Acute Promyelocytic Leukemia: Another Pseudoleukemia?

In 1875, William Pepper described the bone marrow of a fatal case of pernicious anemia as pseudoleukemia. In the first part of this century, Minot and Murphy abolished anemia in a series of 45 pernicious anemia patients with daily ingestions of beef liver for months. Ultimately, vitamin B12 was demonstrated to be the missing maturation and differentiation inducer, and continuous treatment with that agent uniformly cures the manifestations of the disease, but not the disease itself.

Twenty-five years ago, a variety of chromosomal aberrations, including balanced translocations, were reported in untreated pernicious anemia that "were reminiscent of the findings in certain malignant neoplasms." These findings disappeared with vitamin B12 treatment, but usually reappeared if treatment was stopped.

In this issue, Castaigne et al and Chomienne et al present dramatic evidence that a similar story may be unfolding for one type of acute leukemia, acute promyelocytic leukemia. They report that 14 of 22 patients in relapse with acute promyelocytic leukemia achieved a complete response with the oral administration of all-trans retinoic acid. The agent was administered for 90 days and then discontinued. Many responses were brief, lasting only several months, but some lasted a year or more. The classic cytogenetic translocation of acute promyelocytic leukemia, t(15;17), was found in 20 of 21 patients before treatment, but could not be found during complete remission. The leukemic cells of 19 of the patients were studied for in vitro differentiation induction by trans-retinoic acid, and in 18 cases differentiation and maturation were observed. The only in vitro nonresponder was also the only patient completely refractory to trans-retinoic acid clinically.

The cytogenetic abnormalities observed in pernicious anemia occur randomly, probably as a result of disordered DNA metabolism, whereas the cytogenetic aberration characteristic of acute promyelocytic leukemia is clonal, nonrandom, and more likely to be pathogenetic than are karyotypic abnormalities in pernicious anemia. Nevertheless, the observation that cytogenetic abnormalities in both diseases may be repaired coincident with the induction of differentiation and maturation is provocative.

The clinical results reported by Castaigne et al and Chomienne et al are even more impressive when one considers only those patients in first relapse, because a complete response was obtained in 10 of 11 such patients. These results are identical to those of Huang et al, who were the first to report complete responses with trans-retinoic acid in acute promyelocytic leukemia, and who supplied the French workers with the retinoid initially.

Trans-retinoic acid induced complete remission slowly in both the Chinese and the French experience (30 to 90 days or more), and remission was accomplished without the imposition of bone marrow hypoplasia, a phenomenon observed with standard therapy of this disease, on occasion. The therapy was essentially without toxicity compared with standard chemotherapy induction regimens and, in the French study, a median of only 8 days was required for initial hospitalization. However, in that study, there were three early deaths associated with hyperleukocytosis after the onset of trans-retinoic acid therapy. The investigators caution that trans-retinoic acid must be administered under close observation to those patients who present with elevated white blood cell counts, because drug-induced hyperleukocytosis may have been a factor in the early deaths observed.

Rebound peripheral leukocytosis has been observed with other induction treatments for this disease, but unlike the mature leukocytosis observed after trans-retinoic acid administration, the rebound leukocytosis after standard chemotherapy is usually blastic.

The mechanism of action of trans-retinoic acid in acute promyelocytic leukemia is unknown, but the presence of Auer rods in the maturing cells of some responders, and in vitro studies strongly suggest that response results from induction of differentiation rather than cytotoxicity. 13-cis retinoic acid, the more stable retinoid, has been extensively studied as an in vitro inducer of differentiation of leukemic cell lines and fresh leukemic cells. Attempts to demonstrate the role of retinoic acid nuclear receptors (RAR) in differentiation induction by that retinoid have yielded negative and positive results that require further study. It is intriguing that the DNA-binding domains of the RAR-α and β, and those of the thyroid-hormone receptors, are highly homologous. Umesono et al demonstrated that human RAR-α could activate thyroid-hormone responsive elements from the rat growth hormone gene, and Graupner et al found that RAR-β and thyroid-hormone receptors act through the same DNA sequence. These investigators postulated that retinoic acid and thyroid hormones acting through their respective receptors could control overlapping gene networks involved in the regulation of morphogenesis and hemostasis. These postulations are intriguing in view of the increased incidence of thyroid disease in patients with acute leukemia.
Most clinical studies of retinoids in leukemia have involved 13-cis retinoic acid rather than all-trans retinoic acid. Although the former has been active in vitro, clinical trials have been largely disappointing. Chomienne et al\(^6\) postulate in this issue that all-trans retinoic acid may induce response in a concentration one order of magnitude lower than that required for 13-cis retinoic acid activity. Other possible mechanisms of the differential clinical effect of the two retinoids include binding with different affinity to the same or different serum proteins, or different interactions with RAR.

Serum inhibitors of retinoids found in normal and leukemic sera\(^{18}\) may modulate the antileukemic activity of retinoids and account for some of the conflicting data on the role of some retinoids in in vitro versus in vivo differentiation. Such inhibitors have been found in normal serum and serum from patients with acute promyelocytic leukemia.

The clinical trans-retinoic acid studies\(^2\) reiterate an interesting point first observed in pernicious anemia: lack of detection of a clonal karyotypic abnormality by cytogenetic techniques during remission is not equivalent to cure. Molecular techniques will be required to determine the true presence or absence of an abnormal gene. On the other hand, eradication of the abnormal gene associated with a malignant clone may not be necessary for long-term disease-free survival.\(^{19}\) This may be especially true if differentiation and maturation, rather than cell kill, is the goal of antileukemia therapy.

We have been fortunate enough to obtain all-trans retinoic acid from Castaigne et al\(^5\) and Chomienne et al,\(^6\) and to confirm the activity of this agent in a patient with relapsed acute promyelocytic leukemia and in a patient with a promyelocytic blast crisis of chronic myelocytic leukemia who did not have the t(15;17) translocation. Our results will be presented shortly.

Huang et al,\(^8\) and now Castaigne et al\(^5\) and Chomienne et al,\(^6\) have demonstrated a major clinical effect of trans-retinoic acid on acute promyelocytic leukemia. Although remissions may be brief and relapses do occur in most patients, the results are fascinating. Trans-retinoic acid should be considered as initial therapy for relapsed acute promyelocytic leukemia patients. Studies designed to prolong remission duration, and to determine the role of the retinoid in newly diagnosed patients are urgently needed and should be conducted on a national scale. Studies in other leukemias and in myelodysplasias are also warranted. Although there is some question about the purity of the all-trans retinoid acid used in the Chinese and French studies, there is little doubt that the preparations yield reproducible therapeutic results. Trials to be conducted under the auspices of the National Cancer Institute (NCI) will use pure acid in a stable formulation. Phase I studies with this new preparation have already begun, and the Investigational Drug Branch of the NCI will provide drug now for patients with relapsed acute promyelocytic leukemia under certain circumstances.

Perhaps combinations of agents such as trans-retinoic acid and \(\alpha\)-interferon\(^{11}\) will enhance treatment results in acute promyelocytic leukemia in the future. Another pseudoleukemia could be on the way out.

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REFERENCES

2. Minot GR, Murphy WP: Observations on patients with pernicious anemia partaking of a special diet. A. Clinical aspects. Trans Assoc Am Physicians 41:72, 1926

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