

## All-Trans Retinoic Acid as a Differentiation Therapy for Acute Promyelocytic Leukemia. I. Clinical Results

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Twenty-two patients with acute promyelocytic leukemia were treated with all-trans retinoic acid (RA, 45 mg/m<sup>2</sup> per day) for 90 days. Of the 22, four patients were previously untreated, two were resistant after conventional chemotherapy, and 16 were in first (n = 11), second (n = 4), or third (n = 1) relapse. We observed 14 complete response, four transient responses, one failure, and three early deaths. Length of hospitalization and number of transfusions were notably reduced in complete responders. Correction of coagulation disorders and an increase of WBCs were the first signs of all-trans RA efficacy. Morphologic analysis performed at days 0, 15, 30, 45, 60, and 90 showed that complete remissions were obtained without bone marrow (BM) hypoplasia. Presence of Auer rods in the maturing cells confirmed the differentiation effect of the treatment. At remission, the t(15;17) initially present in 20

patients was not found. The in vitro studies showed a differentiation in the presence of all-trans RA in 16 of the 18 tested cases. The single nonresponder to all-trans RA in vitro did not respond in vivo. Adverse effects of RA therapy—skin and mucosa dryness, hypertriglyceridemia, and increase of hepatic transaminases—were frequently noted. We also observed bone pain in 11 patients and hyperleukocytosis in four patients. Whether maintenance treatment consisted of low-dose chemotherapy or all-trans RA, early relapses were observed. Five patients are still in complete remission (CR) at 4 to 13 months. Our study confirms the major efficacy of all-trans RA in M3, even in relapsing patients. Remissions are obtained by a differentiation process.

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**A**CUTE PROMYELOCYTIC leukemia [M3 in the French-American-British (FAB) classification]<sup>1,2</sup> represents 5% to 15% of cases of acute nonlymphocytic leukemia (ANLL). Several well-recognized features are characteristics of this entity: a distinct cytologic characteristic within the FAB classification (M3 or M3 variant), an associated coagulopathy often increased by chemotherapy,<sup>3</sup> and a distinct chromosomal abnormality—a balanced translocation between the long arm of chromosome 15 and the long arm of chromosome 17.<sup>4</sup> Although M3 is very sensitive to chemotherapy,<sup>5-7</sup> 10% to 20% of the patients die early of fatal hemorrhage resulting from coagulopathy. Studies of the length of complete remission (CR) show controversial results, some of them indicating a greater disease-free survival than in the other ANLLs.<sup>7,8</sup> An alternative approach to treatment of ANLL has been suggested in recent years by studies of leukemic cell differentiation. Of the differentiating agents, retinoic acid (RA), the active metabolite of vitamin A is the most potent. The two naturally occurring isomers of RA, all-trans RA and 13-cis RA, are active inducers of differentiation in human myeloid leukemic cell lines (HL-60, U-937, and THP-1). Although other synthetic analogues may be more potent some, like etretinate, have no effect on

leukemic cell differentiation.<sup>9</sup> On fresh human promyelocytic leukemic cells in primary culture, both isomers have been shown to have a constant effect at 10<sup>-6</sup> mol/L with very few exceptions.<sup>10</sup> Until now, only 13-cis RA and the etretinate were available for human treatment, and few responses have been reported in treatment of M3.<sup>11-15</sup>

Recently, Huang et al documented the efficacy of all-trans RA in 24 patients with M3 by obtaining 23 CRs.<sup>16</sup> We subsequently showed the superiority of all-trans RA as compared with the 13-cis RA in inducing differentiation in vitro and in vivo of leukemic cells from M3.<sup>17</sup> Thanks to a close collaboration with Shanghai University II, we were provided with all-trans RA by Professor Wang Zhen-Yi (Shanghai). Since June 1989, the drug has been provided by Hoffman LaRoche, France. We report the results obtained in the first 22 M3 patients treated in France with all-trans RA.

### PATIENTS AND METHODS

#### Patients

From October 1988 to July 1989, 22 patients with an M3 (n = 21) or an M3 variant (n = 1) leukemia were treated with all-trans RA. Informed consent was obtained from all patients. Eleven men and 11 women with a mean age of 44 years (range 19 to 81 years) were treated.

Reasons for treatment with all-trans RA were as follows. One man aged 81 years with an M3 variant form, one woman aged 78 years who had previously been treated with radiotherapy and chemotherapy for a lymphoma, one 72-year-old man with a past history of pulmonary silicosis, and one 51-year-old woman who had been treated for breast cancer with chemotherapy 3 years earlier, and who refused chemotherapy for her leukemia, and two patients who had failed to respond to two courses of conventional high-dose induction chemotherapy were treated with all-trans RA for their first attack of the disease.

