

Review

Treatment of Acute Promyelocytic Leukemia

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Contents

*Molecular Biology
Induction Therapy
Consolidation Therapy
Maintenance Therapy
Monitoring
Relapse
Special Considerations
Future Perspectives
References*

Acute promyelocytic leukemia (APL) makes up 10-15% of all acute myeloid leukemia cases (1). It is estimated that there are 600 to 800 cases diagnosed in the United States each year (2,3). APL constitutes a medical emergency, with mortality rates, without treatment, reaching as high as 50%, within one month due to hemorrhagic complications (4-9). The associated bleeding diathesis is primarily due to fibrinolysis and disseminated intravascular coagulation (10, 11). This startling mortality rate is what originally identified APL as a distinct subtype of acute myeloid leukemia in 1957 by Hillestad (1, 2).

APL may be treated based on a presumptive diagnosis, which can be made by review of the peripheral blood smear alone (13, 14).

APL, treated with conventional chemotherapy and supportive measures, is associated with a 30-40% cure rate (2, 6, 15, 16). However, a relatively recent therapeutic paradigm shift using all-trans retinoic acid (ATRA) and

Arsenic Trioxide (ATO) has resulted in complete remission rates approaching 90% (17-19). Predictive models have highlighted low and high-risk groups. ATO has proven to be beneficial in high-risk groups and in front-line treatment.

Molecular Biology

A reciprocal chromosomal translocation affects the long arm of chromosomes 17 and 15 at the site of the retinoic acid receptor alpha (*RARA*) gene and promyelocyte (*PML*) gene, respectively, resulting in a *PML-RARA* fusion gene in 95% of APL cases (20-23). The resulting fusion protein tightly associates with the nuclear co-repressor/histone deacetylase complex which deacetylates histones, resulting in a closed chromatin conformation preventing transcription, thus halting differentiation and myeloid cell maturation (14). Four variations of translocations that replace the *PML* gene have been reported including PLZF, NPM, NuMA, and STAT5B. Each of these variations makes up fewer than 5% of all cases and results in different responses to treatment with ATRA, as outlined in Table I (24-30).

Retinol (vitamin A) derivatives and retinoids are involved in differentiation and cell maturation. These compounds have specific affinity for the *RAR* α receptors. In 1986, and for the first time, ATRA was used as primary treatment for APL (31). This was an unprecedented moment in the history of cancer therapy as it shattered the old dogma that cancer is an irreversible condition (32). Surprisingly, this discovery preceded the knowledge of the presence of t(15;17) and its effect on the *RAR* that was not unraveled until the early 1990s (22, 23, 32, 33).

ATO has been an established therapy for leukemia since the latter period of the 19th century (34-36). In 1992, Chinese researches evaluated its use in APL (37). The mechanism of action of ATO seems to be dose-dependent, resulting in terminal differentiation of promyelocytic cells at low concentrations, and apoptosis cells at high concentrations (38, 39). Furthermore, ATO has other mechanisms of action that include an increase in superoxide radicals and inhibition of NF- κ B (40).

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Table I. *Molecular Biology of Acute Promyelocytic Leukemia.*

Fusion	Translocation	Percentage	Response to ATRA (Ref)
Promyelocytic leukemia gene + <i>RARA</i>	t(15;17)	92%	Responsive (118)
Promyelocytic leukemia zinc finger gene + <i>RARA</i>	t(11;17)(q23;q21.1)	~1%	Refractory (119)
Nucleophosmin gene + <i>RARA</i>	t(5;17)(q35;q21.1)	<0.5%	Responsive (118)
Nuclear matrix-mitotic apparatus protein gene + <i>RARA</i>	t(11;17)(q13;q21.1)	<0.1%	Responsive (120)
<i>BCL6</i> Corepressor gene + <i>RARA</i>	t(X;17)(q11;q21.1)	<0.1%	Responsive (121)*
Signal transducer and activator of transcription 5B + <i>RARA</i> & chromosome 17 del	<i>STAT5B-RARA</i>	<0.1%	Resistant (110)

RARA: Retinoic acid receptor- α gene; ATRA: All-trans retinoic acid; *Clinically responsive although with several episodes.

