# Acute Promyelocytic Leukemia

## A Review and Discussion of Variant Translocations

*Julia Adams, MD; Mehdi Nassiri, MD*

**• The majority of patients with acute promyelocytic leukemia (APL) manifest the t(15;17)(q24.1;q21.2) translocation; however, a minor but significant proportion of patients with APL harbor complex, cryptic, or variant translocations, which typically involve *RARA*. With the exception of *ZBTB16/RARA*, these variants have similar morphologic and immunophenotypic features as classic APL. Study of the variant forms of APL not only gives insight into the pathogenesis of APL but also allows us to understand the mechanism of retinoid therapy. It is important to identify these cryptic and variant translocations because certain variants, including *ZBTB16/RARA* and *STAT5B/RARA*, are resistant to treatment with all-*trans* retinoic acid, arsenic trioxide, and anthracyclines.**

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Acute promyelocytic leukemia (APL), comprising 5% to 8% of cases of acute myeloid leukemia (AML), is one of the best studied and understood hematopoietic malignancies. Unlike other forms of AML, APL is unique in that it can cause coagulopathy and death if not readily diagnosed.[1,2] Morphologically classified as AML-M3 by the French-American-British (FAB) classification, APL is typically characterized by neoplastic proliferation of cells in the bone marrow with a promyelocytic phenotype and the balanced reciprocal translocation t(15;17) (q24.1;q21.2), which results in the expression of the promyelocytic leukemia (PML)–retinoic acid receptor-α (RARA) fusion protein.[1,3–5] The newly produced fusion protein functions to repress *RARA* and non-*RARA* target genes, resulting in uncontrolled proliferation and inhibition of cellular differentiation.[4,5] Usually, APL is sensitive to the differentiating effect of all-*trans* retinoic acid (ATRA) and arsenic trioxide (ATO).[1,2]

Rarely, patients with the clinical and morphologic presentation of APL do not have an identifiable t(15;17) by cytogenetic studies.[3] Usually, these cases are subsequently found to have compound or cryptic *PML-RARA* rearrangement by molecular analysis.[1,3] However about 1% to 2% of APL cases are due to rare variant translocations, which typically involve *RARA*.[1,4,6] No APL variants with *PML* involvement alone have been identified to date; thus, *RARA* is assumed to have a key role in the pathogenesis of APL. Several variant translocations have been identified, including *ZBTB16/RARA*, *NMP/RARA*, *NUMA/RARA*, *STAT5B/RARA*, *PRKAR1a/RARA*, *BCOR/RARA*, and *FIP1L1/RARA*[7,8] (Table). In this article, we review the clinical, histologic, cytogenetic, and molecular features of these rare variants of APL, as well as the differential diagnosis and treatment.

### CLINICAL FEATURES

Typically, APL with complex, cryptic, and variant translocations has presented with the same clinical features as classic APL, with t(15;17) identified by cytogenetic studies. Acute promyelocytic leukemia is most common in adults in their midlife and has a decreased incidence after age 60 years.[6] It is uncommon to diagnose APL before age 10 years; however, rare variant APL cases with t(5;17) *NPM-RARA* have been diagnosed in pediatric patients younger than 10 years.[9] Unlike other subtypes of AML, the rate of APL is higher among Hispanics.

Patients frequently present with leukopenia and the symptoms of pancytopenia, including weakness, fatigue, infection, and bleeding; however, in the less common hypogranular variant of APL, leukocytosis is the norm.[10] Cases without *RARA* rearrangements but still morphologically and immunophenotypically compatible with a diagnosis of APL have also been found to present with leukocytosis.[10]

An early diagnosis of APL is imperative because it is associated with a high risk of disseminated intravascular coagulation, a life-threatening hemorrhagic syndrome.[11] Patients with disseminated intravascular coagulation can have numerous laboratory abnormalities, including elevated D-dimer, low fibrinogen, and prolonged bleeding times. The risk of disseminated intravascular coagulation is highest in patients with the microgranular variant of APL.[11]

### HISTOLOGIC AND PATHOLOGIC FEATURES

There are 2 morphologic variants of APL, hypergranular or "typical" APL (M3 by the FAB classification) and hypogranular or "microgranular" APL (M3v by the FAB classification)[10] (Figure). Both forms have promyelocytes with abnormal bilobed nuclei. Hypergranular APL compris-

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From the Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis.

