

Integrative Clinical and Practical Hematology

Acute Promyelocytic Leukemia: Pathophysiology, Laboratory and Clinical Characteristics, Treatment and Minimal Residual Disease: A Literature Review

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Abstract

Acute Promyelocytic Leukemia is a subtype of acute leukemia characterized by a predominance of cells with characteristic morphology, by t(15;17) and coagulopathy. It is designated as M3 by FAB classification and as acute promyelocytic leukemia with t(15;17) or PML/RAR α rearrangement by the World Health Organization. Unlike other subtypes of acute myeloid leukemia, acute promyelocytic leukemia occurs most often in young adults and has a stable incidence between 20 to 59 years old. This disease, which used to be highly mortal, has become a curable disease since the establishment of standard treatment with all-trans-retinoic acid and anthracyclines in the 90s. Therefore, this study aimed to review the pathophysiology, diagnosis, prognosis, treatment, and monitoring response to treatment of acute promyelocytic leukemia.

Keywords: Acute promyelocytic leukemia, PML-RAR α , Minimal residual disease

Introduction

Acute Promyelocytic Leukemia (APL), also known as M3 subtype by French-American-British (FAB) classification of Acute Myeloid Leukemia (AML), is characterized by the formation of Retinoic Acid Receptor- α (RAR α) of chromosome 17 with Promyelocytic Leukemia (PML) gene on chromosome 15, generating the PML-RAR α fusion gene, being this fusion the central event of APL, and present in 98% of cases [1].

APL is a rare disease, accounting for 5 to 10% of AML, with an estimated incidence of 1 in every 100,000

individuals in Western countries [2]. In most developed countries, prevalence rate varies from 4% to 15% [3], while in countries of Latin American colonization and some regions of Spain, it is 20% to 28% [4,5]. However, real prevalence and incidence of APL are not known and most studies are based on hospital records [6].

This disease was first described in 1950 in Norway and in France as a fatal hyperacute illness associated with hemorrhagic syndrome [7]. In 1977, a chromosome translocation t(15;17) (q22; q21) was reported in two patients with APL by Golomb et al., and this translocation results in the fusion between RAR α and PML genes, as

later proven [8,9].

Identification and characterization of PML-RAR α has proved relevant in clinical practice, especially for refinement of diagnosis of APL at genetic level and for evaluation of response to treatment and early identification of relapse through monitoring of Minimal Residual Disease (MRD) [10].

Currently, APL represents a model of therapeutic success in clinical hematology. Main treatments include All-Trans-Retinoic Acid (ATRA) and Arsenic Trioxide (ATO). Since the advent of ATRA, rates of Complete Remission (CR) have exceeded 90% and cure rate has been estimated in more than 70% of cases. However, despite the efficacy of treatment, relapses still occur, and molecular monitoring of MRD as a standard practice in patients with APL serves to guide therapy and has been recommended in international treatment guidelines [11].

The knowhow, prompt diagnosis and treatment of APL, the M3 subtype of AML, is very important because patients with APL can quickly develop life-threatening blood-clotting or bleeding problems if not treated. In this article we review pathophysiology, diagnosis, prognosis, treatment, and monitoring of response to APL treatment.

Pathophysiology of APL

APL is a disease common in middle-aged adults, and its incidence declines after age 60 years. Diagnosis is unusual before 10 years, however, a rare variant of APL with translocation t(5;17) PML-RAR α has been observed in pediatric patients [12].

Patients with clinical and morphological presentation of APL rarely do not have identifiable translocation t(15;17) by cytogenetic studies [13]. However, about 1-2% of APL cases are due to rare variant translocations, which usually involve RAR α . Several variant translocations have been identified, including: ZBTB16/RAR α , NMP/RAR α , NUMA/RAR α , STAT5B/RAR α , PRKAR1 α /RAR α , BCOR/RAR α , and FIP1L1/RAR α . In these cases of variant translocations, therapy with ATRA is not effective [14-16].