Induction Therapy

Historically, the treatment of patients newly-diagnosed with APL consisted of chemotherapy regimens similar to those used for the treatment of AML, with resulting complete remission (CR) rates of 30-40% (2, 6, 15, 16). These regimens included an anthracycline with or without cytarabine. One randomized trial did not demonstrate a statistically significant difference between the two regimens with regard to CR rates, and the decision to use an anthracycline alone or in combination with cytarabine for induction therapy remains controversial (41). An increase in relapse rate was noted when cytarabine was excluded from induction and consolidation therapy (41). Furthermore, there have been no head-to-head, prospective trials comparing the outcomes of different anthracycline agents

Two randomized trials comparing the efficacy of ATRA with chemotherapy *versus* chemotherapy-alone have shown similar CR rates, but the relapse rates were higher in the chemotherapy-alone group (41-46).

The timing of ATRA administration was investigated by the European APL group. A higher CR rate was seen with simultaneous administration of ATRA and chemotherapy. This conclusion was corroborated in later trials (43, 47-51). The GIMEMA and PETHEMA groups reported a CR rate of 87% to 95% with the combination of ATRA and an anthracycline (50, 52-55). The European APL group showed that addition of cytarabine to ATRA and an anthracycline induced CR rates of 90-94% (55). Today, the standard approach to induction therapy for newly-diagnosed APL is ATRA in combination with an anthracycline-based regimen (56) (Table II).

Two studies showed that the use of ATO in combination with ATRA resulted in comparable CR rates to ATRA with chemotherapy (57, 58). In fact, ATO may be the single most potent agent for newly-diagnosed APL, showing improved outcomes with longer exposure (59). Furthermore, when ATO is combined with ATRA, the relapse rates are significantly lower than when used individually (60). Rivandi *et al.* studied the utility of ATRA and ATO as first-line induction and post-remission therapy. In a subset of high-risk patients (WBC count

greater than 10,000/ μ l) the chemotherapy-free combination of gemtuzumab ozogamicin, ATRA and ATO demonstrated an overall response rate of 92%. More importantly, patients aged 60 years or older had an 83% CR rate at 23 months (61). Data from the intergroup APL0406 study was presented at the American Society of Hematology meeting in 2012. This first phase III, randomized, prospective trial compared frontline induction therapy with ATO and ATRA combination against ATRA in combination with chemotherapy. With a median follow-up of 31 months, the 2-year EFS, in the non-high risk patient population (WBC \leq 10,000/ μ l), was 97% and 86.7% respectively (62). Given the additional factors of low cost and a limited side-effect profile, many investigators are suggesting the use of ATRA and ATO combination as front-line therapy.

Consolidation Therapy

The goal of consolidation therapy is the achievement of molecular remission, defined as negative PCR for PML-*RARA* from a bone marrow aspirate at weeks 6 to 8 (55, 63-65).

As in induction therapy, the role of cytarabine in consolidation therapy remains controversial. Studies prior to the introduction of ATRA did not reveal any benefit for its use in achieving molecular remission. In the post-ATRA era, the European APL group demonstrated that when an anthracycline was used without cytarabine there was an increase in relapse (66). A joint analysis of the PETHEMA and European APL groups, as well as the GIMEMA group has shown that patients younger than 60 years and a WBC count higher than 10,000/ μ l, had a lower relapse rate with the use of cytarabine. However, no difference in overall survival was noted

Since its introduction, ATRA has been used in consolidation therapy. In two prospective, non-randomized Italian trials (LPA96 and LPA99), the addition of ATRA was beneficial, particularly in an intermediate-risk group defined as WBC count less than 10,000/ μ l and platelets less than 40,000/ μ l.

The success of ATO in induction therapy prompted further interest for its use in consolidation therapy. The North American Intergroup randomized trial comparing the

Table II. *Anthracycline-based therapy.*

Group	Induction	Consolidation		Maintenance	Year	N	CR	DFS	OS	
AIDA0493 (64)	ATRA+ Idarubicin	C1: ARA-C+IDA C2: MTZ+VP-16 C3: IDA+ARA-C + 6-TG		ATRA	1993-2000	642	94%	70%	78%	
AIDA2000 (48)	ATRA + Idarubicin	(High risk) C1: Ara-c+IDA C2: MTZ+VP-16 C3: IDA+Ara-c+6-TG		C1: ARA-C+IDA+ATRA C2: MTZ+VP-16+ATRA C3: IDA+6-TG+ATRA	Atra+MP+MTX	2000-2006	453	94%	86%	87%
LPA96 (48)	ATRA + Idarubicin	C1: IDA C2: MTZ C3: IDA		ATRA+MP+MTX	1996-1999	129 172		85%	83%	
LPA99 (48, 63)	Atra + Idarubicin	(Low risk) C1: IDA C2: MTZ C3: IDA		ATRA+MP+MTX	1999-2002	107	96%	89%	89%	
LPA2005 (63)	Atra + Idarubicin	C1: ATRA+DNR C2: MTZ+ATRA C3: ATRA+IDA				453	90%	80%	81%	
EAPLG (41)	Atra + + Ara- C (high) ATR + DNR	(High risk) C1: Atra+IDA C2: MTZ+ATRA C3: ATRA+IDA		C1: ATRA+DNR C2: MTZ+ATRA C3: ATRA+IDA + ara-c	ATRA+MP+MTX	2005-2009	284	96%	89%	89%
		(Ara-C group) C1: DNR+Ara-c C2: DNR+Ara-c		C1: DNR C2: DNR			118	83%	82%	79%
							95	99%	93%	97%
							101	94%	77%	89%
									(EFS)	
									(EFS)	
APML3114	ATRA+ Idarubicin	C1: ATRA+IDA C2: ATRA C3: ATRA		ATRA+MP+MTX	1997-2002	101	90%	86%	93%	