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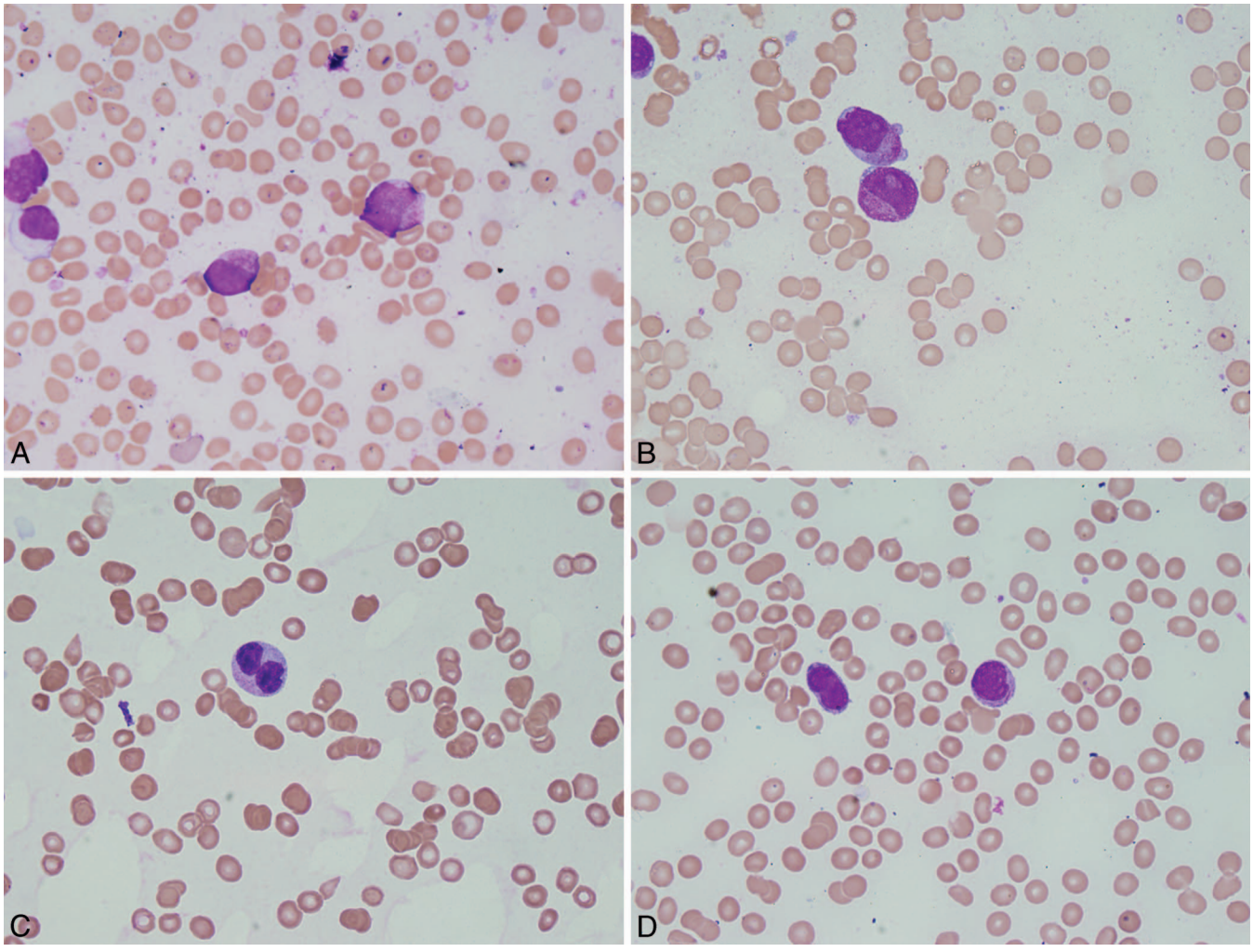
Reprints: Julia Adams, MD, Peoria Tazewell Pathology Group, 221 NE Glen Oak Ave, Peoria, IL 61636 (e-mail: juliaadams314@gmail.com).

