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Acute myeloid Leukemia: Recent progress in AML with recurrent genetic abnormalities and Molecular targeted therapy

Risk factors and remaining challenges in the treatment of acute promyelocytic leukemia

Yasuhisa Yokoyama[1]

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Abstract
The treatment of acute promyelocytic leukemia (APL) has evolved with the introduction of all-*trans* retinoic acid (ATRA) and subsequent arsenic trioxide (ATO), particularly in standard-risk APL with an initial white blood cell count (WBC) < 10,000/μL, where a high cure rate can now be achieved. However, for some patients with risk factors, early death or relapse remains a concern. Insights from the analysis of patients treated with ATRA and chemotherapy have identified risk factors such as WBC, surface antigens, complex karyotypes, *FLT3* and other genetic mutations, p73 isoforms, variant rearrangements, and drug resistance mutations. However, in the ATRA + ATO era, the significance of these risk factors is changing. This article provides a comprehensive review of APL risk factors, taking into account the treatment approach, and explores the challenges associated with APL treatments.

Keywords Acute promyelocytic leukemia · all-*trans* retinoic acid · Arsenic trioxide · Chemotherapy · Risk factors

Introduction

Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia (AML), which accounts for approximately 5–15% of all AML cases [1, 2]. Almost all cases of APL have *PML::RARA* genetic rearrangement resulted from chromosomal translocation t(15;17)(q24.1;q21.2). Clinically, APL typically presents with disseminated intravascular coagulation (DIC) requiring early intervention to prevent severe bleeding. It is also a unique clinical feature that APL is highly responsive to differentiation therapy with all-*trans* retinoic acid (ATRA) or arsenic trioxide (ATO). Introduction of ATRA drastically improved the outcomes of APL, and treatment with ATRA and chemotherapy (ATRA + Chemo) had been the standard treatment of APL [3–13]. The combination therapy of ATRA and ATO (ATRA + ATO) has further improved the prognosis of APL, and now APL with initial white blood cell count (WBC) < 10,000/μL (standard-risk APL) has become a curable disease by treatment with ATRA + ATO [14–16]. However, approaches to the cases with high-risk backgrounds should still be improved. In addition, the significances of risk factors can change according to the progression in treatment and diagnostic modalities. This review focuses on the risk factors and remaining challenges in APL treatment.

ATRA + Chemo

ATRA binds to PML-RARα fusion protein through the ligand binding domain (LBD) on RARα. Without the binding of ATRA, PML-RARα acts as a transcriptional repressor. Binding of ATRA to PML-RARα induces activation of downstream transcription and also causes degradation of the fusion protein, which leads to the differentiation of leukemic cells [2, 17, 18]. In the treatment of APL, ATRA can induce a complete remission (CR), but a high relapse rate was a problem with ATRA monotherapy [19]. Use of chemotherapy with ATRA (ATRA + Chemo) improved the prognosis of APL drastically [3–13]. In ATRA + Chemo regimens, ATRA, anthracyclines, and cytarabine are commonly used as induction and consolidation

✉ Yasuhisa Yokoyama
y-yokoyama@umin.ac.jp

[1] Department of Hematology, University of Tsukuba, Tsukuba, Ibaraki, Japan

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therapy, and maintenance therapy is often administered after consolidation. Representative ATRA + Chemo regimens and their long-term outcomes are listed in Table 1. Various ATRA + Chemo regimens have been reported from different groups, and they demonstrate comparable long-term survivals exceeding 80%. From these results, ATRA + Chemo had been the standard treatment of newly diagnosed APL, and thus, risk factors had been analyzed in patients treated with ATRA + Chemo. The advent of ATRA + ATO has led to improvement in treatment outcomes, consequently affecting the significance of risk factors elucidated in ATRA + Chemo regimens. Therefore, when considering risk factors in APL, it is important to be aware of whether the patients received the ATRA + Chemo or ATRA + ATO.