PML-RAR α gene fusion, the most frequent, triggers APL by blocking differentiation and increasing self-renewal of leukemic progenitor cells, and the disease is characterized by infiltration of bone marrow by promyelocyte-like leukemic cells [17]. According to the World Health Organization (WHO), APL diagnosis is based on detection of 20% or more blasts with these characteristics among

nucleated cells of bone marrow or peripheral blood, and by detection of PML-RAR α fusion gene [18].

There are three isoforms for PML-RAR α gene according to breakpoint. The breakpoint on chromosome 17 is constantly found in intron 2, but there is a variation in breakpoint on chromosome 15 generating the isoforms. The three breakpoints that can be found on chromosome 15 can occur in intron 3 (L-long or bcr-1 isoform), intron 6 (S-short or bcr-3 isoform) and in exon 6 (V-variable or bcr-2 isoform). Isoform S is associated with a short duration of remission and overall survival when compared to isoform L. The existence of different breakpoint regions in PML gene and presence of alternative splicing of transcripts are responsible for great diversity of PML-RAR α observed among patients [13,19].

Acetylation, the most extensively studied modification, is controlled by two families of enzymes: Histone Acetyl Transferases (HATs) and Histone Deacetylases (HDACs). The imbalance of acetylation and deacetylation of histones in promoter regions contributes to deregulation of gene expression and has been associated with carcinogenesis and progression of cancer [20].

RAR α receptor works as a transcription factor. In the absence of its ligand, retinoic acid is associated with HDAC-containing complexes, and this contributes to a silent state. At physiological concentrations of retinoic acid, a conformational change allows the release of HDAC-containing complex and association of RAR α with transcriptional co-activators (including HAT) and subsequent activation of transcription. In APL, physiological concentrations of retinoic acid are unable to trigger this change, and HDACs remain associated with retinoic acid target. In addition, there is a stoichiometric increase in association of HDAC-containing complexes with target genes of retinoic acid, and this enhances transcriptional silencing [21,22].

Besides these alterations in transcriptional regulatory genes, PML-RAR α may interfere with PML-controlled signaling pathways, conferring resistance to apoptosis and to self-renewal of myeloid progenitors through transcriptional modifications such as: ubiquitination, phosphorylation and sumoylation [23].

Clinical, laboratory and prognostic features

Morphologically, there are two variants of LPA - M3 (by FAB classification), which is considered to be typical APL or hypergranular, and M3 variant (M3v), which is considered hypogranular or atypical. Both have promyelocytes with

abnormal bilobed nuclei. M3 type occurs in 60-70% of cases of APL, which goes along with low count of normal white cells and promyelocytes with many cytoplasmic granules that are typically darker and larger than granules of normal promyelocytes, and presence of Auer rods in cytoplasm. On the other hand, M3v subtype presents leukocytosis and numerous promyelocytes identified in blood smear. Cells are characterized by the presence of irregular and granular nuclei when compared to a M3 variant [13].

Cells with promyelocyte morphology, as well as evidence of microangiopathic anemia (presence of schizocyte), can be seen in peripheral blood smear. Myelogram reveals massive infiltration by neoplastic promyelocytes, which strongly stain with Myeloperoxidase (MPO) reaction and Sudan Black (SB) [6].

Immunophenotyping studies evidence blasts with high autofluorescence, expressing early myeloid markers such as CD117 with low fluorescence intensity, CD13 with homogeneous pattern of fluorescence intensity, and CD33 with heterogeneous pattern. CD34, hematopoietic precursor cell marker, is usually negative, as so is HLA-DR. Contrary to normal promyelocytes, indicative markers of myeloid maturity, CD11b and CD15, are negative or very low in expression. Because immunophenotyping is a rapid method, it reinforces diagnostic suspicion of APL and helps in early therapeutic indication, but it is not considered an adequate method for definitive diagnosis [24].

