 20.3 months	MR2: 89 after induction and consolidation	5-Year: 83.33±15.21 (p=0.001)	—	5-Year: 100.00 ±0.00	7.1	Median follow-up: 32 months Since January 2000, 37 patients with relapsed APL were treated at the centre

TABLE IV Continued

Reference	Study		Treatment description	Pts (n)	Median age (years)	Risk (%)	Response (%)	Survival (%)			CIR (%)	Safety and other efficacy
	Type	Arm or arms						Event-free	Disease-free	Overall		
Thirugnanam *et al.* (continued)												
	Single-centre	No HSCT (ATO alone or ATO plus ATRA)	After MR2 with ATO-based therapy, pts received monthly cycles of ATO as a single agent (n=13) or ATO plus ATRA (n=6) for 6 months	19	6–57)			5-Year: 34.45±11.24	—	5-Year: 38.50 ±11.68	63.2	
Linker *et al.*, 2009[50]												
	—	Two-step auto-HSCT for pts with AML in CR2	Step 1: Consolidation (cytarabine plus etoposide) Step 2: Auto-HSCT with prep regimen of oral busulfan followed by etoposide	50 total (12 FAB M3)	—	—	—	—	5-Year APL vs. non-APL: 67 vs. 16 (p=0.01)	—	—	Median follow-up: 8.2 years (range: 7.2–9.9 years)
Chakrabarty *et al.*, 2014[51]												
	—	Auto-HSCT	Patients in CR2 received either auto- or allo-HSCT during 1995–2006	62	—	—	—	—	5-year: 63 (p=0.10)	5-Year: 75 (p=0.0002)	—	Median follow-up: 115 months in pts who had allo-HSCT and 72 months in pts who had auto-HSCT 3-Year transplant-related mortality: 2% Multivariate analysis: DFS was worse after allogeneic HSCT (HR: 1.88; 95% CI: 1.16 to 3.06; p=0.011) and for those >40 years of age (HR: 2.30; 95% CI: 1.44 to 3.67; p=0.0005); OS was worse after allogeneic HSCT (HR: 2.66; 95% CI: 1.52 to 4.65; p=0.0006) and for those >40 years of age (HR: 3.29; 95% CI: 1.95 to 5.54; p<0.001) and for those with a CR <12 months (HR: 1.56; 95% CI: 1.07 to 2.26; p=0.021) 3-Year transplant-related mortality: 30%
		Allo-HSCT		232	—	—	—	—	5-year: 50	5-year: 54	—	

[a] In the Japan Adult Leukemia Study Group APL97 study[44].

Pts = patients; CIR = cumulative incidence of relapse; ATO = arsenic trioxide; auto = autologous; CR[1,2,3] = complete response (1st, 2nd,3rd); allo = allogeneic; WBCs = white blood cells; ATRA = all-trans retinoic acid; MR[2] = molecular remission [2nd]; AML = acute myeloid leukemia; FAB = French–American–British classification; DFS = disease-free survival; HR = hazard ratio; CI = confidence interval; OS = overall survival.

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