Table 1 Representative ATRA and chemotherapy regimens and their outcomes

Study	Induction	Consolidation	Maintenance	ED	Survival	Other findings	Ref
AIDA0493	ATRA + IDR	Anthracyclines + AraC	± ATRA ± low-dose CT	5.5%	12 yr-EFS 68.9%, OS 76.5%	No differences in DFS among maintenance arms	[2]
APL93	ATRA + DNR + AraC	DNR + AraC	± ATRA ± low-dose CT	7.3%	10 yr-OS 77%	Maintenance reduced relapse particularly when WBC > 5,000	[4, 11]
APL97	ATRA ± IDR ± AraC	Anthracyclines + AraC	± intensified CT	4.5%	6 yr-DFS 68.5%, OS 83.9%	Intensified maintenance resulted in worse prognosis	[5]
APL2000 (Age < 60, WBC < 10,000)	ATRA + DNR ± AraC	DNR ± AraC	ATRA + low-dose CT	2.5%	7 yr-EFS 65.2%, OS 86.1% (non-AraC) 7 yr-EFS 82.8%, OS 92.4% (AraC)	Addition of AraC resulted in lower relapse rate	[6, 12]
APL2000 (Age < 60, WBC > 10,000)	ATRA + DNR + AraC	DNR + AraC	ATRA + low-dose CT	2.7%	7 yr-EFS 82.2%, OS 87.6%		[6, 12]
AIDA2000	ATRA + IDR	ATRA + anthracyclines ± AraC	ATRA + low-dose CT	5.6%	6 yr-DFS 85.6%, OS 87.4%	Addition of AraC in consolidation for those with WBC > 10,000 reduced relapse	[7]
APML3	ATRA + IDR	IDR followed by ATRA	ATRA + low-dose CT	8.0%	4 yr-DFS 69.7%, OS 83.7%	Maintenance was associated with improved DFS	[10]
APL204	ATRA ± IDR ± AraC	Anthracyclines + AraC	ATRA or tamibarotene	4.6%	7 yr-EFS 79%, OS 87%	Maintenance with tamibarotene reduced relapse especially when WBC > 10,000	[13]
LPA2005	ATRA + IDR	ATRA + anthracyclines ± AraC	ATRA + low-dose CT	7.4%	4 yr-DFS 90%, OS 88%	Addition of AraC in consolidation for those with WBC > 10,000 reduced relapse	[9]

ATRA all-*trans* retinoic acid, *IDR* idarubicin. *DNR* daunorubicin, *AraC* cytarabine, *CT* chemotherapy, *ED* early death, *DFS* disease-free survival, *EFS* event-free survival, *OS* overall survival, *WBC* white blood cell count

ATRA + ATO

Physiologically, PML forms nuclear bodies (NBs) and controls cell senescence through p53 signaling [2, 18, 20]. In APL, PML-RARα makes heterodimers with PML and disrupts its NB formation, leading to uncontrolled proliferation and block of differentiation [2, 20, 21]. ATO binds to PML and PML-RARα through B2 domain on PML and facilitates the degradation of PML-RARα and reformation of PML NBs [2, 17, 18, 20]. Clinically, single-agent ATO has been shown to be effective against relapsed/refractory or untreated APL cases [22–24]. Since 2004, the efficacy of ATRA + ATO for untreated APL was reported [25, 26], and finally, for the treatment of untreated, standard-risk APL, the superiority of ATRA + ATO to ATRA + Chemo was demonstrated in 2 randomized controlled trials, APL0406 and AML17 [14, 15, 27]. Outcomes of representative studies for standard-risk APL treated with ATRA + ATO are listed in Table 2. Very favorable long-term survivals of more than 90% were achieved in these studies.

Fatal bleeding, differentiation syndrome, and early death

It is a characteristic feature of APL that almost all cases exhibit DIC concomitantly and that differentiation syndrome (DS) can be induced by differentiation therapy with ATRA and/or ATO. Given the low relapse rate of APL, the success of APL treatment largely hinges on the appropriate management of severe complications such as DIC, DS, and infections to prevent early death (ED) during the remission induction. This remains consistent whether patients are treated with ATRA + Chemo or ATRA + ATO, and risk factors for ED are also analyzed as well, not only for survival.

Prognostic factors in APL treatment

White blood cell count

Among the risk factors in APL, the most potent one is the pretreatment WBC. For patients treated with ATRA + Chemo regimens, Sanz et al. reported the predictive model for relapse-free survival (RFS) designating patients with initial WBC ≤ 10,000/μL and platelet counts > 40,000/μL as low risk, WBC ≤ 10,000/μL and platelet counts ≤ 40,000/μL as intermediate risk, and WBC > 10,000/μL as high risk [29]. In the Japanese JALSG APL92 study, patients with an initial WBC < 10,000/μL exhibited a favorable 4-year disease-free survival (DFS) rate of 67.6%, as opposed to 42.1% for those with WBC ≥ 10,000/μL [30]. Considering that WBC serves as a prognostic factor, some trials of ATRA + Chemo adopted stratified treatment according to WBC at diagnosis [5–9, 31].