According to NCCC (National Comprehensive Cancer Network), diagnostic confirmation should be made by techniques capable of detecting t(15;17) or hybrid gene PML-RAR α [25]. As for available methodologies, there are conventional cytogenetics, Fluorescence in Situ Hybridization (FISH), Reverse Transcription Polymerase Chain Reaction (RT-PCR), and Real-time Polymerase Chain Reaction (RQ-PCR) [26].

Traditional cytogenetic analysis has been used to confirm morphological diagnosis of APL. Although t(15;17) is not detected in other types of leukemia, "false-negative" results may come from the analysis of cells that do not belong to neoplastic clone, from difficulty in visualizing the translocation, or even from the existence of cryptic rearrangements that mask such translocation. The advent of nucleic acid technology, such as PCR and FISH, has revolutionized the field of genetic and oncological diseases. The sensitivity of these techniques to diagnosis

and monitoring of diseases at molecular level is being applied in the routine of many laboratories [27].

There are other hematologic diseases, both malignant and nonmalignant, that can be confound with APL and, therefore, should be included in the differential diagnosis of a patient suspected of having APL. Agranulocytosis with maturation to promyelocyte stage may be mistaken with LPA, yet, in cases of agranulocytosis, patient's platelet and hemoglobin counts are typically normal, bone marrow is not hypercellular, and Auer rods are not observed. Hypogranular variant of APL (M3v) may resemble AML, with monocytic differentiation exhibiting lobed nuclei. In such cases, for APL to be distinguished, cytochemical staining for MPO and immunophenotyping by flow cytometry must be done [13].

Regarding clinical characteristics, patients often present leukopenia and pancytopenia symptoms including anemia, weakness, fatigue, infection, bleeding, and organomegaly; however, in some cases, leukocytosis may occur, as in M3v and in cases without RAR α rearrangement, but still morphologically and immunophenotypically consistent with APL diagnosis [13]. Characteristically, there is a propensity to increased bleeding, disproportionate to thrombocytopenia. Hemorrhagic events are present in almost 60% of patients at the time of diagnosis and their incidence tends to increase in the first days of treatment [28].

Early diagnosis of APL is fundamental because this pathology is associated with a high risk of developing Disseminated Intravascular Coagulation (DIC), which is a rapidly evolving and a high-risk hemorrhagic syndrome [9]. Other less frequent features are observed in 15% to 20% of patients, and infiltration of central nervous system and skin are rare [29].

Several prognostic factors were identified in APL. High initial count of white blood cells seems to be associated with higher mortality during induction and higher incidence of relapse. Although limit value for definition of worse prognosis varies between studies, most groups adopt the value of 10,000 leukocytes/ μ L [6].

Prognostic significance of additional chromosomal abnormalities at t(15;17) is not completely established, and in most studies, presence of these alterations does not influence prognosis [30]. On the other hand, another study describes that presence of ZBTB16/RAR α and STAT5B/RAR α is related to worse prognosis and NMP/RAR α translocation related to greater chance of relapse [31].

Treatment

Treatment of APL has undergone important modifications in the last 30 years and what is established for APL differs from the schedules used for other myeloid leukemias [6].

According to the Adult Acute Myeloid Leukemia Diagnostic and Therapeutic Guidelines, APL is sensitive to daunorubicin, idarubicin and ATRA, which acts inducing maturation of blast cells, leading to CR and resolution of coagulation disorder. Subsequently, patient receives consolidation therapy with three courses of idarubicin and ATRA. Then, consolidation and maintenance treatments are performed with ATRA. Monitoring of PML/RAR α with Polymerase Chain Reaction (PCR) is recommended to detect molecular remission [32]. Although ATRA use as monotherapy leads to hematologic remission, most patients relapse. Thus, induction treatment should consist of administration of ATRA associated with anthracycline and cytarabine (Ara-C), except for patients with some clinical contraindication to the use of anthracyclines, thus achieving molecular remission in 90% of cases, with disease-free survival of 78% three years from diagnosis [33].

