Treatment of Myelodysplastic Syndromes With All-Trans Retinoic Acid

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We treated 23 patients with myelodysplastic syndromes (MDS): 2 refractory anemia (RA) with prior therapy, 11 RA with excess of blasts (RAEB), and 10 RAEB in transformation (RAEB-T), with daily oral 45 mg/m² all-trans retinoic acid (ATRA) in a multiinstitutional prospective study. The result was transient and did not last for more than 5 weeks despite the continuation of ATRA therapy. In one patient with RAEB-T, slight increase of hemoglobin levels or reduction of blast percentage in bone marrow was noted. Toxicities attributable to ATRA were minimal and included cholestasis, xerosis, dermatitis, gastrointestinal disorders, abnormal liver function tests, and high serum triglyceridemia. Although ATRA works remarkably as a differentiation therapy in acute promyeloctic leukemia, its effect in MDS included in this study was modest. Further study of this agent alone or in combination may be warranted in less advanced stages of this disease.

MYELODYSPLASTIC syndromes (MDS) are a heterogeneous group of clonal hematopoietic disorders characterized by cellular marrows with impaired maturation, ineffective blood cell production, and relatively indolent clinical courses. Despite numerous therapeutic efforts using steroid hormones or chemotherapeutic drugs, the overall effects on survival were not encouraging, and there is no effective standard therapy that sustains improved hematopoesis or postpones the leukemia transformation.

Because defective maturation involving one or more of the hematopoietic lineages is the central pathophysiological feature of this disease, and because it has been well documented that many leukemia cell lines are induced into differentiation to more matured cells in vitro by a variety of agents, there have been a considerable number of clinical trials to treat MDS by stimulating differentiation with retinoids, vitamin D₃, or colony-stimulating factors (CSFs).

Although several investigators reported a beneficial effect of 13-cis retinoic acid in the therapy of MDS, the results were not convincing when the drug was tested in randomized studies. However, recently Chinese investigators reported a high rate of complete remission (CR) with all-trans retinoic acid (ATRA) in acute promyelocytic leukemia (APL), and subsequently, other investigators, including us, confirmed the remarkable effect of this drug on APL.

ATRA was given at least for 4 weeks, and was continued further if there was any sign of improvement in peripheral blood counts. Karyotypes were analyzed with the use of Giemsa- or quinacrine-banding techniques. Response to ATRA was determined by a scoring method described previously. In short, increase of absolute neutrophil counts in peripheral blood over 1,000/µL was scored as 25 points, and from 500 to 1,000/µL as 15 points. Increase of hemoglobin (Hb) levels over 3 g/dL was scored as 25 points, and from 1.5 to 3 g/dL as 15 points. Increase of absolute platelet counts over 80 × 10³/µL was scored as 25 points, and from 40 to 80 × 10³/µL as 15 points. Reduction of frequency of blood or platelet transfusion was scored as 10 points. More than 50% reduction of percentage of blasts in bone marrow was scored as 10 points. Good response was recorded for a total score of 50 or more, partial response (PR) for 25 to 49 points, and minor response (MR) for 10 to 24 points. The study was approved by the institutional review board of each hospital.

RESULTS

Twenty-three patients with MDS were prospectively registered from 16 hospitals from May 1991 to May 1992. There were 2 RA, 11 RAEB, and 10 RAEB-T. All patients were eligible, and all were evaluated for response. Patient's age ranged from 10 to 78 years with a median of 64. There were 18 males and 5 females. Peripheral leukocyte counts ranged from 600 to 5,900/µL with a median of 2,400/µL, erythrocyte counts from 1,620 to 4,500 × 10³/µL with a median of 2,350 × 10³/µL, hemoglobin from 5.6 to 13.0 g/dL with a median of 7.8 g/dL, and platelet counts from 5 × 10³ to 160 × 10³/µL with a median of 56 × 10³/µL. Percentage of blasts in peripheral blood ranged from 0% to 29% with a median of 3%, and that...
in bone marrow ranged from 2% to 26% with a median of 13%