Being based on the insights from ATRA + Chemo, ATRA + ATO designates WBC < 10,000 as standard risk and WBC > 10,000 as high risk. GIMEMA APL0406 study, which was a randomized controlled trial comparing ATRA + ATO and ATRA + Chemo, only included standard-risk patients [14], but some other studies incorporated high-risk participants [15, 16, 28]. In ATRA + ATO for high-risk patients, gemtuzumab ozogamicin (GO) or idarubicin is administered in the early phase of induction therapy to effectively suppress elevated WBC. The treatment outcomes of ATRA–ATO for high-risk cases are presented in Table 3. The survival rates for high-risk cases were approximately 85%, and these rates appear to be lower than those observed in standard-risk cases (Table 2). To date, there have been no randomized trials demonstrating the superiority of ATRA + ATO over ATRA + Chemo in high-risk patients [15].

The high WBC at diagnosis was also one of the independent risk factors of ED in both ATRA + Chemo and ATRA + ATO [32–35].

Table 2 Outcomes of ATRA and ATO for standard-risk APL

Study	Induction	ED	Consolidation	Survival	Ref
APL0406	ATRA + ATO	0.0%	ATRA × 7, ATO × 4	50mo-EFS 97.3%, OS 99.2%	[27]
AML17	ATRA + ATO	4.3% (*1)	ATRA × 7, ATO × 4	4 yr-EFS 92%, OS 95%	[15]
USA	ATRA + ATO	3.7%	ATRA × 7, ATO × 4	5 yr-EFS 87%, OS 89%	[28]
APML4	ATRA + IDR + ATO	1.9%	ATRA + ATO × 2 (then ATRA + 6-MP + MTX for 2 years)	5 yr-EFS 92%, OS 96%	[16]

ATRA all-*trans* retinoic acid, *ATO* arsenic trioxide, *IDR* idarubicin, *6-MP* 6-mercaptopurine, *MTX* methotrexate, *ED* early death, *EFS* event-free survival, *OS* overall survival. *1 includes high-risk patients

Table 3 Outcomes of ATRA and ATO for high-risk APL

Study	Induction	ED	Consolidation	Survival	Ref
AML17	ATRA + ATO + GO	4.3% (*1)	ATRA × 7, ATO × 4	4 yr-EFS 87%, OS 87%	[15]
USA	ATRA + ATO + GO	3.7%	ATRA × 7, ATO × 4	5 yr-EFS 81%, OS 86%	[28]
APML4	ATRA + IDR + ATO	8.7%	ATRA + ATO × 2 (then ATRA + 6-MP + MTX for 2 years)	5 yr-EFS 83%, OS 87%	[16]

ATRA all-*trans* retinoic acid, *ATO* arsenic trioxide, *IDR* idarubicin, *6-MP* 6-mercaptopurine, *MTX* methotrexate, *ED* early death, *EFS* event-free survival, *OS* overall survival. *1 includes high-risk patients

Surface antigens

Aberrant expression of CD56 is observed in 10–15% of APL cases, and is known to correlate with the expression of CD2, CD7, CD34, and HLA-DR [36–40]. CD56 positivity is also associated with bcr3 isoform (short form) of *PML::RARA* [36, 39, 40]. An analysis of 651 cases that underwent ATRA + Chemo treatment through PETHEMA and HOVON trials LPA96, 99, and 2005 showed that CD56 positivity, along with elevated WBC, was an independent risk factor for relapse with a hazard ratio (HR) of 2.3 compared to CD56-negative cases [36]. In the analysis of JALSG APL97, CD56-positive cases showed a tendency towards unfavorable event-free survival (EFS). Particularly, among patients with WBC > 3000/μL, a significantly worse prognosis of CD56-positive cases was demonstrated (9-year EFS 30.8% vs 63.6%) [37]. JALSG APL204 is a randomized study that compared ATRA and tamibarotene as maintenance therapies in ATRA + Chemo treatment [8] and revealed that, together with high WBC and ATRA maintenance, expression of CD56 was still an unfavorable prognostic factor for RFS (HR 3.19) [38]. Analyses of GIMEMA AIDA0493 and 2000 suggested that, in addition to CD56, CD15-positive cases also had poor outcomes [39]. Along with high WBC (HR 2.4) and *PML::RARA* bcr3 isoform (HR 2.2), expression of CD56 or CD15 was an independent adverse factor for overall survival (OS) (HR 1.9). Thus, in the ATRA + Chemo era, expression of CD56 is considered an unfavorable prognostic factor.