PML-RAR α oncoprotein leads to interruption of myeloid maturation at the stage of promyelocytes. In pharmacological doses, ATRA allows progression of this cellular differentiation. In this way, the leukemic clone progresses in myeloid maturation, becoming susceptible to mechanisms of cell death [6].

Treatment is usually divided into three phases:

induction of remission, consolidation and maintenance. The first two are based on the use of ATRA and some anthracycline, while the latter is composed of ATRA cycles associated with methotrexate and mercaptopurine in low doses (6).

Despite the excellent response to ATRA in patients with APL associated with PML-RAR α , patients with other translocations involving RAR α present variable sensitivity to this drug. About 10% of patients treated with ATRA associated with anthracyclines present hematologic relapse [33-36]. For these groups, other options of treatment should be sought, ATO among them [6].

High dose ATO leads to apoptosis, while low doses promote cell differentiation. The drug has three main mechanisms of action:

1) Production of reactive oxygen products that induce phosphorylation and activation of Jun N-terminal Kinase (JNK) pathway, triggering apoptosis.

2) Phosphorylation and sumoylation of PML-RAR α , causing its degradation.

3) Inhibition of hTERT transcription and consequent decrease in telomerase activity, inducing chromosomal fusion and apoptosis [6].

Also according to DDT, ATO has been used to treat refractory or relapsed patients following initial therapy with anthracyclines and ATRA. However, there is no evidence of ATO's superiority compared to ATRA and anthracycline association in first induction of remission, and ATRA with cytarabine and anthracycline association in relapse involving central nervous system [32].

In 2001, Soignet and colleagues evaluated ATO's efficacy for induction of remission and consolidation in patients with APL who presented relapses after treatment with retinoids and anthracyclines. 44 patients were selected with a diagnosis of relapse and/or refractoriness of APL, who had first or second relapse. ATO was administered for induction of remission. After CR, patients received one more cycle of the drug for consolidation therapy and, thereafter, up to 4 additional cycles for maintenance therapy. 85% (n = 34) of patients obtained CR and 91% (n = 31) of patients in remission presented negative cytogenetic tests for t(15;17) after treatment; 86% patients who were evaluated by RT-PCR assays presented negative (previously positive) tests for PML-RAR α after induction therapy or subsequent consolidation [37].

In 2013, guidelines of the Brazilian Society of Hematology and Hemotherapy (SBHH) recommend ATO to be avoided throughout pregnancy, and ATRA to be avoided only during first trimester, being daunorubicin recommended during this period. ATRA use, associated or not to chemotherapy, during second and third trimesters of pregnancy, appears to be effective in reversing coagulopathy and obtaining CR without evidence of teratogenicity [38].

Still according to SBHH guideline, if patients experience hematological relapse, they should be treated with ATRA or ATO associated with cytarabine and anthracycline. This

guideline reports the absence of evidence on superiority of ATO compared to ATRA combined with anthracyclines in treatment of induction in patients with newly diagnosed APL, thus remaining ATRA as first treatment option [38].

One of the side effects that can occur in leukemia patients treated with ATRA or ATO is Differentiation Syndrome (DS), characterized by increased leukocyte transmigration, which can be fatal. Clinical manifestations are quite varied, but respiratory symptoms predominate, associated or not with edema or pulmonary infiltrates. Fever, bone pain, weight gain, edema, cardiac failure, renal failure, cavity (pleural) effusions, and headache are other observed findings, commonly preceded by elevated white blood cell count. Onset usually begins between the third and the fourteenth day of treatment with ATRA, but there are reports of occurrence soon after the first dose [39].

There are few recent reports of hematopoietic stem cell transplantation (autologous or allogeneic) after first remission, since ATRA treatments have a better effect. This approach has been applied in patients who relapse after second remission or patients who do not present molecular remission [40].