ATRA: All-*trans* retinoic acid; Ara-C: cytarabine; DNR: daunorubicin; IDA: idarubicin; MP: 6-mercaptopurine; MTX: methotrexate; MTZ: mitoxantrone; VP-16: etoposide; 6-TG: thioguanine; C#: cycle #.

administration of ATO, ATRA, and daunorubicin to ATRA and daunorubicin demonstrated a survival benefit in the group receiving ATO. Of note, the survival rates in the non-ATO group did not match the typical survival rates of previous studies (86% *versus* 79%) (40, 46, 63-65). Patients with WBC counts greater than 10,000/ μ l who received ATO showed a significantly prolonged disease-free survival compared to those with WBC counts less than 10,000/ μ l (40). Gore *et al.* reported a reduced exposure to daunorubicin with the addition of a single cycle of ATO-based consolidation chemotherapy, with survival rates comparable to traditional treatment regimens (40, 67). A summary of the most important studies using ATO in APL patients is given in Table III.

Maintenance Therapy

Before the advent of ATRA, post-remission treatment strategies were extended from strategies used in AML that used methotrexate and mercaptopurine as maintenance therapy (4, 68). After the introduction of ATRA, several studies looked at the role of ATRA in maintenance treatment

of APL (46, 49, 51, 52). Both the European APL group APL93 and the North American Intergroup Trial showed a benefit with ATRA (46). Long-term follow-up of these two groups for over 10 years has shown a significant decrease in the incidence of relapse from 43.2% in patients without maintenance to 13.4% in patients receiving low-dose chemotherapy with ATRA (69-71). The North American group reported a 5-year DFS of 74% in patients who received ATRA maintenance after induction therapy with ATRA-based regimen (71). Even in patients who did not receive ATRA-based induction therapy, ATRA maintenance improved 5-year DFS from 16% to 47%.

The Japanese Adult Leukemia Study Group APL97 did not show benefit with the administration of multiple cycles of intensive chemotherapy as maintenance in molecularly-negative patients after intensive consolidation therapy. In that study, ATRA was not part of the maintenance therapy (72). The GIMEMA trial randomized patients in complete molecular remission after standard intensive consolidation chemotherapy to observation, low-dose chemotherapy, ATRA-alone, and ATRA-plus-low-dose chemotherapy (64). This study showed no difference in DFS among the four

Table III. Arsenic Trioxide (ATO)-based therapy.

Group	Induction	Consolidation	Maintenance	Year	N	CR	DFS	OS
Ghavamzadeh (59)	ATO	C1: ATO C2: ATO	ATO	1999-2010	197	86%	67%	64%
Ravandi (61)	ATRA+ATO ± GO	C1-C4: ATO + ATRA		2002-2008	82	92%	81%	85%
Gore (67)	ATRA+DNR ±Hydroxyurea	C1: Ara-c+DNR+ATO	ATRA+MP+MTX	2004-2007	45		88%	88%
North American Intergroup C9710 (115)	ATRA+DNR+ARA-c	C1: ATRA+ATO C2: ATRA+ATO C3: ATRA+DNR C4: ATRA+DNR	ATRA+MP+MTX	1999-2005	243	90%	90%	86%
APML4 (116)	ATRA+ATO+IDA	C1:ATRA+ATO C2:ATRA+ATO	ATRA+MP+MTX	2004-2009	129	95%	98%	93%
Shanghai (117)	ATRA+ATO	C1: DNR+Ara-C C2: Ara-C C3: Homoharringtonine +Ara-C	ATRA+ATO+ chemotherapy	2001-2007	85	94%	95%	92%

ATO: Arsenic Trioxide; ATRA: All-*trans* retinoic acid; Ara-C: cytarabine; DNR: daunorubicin; IDA: idarubicin; MP: 6-mercaptopurine; MTX: methotrexate; GO: gemtuzumab ozogamicin; C'#: cycle #.

groups of patients after 12 years of follow-up (73). Based on these data, the need for maintenance therapy appears to have decreased with the use of more effective induction and consolidation regimens.