| Translocations in Acute Promyelocytic Leukemia | | | | | |
|---|---|---|---|---|---|
| Cytogenetics | Fusion Proteins | Frequency | Response to All-*trans* Retinoic Acid | Prognosis | Unique Features |
| t(15;17)(q22;q21) | PML/RARA | 98% | Responsive | Favorable | None |
| t(11;17)(q23;q21) | ZBTB16/RARA | 0.8% | Resistant | Worse prognosis | Regular nucleus, fine or absent granules, increased CD56 expression |
| t(5;17)(q35;q21) | NPM/RARA | Rare | Responsive, but higher risk of relapse | Favorable, but higher risk of relapse | Pediatric patients |
| t(11;17)(q13;q21) | NUMA/RARA | Rare | Responsive | Favorable | None |
| der(17) | STAT5B/RARA | Rare | Resistant | Worse prognosis | None |
| der(17) | PRKAR1a/RARA | Rare | Responsive | Favorable | None |
| t(X;17)(p11;q12) | BCOR/RARA | Rare | Responsive | Favorable | None |
| t(4;17)(q12;q21) | FIP1L1/RARA | Rare | Responsive | Favorable | None |

es approximately 60% to 70% of cases of APL and presents with a low white blood cell count and abnormal promyelocytes with numerous red to purple cytoplasmic granules that are typically darker and larger than normal neutrophil granules. Most cases have identifiable faggot/matchstick cells with numerous Auer rods.[10,12] On the other hand, hypogranular APL presents with leukocytosis, and numerous abnormal promyelocytes are readily identified on a peripheral blood smear. The cells are characterized by a markedly irregular nucleus, and granulation is sparser and




*Various morphologies of promyelocytes in acute promyelocytic leukemia (APL). A, A case of 46,XY, t(1;12;17)(p36.3;q12;q21), add(6)(q12), add(7)(q11.1), der(11)t(11;15)(q13,q22), add(13)(q14), add(15)(q11.2),der(17)t(11;17)(q13;q21) APL with large promyelocytes with irregular nuclear contours, hypergranular cytoplasm, and occasional Auer rods. B, A case of 47,XX,+8,der(15)t(15;17)(q24;q21),i-der(17)(q10)t(15;17)(q24;q21) APL with monolobate promyelocytes with densely packed cytoplasmic microgranules. C, A case of 46,XY, t(15;17) APL with pelgeroid promyelocytes with hypogranular cytoplasm. D, A case of t(15;17) APL with* FLT3 *mutation with hypogranular promyelocytes and rare Auer rods (Wright Giemsa stain, original magnification ×500).*

finer compared with the hypergranular variant. Faggot cells with multiple Auer rods are less commonly seen. Despite these differences, at least a few cells with all the cytoplasmic features of M3 are usually identified in the hypogranular variant of APL.[10,12]

Cases of APL that do not harbor a classic t(15;17)(q24.1;q21.2) but still have *PML/RARA* rearrangements have not been found to have any major differences in morphology or immunophenotype compared with classic APL. However, Sainty et al[10] found that there is a slight excess of the hypergranular variant of APL in these cases compared with classic APL.

