5. Current approaches to acute promyelocytic leukemia

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Clinical characteristics of acute promyelocytic leukemia

Acute promyelocytic leukemia (APL), the M₃ subtype of acute myeloid leukemia (AML) in the French–American–British (FAB) classification system [1], is a distinct clinical and pathologic subtype that accounts for approximately 10% of acute myeloid leukemia (AML) cases. The unique features of APL have been well described [2–4] and include a characteristic morphologic appearance [5], a reciprocal translocation between the long arms of chromosomes 15 and 17 [6], younger age of onset [7], and severe consumptive coagulopathy with a high incidence of early fatal hemorrhage [3,8–10]. This coagulopathy is frequently exacerbated by cytotoxic chemotherapy, probably a result of leukemia cell lysis with release of procoagulant intracellular contents [11,12].

Diagnostic criteria for APL

Because the therapy for APL must now differ from other subtypes of AML, the critical initial act is to make an accurate diagnosis. The availability of therapeutic agents that are uniquely suited to treat APL necessitates quick and accurate diagnosis. Light microscopic evaluation of bone marrow aspirate smears provides the initial hint of the correct diagnosis. The classical FAB M₃ morphologic includes hypergranular cells and multiple Auer rods. Variant forms may present with hypogranular bilobed cells, basophilic cells, differenti-ated promyelocytes, and a few blast cells (M₂-like), with another form consisting largely of blast cells and a few early promyelocytes (M₁-like) [13,14].

Immunophenotype provides supportive evidence of the diagnosis of APL. A pattern of CD33 and/or CD13 positivity and CD14 and HLA-DR negativity is seen in 96% of cases. CD2 was positive in the FAB variant and in the subtype with basophilic cells, but negative with other subtypes [14]. The clinical correlates of molecular and immunophenotypic subtypes, including expression of CD34, CD2, and CD19, remain controversial [15].

The detection of chromosomal translocation t(15;17) provides conclusive
evidence of the diagnosis of APL. In addition to standard metaphase evaluation of karyotype, fluorescence in-situ hybridization probes may also be used to make a cytogenetic diagnosis [16–19].

Since variant translocations are also found, further evaluation by RT-PCR for the PML/RARA transcript is valuable in confirming the diagnosis and providing a tool to evaluate patients throughout their therapy for residual disease [20–24]. The discovery of the ability of retinoic acid to induce clinical remissions was paralleled by the description and explication of the molecular genetic basis of the disease. The molecular biology of this disease is detailed in the previous chapter, and only the applications of these data will be discussed in this chapter. The availability of rapid highly specific and sensitive RT-PCR assay using microfuge extraction of RNA and a single amplification round may speed the diagnosis of APL [25].

An alternative to molecular testing is the use of monoclonal antibodies directed against PML in an immunofluorescent assay [26,27]. This antibody can demonstrate the disruption of the PML nuclear bodies to produce a change of the nuclear staining pattern from speckled (wild-type PML protein) to microgranular (PML-RARα fusion protein). Because the epitope identified by PG-M1 is located in the amino terminal portion of PML, it can detect APL cases characterized by breakpoint occurring at different sites of PML (bcr-1, bcr-2 and bcr-3) [28]. This method provides a rapid, sensitive, and highly specific test for the diagnosis of APL that bears the t(15;17).

**Therapy of APL**

The therapy of APL was transformed by the discovery that all-retinoic acid can induce terminal differentiation and apoptosis of the malignant leukemic cells, resulting in a clinical remission [29–33]. This observation provided the first evidence of effective differentiation therapy and also provided a rationale for biologically targeted therapy based upon subtype of leukemia.

While combinations of anthracyclines and cytosine arabinoside were able to induce clinical remissions of long duration in patients with APL at a higher frequency that other FAB subtypes, historical and randomized comparisons of regimens that included all-trans retinoic acid (ATRA) have shown substantial superiority. Therefore, a retinoid should be included as a standard component of antileukemic therapy for patients with APL. The optimal dose, duration, and sequence of retinoid-containing therapy in APL remains uncertain.

*Role of ATRA therapy in APL*

The concordance of studies in APL therapy with ATRA suggests that there is a benefit to addition of ATRA to induction therapy. The question of whether ATRA induction without chemotherapy offers benefits compared to ATRA