Monitoring

The goal of induction therapy is to achieve normal hematopoiesis, whereas the goal of consolidation therapy is to achieve and maintain molecular CR, defined as two positive PCR tests completed four weeks apart. In APL, and unlike AML, bone marrow evaluation at day 14 during induction therapy is likely to be misleading, because promyelocytes remain increased for approximately four weeks (56). With this delay in bone marrow evaluation, there have been no reported cases of resistance in over 1000 patients with confirmed APL in studies conducted by the GIMEMA and PETHEMA groups (74, 75). After consolidation therapy, testing for molecular CR should begin in four weeks. After molecular CR is attained, testing of the bone marrow with PCR can continue every three to four months for three years (76). If molecular CR is not achieved, then the patient is considered to have refractory or relapsed APL, which should prompt immediate initiation of treatment (77, 78).

Close monitoring of fibrinogen, PT/PTT/INR, platelet count, and fibrin D-dimer for evidence of DIC is an essential component in the management of patients with APL because pulmonary and cerebrovascular hemorrhages may occur in up to 40% of cases, with 10% of patients experiencing fatal hemorrhage (13, 52, 53, 79, 80). Treatment consists of maintaining the platelet count greater than 20,000/μl and fibrinogen level greater than 150 mg/dL (13, 81). The use of

factor VIIa for life-threatening hemorrhages has been limited to case reports (82, 83).

Hyperleukocytosis continues to represent the most important factor for relapse and early death (42, 48, 50, 51, 71, 84, 85). It is seen in the microgranular subtype of APL (86). Treatment of hyperleukocytosis with leukapheresis is usually unwarranted given the possibility of worsening coagulopathy (83).

ATRA has been implicated in the development of elevated idiopathic intracranial pressure. If symptoms continue after an initial therapeutic lumbar puncture, decreasing the dose has been shown to be effective in alleviating symptoms (56).

A very important and notable risk associated with ATRA use is the development of the differentiation syndrome. It is characterized by any combination of fever, hypoxia, pulmonary infiltrates, respiratory distress, pericardial effusion, and hypotension. It can occur, between day 2 and day 21, in 25% of patients with APL receiving ATRA (82, 87). This syndrome is clinically and physiologically similar to the capillary leak syndrome (88). Preventive measures should be instituted early on as treatment is primarily ineffective once the development of respiratory distress occurs. Early treatment with steroids along with administration of chemotherapy as the WBC count begins to rise has been shown to prevent development of the differentiation syndrome (87, 89).

The administration of ATO has also been associated with the development of the differentiation syndrome, requiring steroid therapy and brief withholding of ATO (56, 61, 90). ATO has also been implicated in the occurrence of electrolyte and cardiac abnormalities, which require for frequent monitoring specifically regarding potassium and

magnesium levels. Up to 60% of patients receiving ATO may develop QTc prolongation with possible progression to torsades de pointes, requiring for temporary discontinuation of ATO (61).

Relapse

Relapse of APL occurs in approximately 15% of patients, with 95% of the relapses taking place in the first three years (12, 14). Of these relapses, about one-third were high-risk at diagnosis (WBC count greater than 10,000/ μ l). Due to the high CR rates achieved with induction therapy, studies investigating relapse are limited (91, 92), and pre-emptive treatment instituted at the time of documented molecular relapse has been shown to decrease the incidence of hematological relapse (77, 78).

Relapse following ATRA-based regimens has been treated with ATO. However, prior to the use of ATO, ATRA and chemotherapy were utilized for re-induction followed by re-consolidation, leading to 20-40% secondary CR rates (93, 94).

With the early reports from China, ATO has spared the need for further chemotherapy for relapsed APL. In a pilot study conducted on 12 patients in the US who had disease relapse post-ATRA and chemotherapy, the secondary CR rate was 90% and the molecular CR was 60% (1). This prompted Soignet *et al.* to conduct a larger, multicenter trial studying ATO in relapse. This study documented a CR rate of 85% (90). Since then, several multi-center studies have been published showing secondary CR rates of 80-90%, resulting in the implementation of ATO as the first-line therapy for relapsed and refractory APL in the United States and Europe (1, 90, 95-99).