As for cases of APL with variant translocations, the majority are similar morphologically to classic APL, with the major exception being *ZBTB16-RARA* t(11;17) APL, which has distinct cytologic findings. Diagnosis of t(11;17) APL can be difficult based on morphology alone because the blasts have a more regular nucleus compared with the bilobed nucleus typically found in APL.[10] In a study[10] of 11 APL cases with t(11;17), only 2 had blasts with an irregular nucleus and hypergranular cytoplasm that allowed them to readily be classified as APL. Aside from the unusual feature of having a regular nucleus, the blasts of t(11;17) APL are also characterized by coarse granules or (less often) fine or no granules, and they occasionally have more condensed nuclear chromatin compared with classic APL. Another important feature of this variant is the presence of an increased number of hypogranular pelgeroid neutrophils. Overall, the t(11;17) APL variant appears to have morphologic features intermediate between FAB M2 (acute myeloblastic leukemia with granulocytic maturation) and FAB M3 in that the blasts are more granular than M2 but less granular than M3, faggot cells are not identified, there is loss of APL's characteristic bilobed grooved nucleus, the nuclear chromatin is more condensed, and there is absence of the obscured nuclear outlining seen in M2 typically.[10] These characteristic features have also been identified in 2 cases[10] that lacked t(11;17) but were found to harbor cryptic *ZBTB16/RARA* rearrangements. Therefore, when these morphologic features are identified, the case should be further investigated for a cryptic *ZBTB16/RARA* rearrangement.

Morphologic associations have been noted with several other variant forms of APL; however, the significance of these associations is not fully known because so few cases have been observed. For example, several cases of APL with t(5;17) have been found to have a predominant population of hypergranular promyelocytes, as well as a minor population of hypogranular promyelocytes. Auer rods were absent by light microscopy.[9] More cases need to be evaluated to determine if there are indeed morphologic differences between the other variant forms of APL; however, at this time it is believed that they morphologically resemble classic APL.

There are several immunocytochemical and immunohistochemical features of classic APL, many of which are also found in APL with cryptic and variant translocations. Cytochemical stains can be useful in APL because all forms of APL have strong staining for myeloperoxidase and Sudan black reactions, thus aiding in differentiation from AML with monocytic differentiation, which will typically be negative for myeloperoxidase or only have weak staining in promonocytes. Additionally, immunohistochemical staining for *PML* oncogenic domains can be useful because cases of APL show a characteristic labeling pattern with PML antibodies that is distinctly different from non-APL cells. Immunophenotypically, the hypergranular variant shows increased side scatter, does not express human leukocyte antigen-DR (HLA-DR) and CD34, and has bright CD33 expression, bright cytoplasmic myeloperoxidase expression, and variable CD13 expression.[10] The microgranular variant has similar immunophenotypic features in regard to CD13, CD33, and myeloperoxidase but may show dim HLA-DR and dim CD34 expression and is also more likely to show aberrant expression of CD2. Both forms, however, express CD117, are typically CD34 and HLA-DR negative, and rarely express CD15. Many cases also express CD64, and approximately 15% to 20% have CD56 expression, which has been found to be associated with a shorter complete remission and poorer survival.[10]

The *ZBTB16/RARA* APL variant is again unique in that it is more commonly associated with CD56 expression compared with classic APL.[13] Sainty et al[10] found that the CD56 antigen was positive in 4 of 6 *ZBTB16/RARA* cases. They were also able to identify a cryptic *ZBTB16/RARA* rearrangement in a case with CD56 expression and the characteristic morphology of t(11;17) APL. One case[30] of t(5;17) *NPM/RARA* was also found to have CD56 expression; however, other cases have been found to have the same immunophenotype as classic APL.[9,10]

Overall, APL with complex and variant translocations presents with similar morphologic and immunophenotypic features as classic APL. The exception, however, is t(11;17) *ZBTB16-RARA*.

## CYTOGENETIC AND MOLECULAR FEATURES

As previously mentioned, the majority of patients with APL manifest the t(15;17)(q22;q21) translocation. This alteration results in disruption of the *PML* and *RARA* genes on chromosomes 15q and 17q, respectively, and subsequently the fusion protein PML-RARA is expressed.[4,5] Both *PML* and *RARA* have a role in normal hematopoiesis, with *PML* having both growth suppressor and proapoptotic activity and *RARA* functioning as a transcription factor that mediates the effect of retinoic acid, which is necessary for normal myeloid maturation, at specific response elements. In APL, the gain-of-function PML-RARA fusion protein is believed to impair the normal growth suppressor and proapoptotic activity of *PML* and may prevent differentiation of myeloid cells by repressing the target genes of retinoic acid, thus resulting in constitutive proliferation and inhibition of terminal differentiation.[4,5]