Reports on differences in prognosis based on surface antigens are limited for patients treated with ATRA + ATO. Improved outcomes achieved with ATRA + ATO may have contributed to overcoming the risk associated with surface antigens such as CD56. Nonetheless, a report of 184 cases who underwent ATRA + ATO induction in China indicated that CD56 positivity was an independent prognostic factor for RFS (HR 4.7) [40]. However, it is important to note that this group received chemotherapy-based treatment as post-remission therapy, which differs from the current ATRA + ATO regimen where ATRA and ATO are administered without chemotherapy agents in the post-remission phase. Administering an appropriate dosage of ATO as post-remission therapy might potentially help in overcoming the risk associated with CD56 expression.

Additional chromosomal abnormalities

Additional chromosomal abnormalities (ACAs) aside from t(15;17) are observed in approximately 30% of APL cases [41–47]. The most commonly observed ACA is trisomy 8, accounting for 30–50%, followed by abnormalities in chromosomes 7, 9, or 17 [41–46]. The presence of ACAs does not appear to impact prognosis, regardless of the treatment, whether it is ATRA + Chemo [41–43, 45, 47] or ATO-containing regimen [44–46]. Meanwhile, some of the studies focused on the number of ACAs and found that complex karyotype with ≥ 2 or ≥ 3 ACAs could adversely affect the prognosis of the patients treated with ATRA + Chemo or ATRA + ATO [45–47].

FLT3 and other genetic abnormalities

In addition to the disease-defining *PML::RARA* fusion gene resulting from chromosomal translocation t(15;17)(q24;q21), approximately 70% of APL patients have at least one additional genetic mutation at the time of diagnosis [48]. *FLT3* mutations are most commonly observed, with *FLT3*-internal tandem duplication (ITD) accounting for 20–40% and *FLT3*-tyrosine kinase domain mutations (TKD) for 10–20% of cases [48–51]. Following *FLT3* mutations, *WT1*, *NRAS*, *KRAS*, *ARID1A/B* are recurrently mutated, whereas mutations in genes frequently observed in other subtypes of AML, such as *DNMT3A*, *TET2*, *IDH1/2*, *ASXL1*, *GATA2*, and *NPM1*, are rare or absent in APL [48, 49]. Except for *FLT3* mutations, roles and impacts of individual mutated gene in the pathogenesis and prognosis of APL are not well understood. Nevertheless, in the analysis of 44 patients, most of whom underwent ATRA + Chemo treatment, cases with ≥ 2 additional mutations had an increased risk of relapse compared to those with fewer mutations [50].

FLT3-ITD mutation is known to be associated with increased WBC, morphological microgranular variant, and bcr3 isoform of *PML::RARA* [52–58]. Impact of *FLT3*-ITD

on the prognosis of the patients treated with ATRA + Chemo is controversial. Several studies indicated in univariate analysis that *FLT3*-ITD have a significant adverse impact on ED and survival [10, 55–58]. Some of these studies demonstrated that *FLT3*-ITD mutation remained an independent adverse prognostic factor for survival in multivariate analysis [10, 57, 58], while in others, the significance was lost [55, 56]. This discrepancy could be attributed to the strong correlation between *FLT3*-ITD and elevated WBC, which could complicate the assessment of the prognostic impact of *FLT3*-ITD due to the potent effect of WBC as a risk factor.

In the ATO era, a report that analyzed 134 patients who received ATO alone as induction therapy demonstrated that *KRAS* and *GATA2* mutations were independent risk factors for ED, while *FLT3*-ITD was not [59]. Prospective and retrospective studies incorporating ATO as part of induction and/or post-remission therapy alongside ATRA + Chemo also failed to demonstrate the significance of *FLT3*-ITD for survival [16, 40, 45, 60–62]. Furthermore, in the sub-analysis of the APL0406 trial, *FLT3*-ITD did not have a significant effect on EFS in the ATRA + ATO arm, although there was a non-significant trend of worse EFS in positive *FLT3*-ITD cases in the ATRA + Chemo arm [63]. According to these reports, it appears that *FLT3*-ITD has a diminished impact on survival outcomes in patients who received an ATO-containing regimen as initial therapy.

