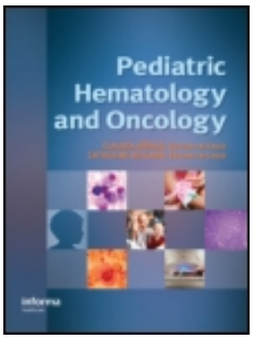

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Editorial

ACUTE PROMYELOCYTIC LEUKEMIA IN CHILDREN

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Keywords acute myeloid leukemia, acute promyelocytic leukemia, chemotherapy, retinoic acid

Acute promyelocytic leukemia (APL) is a clonal expansion of malignant cells blocked at a specific stage of myeloid differentiation. APL is a specific type of acute myeloid that is characterized by the morphology of blast cells; by the translocation t(15;17); and by coagulopathy combining disseminated intravascular coagulation, fibrinolysis, and proteolysis. The typical form of promyelocyte blasts, M3 in the French-American-British classification, shows bundles of rodlike structures (faggots) that are aggregates of granules and can be seen with special stains. These cells contain procoagulant materials that are released into the circulation, leading to disseminated intravascular coagulation. This type has also a microgranular form (LAM3 variant). In 1977, Janet Rowley reported that the t(15;17) translocation was a consistent chromosome finding in APL. The t(15;17)(q12;q22) fuses the promyelocytic leukemia (PML) gene on chromosome 15q22 to the retinoic acid receptor α (RARα) gene on chromosome 17q22-q21 [1, 2].

The breakpoints in PML are grouped in three clusters (bcr1, bcr2, bcr3) and the incidence of these localizations has been reported to differ in children and adults with an excess of localization in bcr1 in children [3] and a poorer prognosis. APL represents approximately 10% of acute myeloblastic leukemia (AML) in adults and 5% in children. APL is very infrequent in patients younger than 2 years.

Until 1990, intensive chemotherapy combining cytosine arabinoside (Ara-C) and an anthracycline was the most effective treatment of APL, with cure of 30–50% of patients who achieved complete remission (CR) [4]. All-*trans*-retinoic acid (ATRA) was initiated by the Shangai group and the French group [5, 6]. CR rates were reported for 90% of patients. Response was obtained not by cytotoxicity, but by differentiation of malignant pro-

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myelocytes into neutrophils. The differentiation is ascertained by the absence of bone marrow aplasia (without severe infections) and by the presence of Auer rods in mature cells [7]. Maturing bone marrow cells appear progressively during ATRA treatment and the clonal proliferation is progressively replaced by polyclonal hematopoiesis. A rapid improvement of coagulopathy, instead of worsening with conventional therapy, was seen. The karyotype of myeloid cells is normal at the time of CR. ATRA has opened new perspectives for differentiation therapy in oncology and hematology [8].

ATRA treatment has two important disadvantages.

1. After starting treatment, a rapid increase in white blood cells (WBCs) was seen in one-third of the patients, accompanied by clinical signs of retinoic acid syndrome (RAS) [9, 10]. Clinical symptoms are weight gain, lower extremity edema, hypotension, pleural and pericardial effusion, and sometimes renal failure. This RAS can be fatal in some patients. It is usually preceded by an increase of leukocyte counts [10], but RAS is not due to leukostasis. Once RAS has developed, the addition of low-dose chemotherapy is ineffective in lowering the WBC count, but in contrast to most publications. Ajai et al. report in this issue that hyperleukocytosis was prevented by the addition of hydroxyurea. Two different approaches are used: addition of intensive therapy for patients with high WBC counts or when an increase in WBCs is seen [11] and addition of high-dose intravenous corticosteroids as soon as the first symptom occurs [12]. Both approaches can be associated. The dosage used in adults is 45 $mg/m^2/d$. In children, headache due to intracranial hypertension can be severe and associated with signs of pseudotumor cerebri [13]. Low doses of ATRA, 25 mg/m^2, reduce this side effect and seem as effective as the conventional dose of 45 mg/m^2, but are unable to prevent retinoic acid syndrome.

2. Resistance to the drug develops. All patients who received ATRA for maintenance therapy had relapses within a few weeks of CR achievement [14]. No response was observed in patients who had received ATRA and had relapses within 3–4 months after discontinuation of ATRA. Therefore, continuous therapy with ATRA is not useful: ATRA alone cannot eliminate the leukemic clone [15]. These findings justify the superiority of combined treatment with ATRA and intensive therapy over intensive therapy alone or ATRA alone in newly diagnosed APL. Actuarial survival at 4 years was 40% after chemotherapy alone and 77% after ATRA and chemotherapy [16]. Cooperative studies have shown that patients receiving intensive therapy after achieving CR with ATRA have a lower risk of relapses [17]. Because more than 70% of the patients in CR are long-term survivors, the role of allogeneic bone marrow transplantation in first remission is questionable.

Allogeneic and perhaps autologous bone marrow transplantations are indicated only for patients in second CR who have relapses.

The quick normalization of the fibrinogen level with ATRA seems to be related to the disappearance of primary fibrinolysis. Bleeding diathesis disappears during the first week, but a tendency for thrombosis exists during the first month. The persistence of moderate thrombotic activity leads to a period of hypercoagulopathy, which could explain a few cases of thromboembolic events in patients with APL treated with ATRA [16].

The PML/RARα fusion gene encodes a fusion protein. Clustering of the chromosome breakpoints around exons 3 and 4 of the RARα gene allows the use of in vitro polymerase chain reaction (PCR) to assess the molecular rearrangement at diagnosis and during follow-up. Amplification of the PCR RARα fusion transcript by reverse transcription (RT)-PCR provides a tool for monitoring minimal residual disease, whatever the treatment [16]. After ATRA-induced CR, all studies demonstrate the persistence of a fusion transcript, confirming that the leukemic clone is not completely eradicated by the retinoic acid [18], but RT-PCR is generally negative after consolidation therapy using anthracycline and Ara-C [19].

Patients with positive RT-PCR for PML/RARα after a negative period could be candidates for bone marrow transplantation, but the sensitivity seems low compared with other tests performed in other types of AML.

Arsenic trioxide, As_2O_3, was introduced in China in the treatment of APL in 1970. As_2O_3, at a dose of 10 mg/d for 28 to 54 days, induced clinical CR in 14 of 15 APL patients with relapses. During the treatment, there was no bone marrow aplasia and laboratory coagulation abnormalities were progressively corrected. It appears to be a safe drug for adult patients refractory to ATRA and conventional therapy. The combination of partial differentiation and apoptosis appears to be the cellular effect of As_2O_3 in the treatment of APL [21].

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