Patients with variant forms of APL frequently possess the clinical, morphologic, and immunophenotypic features of APL but may not have a demonstrable t(15;17) by cytogenetic studies.[3] The European Working Party was formed to characterize this group of APL lacking t(15;17). In the majority of t(15;17)-negative APL cases, the *PML-RARA* fusion gene is still formed secondary to insertion events or more complex cryptic rearrangements that can eventually be identified by molecular studies.[1,3] These represent approximately 4% and 2% of all cases of APL, respectively, and *PML/RARA* fusion is usually identified at 15q.[1] In a study of 60 APL cases that were cytogenetically negative for t(15;17), the European Working Party[1] found that only 18 did not have a demonstrable *PML-RARA* rearrangement, consisting of 11 cases with *ZBTB16/RARA* fusion, 2 cases with *NPM/RARA*, and 5 cases without *RARA* rearrangement, all of which will be discussed herein. Of the 42 cases with *PML/RARA* rearrangement, 28 rearrangements were due to

insertions, and 14 were due to complex rearrangements that involved at least 3 chromosomes. Three-way and four-way variant translocations in APL have been described.[13] It is also important to note that fluorescence in situ hybridization may be negative for *PML-RARA* because the fusion gene may be too small for the probe to bind.

Rarely, in approximately 1% to 2% of APL cases, when *PML-RARA* rearrangement is not present, variant cytogenetic translocations have been identified. These variants have been found to involve the *RARA* gene on chromosome 17 but not the *PML* gene on chromosome 15, thus supporting the central role of *RARA* in the pathogenesis of APL. The variant translocations identified to date all involve *RARA* and include *ZBTB16/RARA*, *NPM/RARA*, *NUMA/RARA*, *STAT5B/RARA*, *PRKAR1a/RARA*, *BCOR/RARA*, and *FIP1L1/RARA*.[7,8,14–19] These variants have been found to harbor the C-terminal *RARA* B through F domains, which encode DNA binding, retinoid X receptor (RXR) heterodimerization, ligand binding, and corepressor and coactivator interaction functions of *RARA*.[3]

The best studied and most common APL variant is t(11;17)(q23;q21), which fuses *ZBTB16* (formerly *PLZF* [promyelocytic leukemia zinc finger]) with *RARA* and results in the production of the ZBTB16-RARA fusion protein and the RARA-ZBTB16 reciprocal fusion protein.[15,16,20] This variant was first described by Chen et al[15] in 1994 and comprises 0.8% of all cases of APL. The European Working Party[1] identified 11 cases with *ZBTB16/RARA* rearrangements. Of these cases, 2 had cryptic rearrangements and lacked t(11;17)(q23;q21) by cytogenetic testing. It is important to identify this variant translocation in APL because it alters patient treatment and prognosis.

The second most common APL variant is t(5;17)(q35;q21), which results in the fusion of *NPM* (nucleophosmin gene) to *RARA* and the production of the *NPM-RARA* fusion protein.[17] The production of the reciprocal fusion protein has also been described.[17] The other variants are much less common and are represented by only a few case reports[3] in the literature. As previously mentioned, all are believed to encode the C-terminal B through F domains of *RARA* and map to the second intron of the *RARA* gene.[3]

In some instances, rearrangement of 17q12-21, the locus for *RARA*, has been found; however, the fusion partner has not yet been identified. These include t(14;17)(q22;q21), t(8;17)(p21;q21), t(1;17)(p36;q21), and t(7;17)(q36;q22).[21] These cases may represent cryptic rearrangements of the classic t(15;17) APL or one of the other known APL variants, or they may indeed represent new variants themselves. A case of a *PML/RARA* chimeric gene on chromosome 12 (t(12;15;17)(q24;q24;q11) has also been recently described.[22] Other investigators have found cases morphologically and immunophenotypically diagnostic of APL without *RARA* rearrangements; however, *RARA* may still be involved in these instances by a cryptic mutation or epigenetic mechanisms.[3] More studies on both of these types of cases are needed.