p73 isoforms

p73, a member of the p53 family encoded by *TP73*, has a closely related structure with p53 and functions as a tumor suppressor regulating apoptosis and cell cycle [64, 65]. Using the alternative promoters or transcription start sites, full-length p73 (TAp73) containing the N-terminal transactivation domain (TAD) or truncated inactive form (ΔNp73) without entire or part of the N-terminal TAD are transcribed [64, 65]. ΔNp73 dominant-negatively inhibits the activities of p53 and TAp73, and thus overweighed expression of ΔNp73 can contribute to tumorigenesis or resistance to chemotherapy [64, 65]. As for AML, it was reported that ΔNp73 mRNA expression was observed in 96.7% of non-APL AML patients, whereas it was present in only 31.7% of APL cases [66]. This finding may partially explain the better prognosis of APL. Indeed, analysis of 129 patients who were enrolled in the IC-APL study and received ATRA + Chemo demonstrated that a high ΔNp73/TAp73 mRNA ratio (≥ 1.6) was an independent unfavorable factor for OS along with higher age and WBC and lower albumin [67]. A scoring system incorporating ΔNp73/TAp73, *FLT3*-ITD, and expression levels of *ID1*, *BAALC*, *ERG*, and *KMT2E* genes was also proposed [68]. While the importance of ΔNp73/TAp73 ratio has been examined in patients treated with ATRA + Chemo, there is a possibility that ΔNp73/TAp73 may also carry some significance in the context of ATRA + ATO due to the potential involvement of the p73 pathway in the therapeutic mechanisms of both ATRA and ATO [65, 69].

Variant rearrangements, and drug resistance-associated mutations in *PML::RARA*

The therapeutic effects of ATRA and ATO are mediated through their binding to LBD in RARα and B2 domain in PML, respectively [2, 17, 18, 20]. Therefore, it is anticipated that mutations in or lack of LBD or B2 domain could result in resistance to ATRA or ATO.

The vast majority of APL patients have *PML::RARA* fusion gene, but approximately 2% of the cases harbor variant rearrangements, with *ZBTB16::RARA* being the most common, followed by *STAT5B::RARA* [70, 71]. Recently, rearrangements involving *RARG* or *RARB*, instead of *RARA* , are also known [70, 71]. These variant cases exhibit resistance or do not show a clear response to ATO, whereas sensitivity to ATRA is variable, although LBD is retained in RARα even in variant rearrangements [17, 70, 71]. The treatment of patients with variant rearrangements primarily relies on chemotherapy, while the role of hematopoietic stem cell transplantation is not well-defined due to the limited number of patients and requires future investigation [17, 70–72]. Recent case reports implied the benefits of hypomethylating agents and venetoclax [73–75].

Mutations in *PML::RARA* are common in relapsed APL patients. The frequency of these mutations is 15–40% at the first relapse and reaches 40–70% at the second relapse [50, 76, 77]. In relapse after treatment with ATRA- and/or ATO-containing regimens, mutations are found in the LBD region of *RARA* and/or B2 domain region of *PML*, respectively, which contribute to the resistance to each drug [17, 50, 76–78]. Interestingly, the hotspot mutation can occur in unrearranged *PML*, which may also be involved the mechanism of resistance against ATO [79, 80]. Information about these drug-resistant mutations is important for the choice of salvage therapy.

Future challenges in APL treatment

The introduction of ATRA + ATO has led to a high cure rate for standard-risk APL. In addition, analysis of the patients enrolled in the APL0406 trial has demonstrated that a better quality of life was maintained for a long time among patients treated with ATRA + ATO than those treated with ATRA + Chemo [81]. Further, oral arsenic has been shown

to be as effective as intravenous ATO [82], allowing standard-risk APL patients to access less invasive and more convenient treatments. However, cases with risk factors such as high WBC face challenges like ED and relapse even in the ATRA + ATO era. Risk factors may shift as treatment and diagnostic methods advance. It is important to evaluate risk factors appropriately, and, especially when patients are considered as high-risk, careful monitoring of measurable residual disease using *PML::RARA* is essential. There is also a strong need for the development of more effective treatments tailored to high-risk patients.

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Declarations

Conflict of interests The author declares no conflict of interest.

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