Allogeneic and autologous hematopoietic stem cell transplantation (HSCT) have been used primarily as post-remission therapy, with good outcome (78, 100-102). One study, evaluating 50 cases of relapsed APL in second remission who subsequently received an autologous HSCT, reported an 87% seven-year relapse-free survival (93). Allogeneic HSCT has also produced similar results, with relapse-free rates of 59% (57).

It is important to mention that relapse can be extramedullary, involving the skin and central nervous system (CNS). Given the risk of fatal cerebral hemorrhage in relapse, as well as the extensive and prolonged treatment of CNS relapse (intrathecal chemotherapy, craniospinal radiation or whole brain radiation, and re-induction therapy), risk stratification has been implemented to identify patients with APL who are more likely to develop extramedullary relapse (14). DeBotton *et al.* was able to show that patients with WBC counts over 10,000/ μ l had a higher incidence of extramedullary relapse (103). Thus, rather than subjecting all patients with relapsed APL to prophylactic intrathecal chemotherapy, it is more reasonable to target those with high WBC counts (103).

Special Considerations

The incidence of APL during pregnancy is unclear and evidence-based management is limited to case reports. What is clear though is that once the diagnosis of APL is suspected, pre-emptive treatment needs to be pursued to limit the chances of catastrophic bleeding that may harm both the mother and fetus.

Organogenesis occurs during the first trimester, and as such it is the most susceptible period to teratogenic therapies, *i.e.* ATRA, ATO, and chemotherapy (104, 105). During the first trimester, if elective abortion is not pursued, induction with ATRA-based or ATO-based regimens is not acceptable, leaving anthracycline-based chemotherapy as the only option. Despite the relatively safe side-effect profile of anthracyclines during the first trimester, therapy has been associated with increased risk of bleeding, fetal malformations, abortion, and low birth weights (56, 106). Daunorubicin is the preferred agent as it is less lipophilic, reducing the risk of placental transfer (46, 72, 107).

During the second and third trimester, organogenesis has been completed, allowing for treatment with ATRA-based regimens. In fact, pregnant women diagnosed with APL during the first trimester who have progressed to the second trimester should be considered candidates for ATRA. For those diagnosed with APL during the second or third trimester, the use of chemotherapy has been associated with increased risk of abortion, prematurity, low birth weights, neonatal neutropenia, and sepsis (106). In view of that, two approaches have been proposed: sequential administration of ATRA followed by chemotherapy, or simultaneous administration of ATRA with chemotherapy. In the sequential approach, ATRA is used alone until CR is achieved, delaying the need for chemotherapy until at least 32 weeks of gestation (108). The use of ATRA alone increases the risk of differentiation syndrome up to approximately 25% (53). The simultaneous approach, ATRA and chemotherapy administered together, is typically reserved for high-risk patients with hyperleukocytosis.

Currently, the use of ATO is prohibited during pregnancy. However, in one case of relapsed APL, ATO was administered nine months prior to conception of a viable neonate without evidence of bone marrow suppression or fetal abnormalities (109).

Finally, vaginal delivery is the preferred method as it is associated with reduced risk of bleeding (99). It is important for mothers to be aware that breast feeding is contraindicated when chemotherapy or ATO is needed. Management following delivery does not differ from that of non-pregnant patients with APL.

Future Perspectives

With the significant success achieved in the treatment of APL, researchers are now focusing on strategies to reduce

the risk of early mortality and toxicity from therapeutic agents. CR rates are now approaching 95% with the available therapies and recent studies have shown a decrease in early induction mortality rates due to the differentiation syndrome, hemorrhage, and infection (46, 63, 64, 112). Risk stratification of those at increased risk of complications is currently being adopted with the use of risk-adapted strategies that are dependent on the WBC and platelet counts. These strategies are designed to reduce the exposure to unnecessary therapies in low-risk groups without affecting overall survival. Of particular interest, the GIMEMA and M.D. Anderson groups continue to study the use of combination ATRA and ATO for induction and consolidation in low-risk groups (white blood cell counts less than 10,000/ μ l) (62, 113). The Japanese Adult Leukemia group recommends ATRA-alone for low-risk patients, and ATRA in combination with idarubicin and cytarabine for those with high-risk disease. The French-Belgian-Swiss group uses combination therapy including ATO, idarubicin, and cytarabine during consolidation in high-risk patients (55). The results of these studies may prove to be beneficial in reducing exposure to chemotherapy and may in fact help reduce morbidity and mortality.

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