As previously mentioned, APL may be negative for t(15;17) by cytogenetic studies alone for various reasons, including poor metaphase division, complex chromosomal abnormalities, cryptic *PML/RARA* fusion, or the fact that a variant translocation is present.[21] Despite that cytogenetic studies may rarely be negative for t(15;17) in patients with APL, cytogenetic testing should be the first test performed in a patient suspected of having APL because the majority of patients possess t(15;17). In instances where cytogenetic testing is negative, rapid molecular tests such as fluorescence in situ hybridization, real-time polymerase chain reaction, and Southern blot analysis, as well as PML immunofluorescence, can be used to identify *PML/RARA* fusion.[23] More recently, whole-genome sequencing has also been used to identify cytogenetically cryptic events in patients with APL and is an increasingly useful resource in cases where APL is suspected but the translocation cannot be identified by more conventional methods.[24] As cost and time required to complete whole-genome sequencing decrease, it will have an even more pivotal role in the diagnosis of APL.

## DIFFERENTIAL DIAGNOSIS

There are several other diseases, both non-neoplastic and neoplastic, that may mimic APL and must be included in the differential diagnosis of a patient suspected of having APL. Agranulocytosis with arrested maturation at the promyelocyte stage may be confused for APL; however, in agranulocytosis the patient's platelet count and hemoglobin are typically normal, the bone marrow is not hypercellular, and Auer rods are not observed. Several neoplastic processes are also often in the differential diagnosis of APL. Acute myeloid leukemia with fms-related tyrosine kinase (*FLT3*) internal tandem duplication and *NPM1* mutation is associated with cuplike nuclei, which can be confused with the folded nuclei seen in APL. Also, the microgranular variant of APL may mimic AML with monocytic differentiation displaying folded nuclei. In these cases, APL can be distinguished by its strong cytochemical staining for myeloperoxidase and by flow cytometry.

## CURRENT TREATMENT

Classic APL is traditionally treated with retinoid-differentiating agents such as ATRA and ATO. Retinoids not only induce differentiation but also reduce the hemorrhagic complications of APL, whereas ATO causes both differentiation and apoptosis.[25] The use of ATRA and ATO in combination with anthracycline chemotherapy significantly improves overall survival compared with chemotherapy alone, with up to a 90% cure rate.[25]

*RARA* is believed to have a key role in the development of APL. Under normal physiologic conditions, ATRA functions to cause ligand-dependent conformational changes in wild-type *RARA* that induce dissociation of the corepressors SMRT (silencing mediator of retinoid and thyroid hormones) or N-CoR (nuclear corepressor) so that cellular differentiation can proceed. These corepressors are mediators of transcriptional repression that are recruited by the binding of RARA to retinoid acid response elements to the local environment of retinoic acid–responsive promotors. In cases of *PML/RARA* fusion, the physiologic concentration of ATRA is not high enough to induce the conformational change necessary for corepressor release, and cellular differentiation does not occur. Therefore, high concentrations of ATRA are needed to induce release of the corepressor complex from the APL-associated chimeric fusion protein so coactivators can initiate transcription, resulting in differentiation of the APL blasts.[25] Because patients with complex and cryptic t(15;17) rearrangements still produce the PML/RARA fusion protein, they can be treated the same as patients with classic APL.

Study of the variant translocations of APL has helped improve our understanding of the role of refractory

interactions with corepressors in the development of APL. *NPM/RARA*, *NUMA/RARA*, *PRKAR1a/RARA*, *BCOR/RARA*, and *FIP1L1/RARA* have all been found to have a high affinity for corepressor molecules, and like *PML/RARA* they require high levels of ATRA to induce release of the corepressor complex and allow transcription and differentiation to proceed.[1,3] Therefore, these patients have been able to achieve remission with the same treatment regimen as patients with classic APL. Although patients with *NPM/RARA* typically respond to ATRA similarly to patients with classic APL, studies[26,27] have found that these patients have a higher risk of relapse. Also, although the sole case of APL with *BCOR/RARA* fusion responded to ATRA, the patient experienced several episodes of relapse.[7] Full understanding of these exceptions is limited because of the few cases available to evaluate.

