All-Trans Retinoic Acid for the Treatment of Newly Diagnosed Acute Promyelocytic Leukemia

To the Editor:

In their recent report, Kanamaru et al.1 compared all-trans retinoic acid (ATRA), either alone or in combination with chemotherapy (AML-92), with a previous study (AML-89) using standard chemotherapy in patients with newly diagnosed acute promyelocytic leukemia (APL). They conclude that the administration of ATRA (with or without chemotherapy) results in a higher complete remission (CR) rate, lower early mortality rate, and superior survival.

We believe that the comparison with their previous study is flawed, because the induction chemotherapy regimen in both trials differs significantly. In AML-89, the dose of daunorubicin administered was 50 mg/m²/day for 5 to 7 days, compared with 40 mg/m²/d for 3 days in the present trial. Ara-C was administered for up to 12 days in AML-89, compared with 5 days in AML-92. Furthermore, prednisolone (40 mg/m²/d for 7 days) was added in AML-89 but not in AML-92.

The more intensive chemotherapy, with its consequent severe neutropenia, combined with steroids may explain the 20% early death rate in AML-89. Of these deaths, one occurred before day 7, the typical time for death from hemorrhagic complications. The remainder occurred between days 7 through 28 and were likely to be due to neutropenic sepsis. This early death rate is more than double that of a recent randomized trial comparing ATRA (with or without chemotherapy) with standard chemotherapy.2 That trial (European APL-91 Group) reported 4% early deaths in the chemotherapy alone arm, 3 occurring within 8 days of initiating chemotherapy. These deaths were due to bleeding. Only one patient died of infection on day 40. Further comparison between AML-89 and the present trial is hindered by the lack of data on coagulation parameters, which is surprisingly absent in both studies.

In a previous study of the Japan Adult Leukemia Study Group (AML-87), the effect of adding vincristine to a standard induction chemotherapy regimen was evaluated.3 The chemotherapy was identical to that administered in AML-89, except for a shorter duration of prednisolone therapy. In that study, the CR rate for the 26 APL patients who did not receive vincristine (which was shown to be detrimental in all subtypes of acute myeloid leukemia) was 85%, which was very similar to the 89% reported in the present study.

To conclude that ATRA is superior to chemotherapy alone requires a prospective randomized trial (such as that of Fenaux et al.) or, at the very least, a historical control in which the chemotherapy regimens are identical. We propose that the disparity in the CR rate between AML-89 and the present trial is mainly due to the increased early death rate in the former study, which used more intensive chemotherapy.

Shmuel Gillis
Lawrence S. Blaszkoswsky
Division of Hematology-Oncology
New England Medical Center
Boston, MA

REFERENCES


As Drs Gillis and Blazkowsky commented, it is true and we also totally agree that a prospective randomized study is needed to conclude that all-trans retinoic acid (ATRA) therapy is superior to chemotherapy alone in the treatment for acute promyelocytic leukemia (APL). At the start of the AML-92 study of the Japan Adult Leukemia Study Group, we discussed whether we should conduct a comparative study. However, we decided not to do it. The first reason for our decision was the number of patients required for the comparison. Our statistician told us to enroll at least 242 APL patients to study a 15% difference of complete remission (CR) rate at \( \alpha = 0.05 \) and \( \beta = 0.8 \). Thus, it was impossible for our group, and probably for most other groups, to accumulate such a large number of APL patients. The second reason, and probably the stronger one, was the remarkable effect of ATRA on refractory/relapsed APL patients in our previous study.\(^1\) We thought that both patients and participating physicians would refuse the randomization after knowing of such a remarkable effect of ATRA with least complications, even if we could obtain the approval from the institutional review boards. We also believe that the CR rate of the ATRA-containing regimen will be higher when we become more experienced with the differentiation therapy. In fact, our latest data show that the CR rate exceeds 92% in newly diagnosed APL patients in our on-going study.

As for the comparison to the AML-87 study,\(^2\) in which 36 (80%) of 45 APL patients obtained CR, there was no statistical difference in the CR rates between the AML-87 and the AML-92 (\( P = .193 \)), as Drs Gillis and Blazkowsky commented. However, the disease-free survival (DFS) of CR cases and the event-free survival (EFS) of all evaluable cases in the AML-92 study are superior to those of the AML-87 study, as shown in Figs 1 and 2. Because there was a 5-year interval between the two studies, we thought that the interval was too long and did not use the AML-87 study as a historical control. Incidentally, the DFS and EFS of the AML-87 study were almost identical with those of the AML-89 study.\(^3\)

Because ATRA reduces the medical costs required for remission induction,\(^4,5\) we strongly believe that ATRA should be used as a first choice for APL from both a medical and an economical point of view, although a comparative study may be required to show a statistically significant difference.

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S Gillis and LS Blaszkowsky