APL treatment involves not only the correct choice of chemotherapy regimen but also an aggressive hemotherapy support due to coagulopathy in these patients. For the risk of bleeding, platelet count should be kept above $30 \times 10^3/\mu\text{L}$. Fresh frozen plasma and cryoprecipitate should be prescribed as long as there is clinical or laboratorial evidence of consumption of coagulation factors, aiming to keep fibrinogen above 150 mg/ μL [6].

Minimal residual disease and monitoring of treatment response

Minimal residual disease is defined as a small number of leukemic cells, which cannot be detected by morphology or cytogenetic analysis. It has a considerable prognostic value in many hematologic malignancies, including acute lymphoid leukemia, AML, lymphomas, multiple myeloma, and chronic myeloid leukemia, since when complete hematological remission is achieved, a large proportion of leukemic cells remain below detection limit of light microscope [41].

Any method with greater sensitivity than light microscopy can be used to detect MRD. Development and validation of methods that allow a high degree of

automation and processing of samples, such as: RQ-PCR, RT-PCR and flow cytometry with multiple parameters, drastically revolutionized the field of diagnosis and evaluation of patients at different stages of treatment. Every employed technique has advantages and disadvantages. There is no doubt that flow cytometry is an excellent tool for rapid and daily patient assessment, but its obvious disadvantages include lack of specificity and variation over time of abnormal antigen expression defined at the moment of diagnosis. On the other hand, RQ-PCR is more specific and sensitive than flow cytometry, however, it can only be applied to leukemia subtypes associated with specific gene rearrangements or mutations [42].

PML-RAR α fusion transcript allows accurate diagnosis and serves as a marker for MRD or recurrent APL. In fact, PML-RAR α was one of the first targets used to detect MRD in clinical studies performed by RT-PCR technique, after CML [43].

In 1999, Burnett et al. studied 239 patients treated with ATRA in which investigation of PML-RAR α presence was made at the end of consolidation. These authors demonstrated a 57% relapse rate among patients who had positive results for RT-PCR at the end of consolidation, thus reinforcing the importance of MRD monitoring throughout the course of treatment [44].

Following in 2003, Gallagher and colleagues used RQ-PCR technique to evaluate 23 patients with APL at intervals of three months after consolidation therapy, and demonstrated that monitoring had a high predictive value for relapse. It is important to note that analyzes were performed in peripheral blood of patients at high risk of relapse, whereas in previous studies they were made in samples of bone marrow [45].

Another prospective study by Grimwade and colleagues on MRD monitoring by RQ-PCR technique in 406 bone marrow and peripheral blood samples from patients treated with ATRA associated with anthracyclines, successfully identified the majority of patients at high risk of relapse, serving as a potent predictor of disease-free survival as well as a valuable tool for deciding early interventions [46].

Molecular remission after third round of consolidation is considered the therapeutic goal in APL. Besides, treatment for molecular relapse, precisely controlled by RT-PCR, has been shown to provide a survival

advantage compared to overt relapse treatment. Based on this evidence, longitudinal monitoring by RT-PCR and preventive therapy of early relapse are currently adopted by study groups. However, given the low risk of relapse reported for patients receiving ATO-based regimens, cost-benefit of prolonged molecular monitoring has been recently questioned [2,47,48].

Final comments

APL has a better prognosis when compared to acute leukemia in adults. Correct diagnoses, associated with rapid onset of treatment, as well as early detection of complications are essential for managing this patient successfully.

APL treatment using ATRA proved to be very effective and with an excellent initial response, observing remission in the first months of treatment. According to published studies, detection of MRD has proven to provide prognostic information independent of treatment in various types of leukemia. Using MRD monitoring to guide preventive therapy while patient still presents subclinical disease may allow a number of treatment-related toxicity advantages, reducing hospitalizations and improving clinical outcome.

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