Unlike the other variant forms of APL, *ZBTB16/RARA* has a poor response to retinoid therapy. These patients not only fail to respond to ATRA but also are resistant to ATO and anthracycline and therefore cannot be treated with the conventional APL regimen.[20,25] Patients with *ZBTB16-RARA* initially may show a response to ATRA; however, they are frequently unable to entirely clear the disease.[28] Nevertheless, several institutions have successfully treated these patients with a combined regimen of ATRA and ATO; however, the response rate was slower than that for typical APL.[28] It is believed that the ZBTB16/RARA fusion protein binds to corepressors not only through ligand-dependent interactions but also through ligand-independent interactions. These ligand-independent interactions are not able to be induced by ATRA to release the corepressor complex; therefore, myeloid differentiation cannot occur.[25] Not only are patients with t(11;17) resistant to ATRA, but there is also evidence that they are resistant to ATO and do not respond to the reactive oxygen species induced by anthracycline.[29] Fortunately, it is occasionally possible to attain complete remission in these patients using combination chemotherapy. Rarely, ATRA in combination with granulocyte colony-stimulating factor has successfully treated patients with t(11;17) and may prove to be useful in these patients. Finally, like *ZBTB16/RARA*, *STAT5B/RARA* has also been found to be resistant to ATRA, likely owing to similar mechanisms.[19]

Overall, the majority of APL cases can be successfully treated with ATRA, ATO, and anthracycline chemotherapy. Because of the high risk of early mortality, as well as the high potential for cure, patients suspected of having APL should immediately be started on the standard treatment of ATRA plus anthracycline-based chemotherapy, even before cytogenetic and molecular results are available.[30] Once molecular results are attained, specific therapy can be tailored to best fit patient need.

## PROGNOSIS

If left untreated, patients with APL have a median survival of less than 1 month. However, despite the fact that APL has a high risk of coagulopathy and death if not treated quickly, the prognosis for treated patients able to achieve complete remission is better than that for any other category of AML. Patients with APL achieving complete remission have a favorable long-term prognosis because there is a low risk of relapse, and bone marrow transplantation is no longer the standard treatment at the time of first complete remission. Recent clinical trials have shown that more than 90% of patients with classic t(15;17) APL are disease free and off treatment after 5 years.[6,30] The high cure rate is owing to the development of treatment regimens that combine ATRA and ATO.[24] Patients younger than 30 years and those who present with a white blood cell count of less than 10 000/μL and a platelet count of greater than $40 \times 10^3$/μL tend to have the most favorable prognosis. Patients who relapse typically have a survival of only 1 to 3 years.[30]

Despite the fact that *PML/RARA* fusion results in a differentiation block and the development of APL, it is the PML/RARA fusion protein that allows ATRA to successfully mediate cell differentiation and treat APL. Therefore, patients with cryptic *PML/RARA* fusion detected only by molecular techniques can still be treated successfully with ATRA and ATO and share the same favorable prognosis of patients with classic t(15;17) APL.

Most patients having APL with variant translocations can also be successfully treated with ATRA and ATO; however, the prognosis may not be as favorable as in patients with *PML/RARA* fusion. For example, some investigators have found that, despite that patients with *NPM/RARA* fusion respond to ATRA, they may have a higher risk of relapse.[27] However, Chen et al[26] noted the case of a patient with t(5;17)/*NPM-RARA* APL who attained long-term survival with ATO. Finally, patients with *ZBTB16/RARA* and *STAT5B/RARA* are resistant to ATRA and may have a worse prognosis compared with the other variants of APL.[24]

Overall, there is minimal information at this time regarding the prognosis of patients with variant forms of APL. However, it appears that patients with complex and cryptic rearrangements resulting in *PML/RARA* fusion have a prognosis similar to that of classic t(15;17) APL.

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