One patient received ATRA for 16 weeks, 4 patients for 12 weeks, 3 for 8 weeks, and 15 for 4 weeks. Six patients showed some improvement of peripheral blood counts and/or reduction of percentage of blasts in bone marrows, and 3 patients were judged as PR and 3 as MR according to our response criteria (Table 1). In three PR patients, more than 1,000/µL increase of peripheral absolute neutrophil counts was observed in all patients and more than 50% reduction of blast percentage in the bone marrow in one patient 2 to 9 weeks after the start of ATRA, but no improvement was noted in Hb levels and platelet counts. Neutrophil counts started to increase gradually shortly after the start of therapy, but it took 2 to 9 weeks to have a more than 1,000/µL increment from the pretreatment level. The effects were transient and did not last for more than 5 weeks despite the continuation of ATRA therapy. At the start of ATRA therapy in three PR patients, blast percentages in the bone marrow were 19%, 12%, and 24%; leukocyte counts were 4,900, 3,700, and 4,400/µL; Hb levels were 8.1, 8.9, and 7.4 g/dL; and platelet counts were 5,155, and 43 × 10^9/µL, respectively. In three MR patients, a slight increase of Hb levels was seen in two patients and a more than 50% reduction of blasts in bone marrow was noted in one patient, but no increase of neutrophils counts or platelet counts was observed. Both RA, 5 RAEB, and 2 RAEB-T patients were previously treated with androgens, corticosteroids, granulocyte CSF (G-CSF), macrophage CSF (M-CSF), vitamin D3, bestatin and/or low-dose cytarabine. No one responded to the prior therapy except one with RAEB whose neutrophils transiently increased while receiving prednisolone. Of 9 previously treated patients, 1 achieved PR and 1 obtained MR, and of 14 previously untreated patients, 2 achieved PR and 2 obtained MR (Table 1). The patient who had shown a transient response to prednisolone did not respond to ATRA. Chromosome analysis was attempted in all patients before the start of therapy, and adequate analysis was obtained in 19 patients. Thirteen patients had various abnormalities including 5q−, −7/7q−, and +8, two of whom achieved PR and two obtained MR. One PR patient had multiple chromosomal abnormalities including −5q, −7, and +8, and the other PR patient had +8 and 1q+. One MR patient had −5 and −7, and the other MR patient had +8. Of six patients with no chromosomal abnormality, one achieved PR and one obtained MR (Table 1).

Toxicities attributable to ATRA were chelitis in 15 patients, xerosis in 9, dermatitis in 3 (all World Health Organization [WHO] grade 1), gastrointestinal trouble in 4 (all WHO grade 1), and elevation of serum GPT in 4 (WHO grade 1 in 2 and grade 2 in 2) with elevation of total bilirubin in 1 patient (WHO grade 1), and increase of serum triglyceride in 8. They were all minimal to moderate, and hardly required specific medications or discontinuation of ATRA.

**DISCUSSION**

Despite the remarkable effectiveness of ATRA as a differentiation therapy of APL, the drug showed only a minimal effect in MDS. The daily dose, 45 mg/m², is a standard dose in the treatment of APL. Although the purity of Chinese ATRA was about 80% to 85% according to our own analysis, we obtained 82% CR in refractory APL with the same product and with the same dose and treatment schedule. Thus, the same dose and product which is effective in treating APL showed a modest effect in the treatment of MDS. However, it is possible that other dosing regimens of ATRA would be more effective in MDS.

APL is known to be associated specifically with a chromosomal translocation, t(15;17). It was recently found in APL cells that PML gene on the chromosome 15 fuses with retinoic acid receptor-α (RARα) gene on the chromosome 17, and that the chimeric PML-RARα gene presumably inhibits the differentiation of APL cells by a dominant negative fashion. Because t(15;17) and the PML-RARα chimeric gene are not found but other chromosome abnormalities such as 5q−, −7/7q−, and +8 are commonly observed in MDS, the pathogenesis of APL and MDS is apparently different. The difference in cytogenetic abnormalities may be one reason why ATRA has a minimal effect in MDS, although other explanations are possible because six patients with MDS without t(15;17) showed some response to ATRA in our study.

It was reported that 13-cis RA produces about 20% of partial or good response among approximately 150 patients with MDS in nine trials. However, prospective randomized studies, including one in a double-blind placebo-controlled study, failed to demonstrate significant difference in response rates and survival. Nevertheless, it was reported that only patients with RA showed an increase in survival by 13-cis RA therapy. Besides, long-term administration of 13-cis RA is reportedly required to show clinical responses.

In our study, most patients were RAEB or RAEB-T, and only two patients were RA who had been refractory to prior therapy with androgens or M-CSF. Also, ATRA was discontinued when there was no sign of improvement in peripheral blood counts at 4 weeks. Therefore, if patients with less-advanced stages of MDS were included, or if ATRA was administered for a longer period despite no response at 4 weeks, the response rate might have been higher than observed in this study. Just recently it was reported that two patients with

<table>
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<th>Subtype of MDS</th>
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Total: 23 cases with PR 3 (13%), MR 3 (13%), NR 17.
RAEB responded to daily 45 mg/m² ATRA therapy with a temporary improvement of erythropoiesis. Their Hb levels started to increase 2 weeks after the start of ATRA.22 Thus, the administration period may not be the reason for poor response in our study. The increase of neutrophil counts in three PR cases was gradually seen shortly after the start of therapy, and more than a 1,000/µL increment was reached 2 to 4 weeks after the start of therapy in our study.

Because we tried only daily 45 mg/m² ATRA therapy in this study, alternate doses of this agent should be evaluated in MDS in future, especially in less advanced stages of the disease, such as RA. Furthermore, because ATRA shows synergistic effect with several cytokines such as G-CSF or interferons in inhibition of proliferation and in induction of differentiation of several human leukemia cells in vitro,23,24 further trials with ATRA in combination with cytokines, especially G-CSF which has been shown to be a safe and effective drug to improve neutropenia in MDS patients,25 may be worth trying.

ACKNOWLEDGMENT

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REFERENCES

Treatment of myelodysplastic syndromes with all-trans retinoic acid.
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