Eleven patients (relapses occurred 6 to 39 months after the first remission) were treated for their first relapse after conventional chemotherapy. Four patients [of whom two had received an autologous bone marrow (BM) transplantation as treatment of their first relapse] were treated for the second relapse. One patient was treated for a third relapse.

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### Treatment

All patients received the same dose of all-trans RA (45 mg/m<sup>2</sup> per day) orally in two oral doses for 90 days. Fifteen patients were treated with all-trans RA from China and seven received all-trans RA from Hoffman-LaRoche. All-trans RA from China or from Hoffman LaRoche were manufactured in 10-mg capsules in light-proof packages. To prevent RA secondary effects, patients received cold cream, lip salve, and eye drops.

Oral analgesics, including morphine were prescribed, if necessary, for bone pain. Patients received RBCs and platelet transfusions when hemoglobin levels were lower than 8 g/dL or platelet counts were lower than 20.10<sup>9</sup>/L. Three patients were treated with heparin for disseminated intravascular coagulation (DIC) at the beginning of treatment with all-trans RA.

### Survey

All patients were hospitalized at the beginning of treatment. Peripheral blood (PB) counts, BM aspiration for cytologic and cytogenetic examination, in vitro differentiation, and coagulation studies were performed before the start of therapy.

During treatment, patients were surveyed as outpatients as soon as possible. PB counts were performed twice weekly. Complete examination with BM aspiration, hepatic biologic tests, and lipid balance were performed on days 15, 30, 45, 60, and 90.

**Cytologic studies.** Morphologic details were studied on PB films and BM smears stained with May-Grünwald-Giemsa at pH 7. Myeloperoxidase, naphthol-ASD-chloroacetate esterase, and  $\alpha$ -butyrate esterase reactions were applied to each sample.

**Cytogenetic studies.** Cytogenetic studies were performed on BM and/or PB cells before treatment in all patients and controlled during treatment once (n = 5), twice (n = 6), three times (n = 4), or four times (n = 2) in responders. The number of metaphases examined varied among cases and specimens (5 to 40 metaphases).

### Definition of Response

CR was defined as absence of M3 blast cells in a normal cellular BM with a normal PB count (hemoglobin 12 g/dL, polymorphonuclear leukocytes [PMN] > 1.5 10<sup>9</sup>/L, platelet count >100 × 10<sup>9</sup>/L). A transient response was defined as an improvement in blood and BM parameters without attainment of criteria of CR.

## RESULTS

### Biologic Characteristics

Features at diagnosis are shown in Table 1. Only one patient (patient 3) had a microgranular variant form of M3 with hyperleukocytosis. The percentage of M3 blast cells in the marrow ranged from 8% to 100%. In five patients, the low percentage of blast cells corresponded to the beginning of their relapse.

Thirteen patients had biologic signs of DIC. In seven patients, fibrinogen was less than 2 g/L (0.2 to 1.9) with an increase of fibrin degradation products (FDP). In the six other patients, the sole abnormality was an increase in FDP (>8  $\mu$ g/mL).

Twenty patients had t(15;17) (one technical failure and one normal karyotype in one patient with an early diagnosed relapse). In seven patients, all metaphases had the t(15;17). Thirteen patients had a mixture of normal metaphases and metaphases with t(15;17). Ten had additional changes, clonal or nonclonal (Table 1).

### Clinical Results

Patient-by-patient results and follow-up are shown in Table 2.

**Table 1. Characteristics Before Treatment With All-Trans RA**

Patient	Sex/Age	Disease Status	WBC 10 <sup>9</sup> /L	% Blasts in BM	Cytogenetics (no. of metaphases)	DIC
1	F/51	Untreated "secondary"	0.6	70	Failure	+
3	M/81	Untreated M3 variant	33	100	AA+ (32)	+
17	F/68	Untreated "secondary"	2.3	69	AA+ (32)	+
22	M/72	Untreated	1	53	AN (2/1)	—
5	F/31	Induction failure	0.9	58	AN (23/2)	+
9	F/29	Induction failure	0.9	80	AA (23)	+
4	M/36	First relapse	2	14	AN (13/39)	—
6	F/61	First relapse	1.7	57	AN (26/6)	+
7	F/57	First relapse	1.2	68	AA (6)	—
8	F/54	First relapse	4	90	AA+ (26)	+
10	F/67	First relapse	2.6	8	AN (13/3)	—
11	M/52	First relapse	2.1	65	AN (6/14)	+
16	F/19	First relapse	1.5	90	AA+ (27)	+
18	M/35	First relapse	2.2	65	AN+ (6/1)	—
19	M/51	First relapse	3.5	17	AN+ (10/35)	—
20	M/52	First relapse	2.1	16	NN	+
21	M/53	First relapse	1	69	AA+ (26)	—
2	M/48	Second relapse	0.9	32	AN (6/16)	—
12	F/45	Second relapse	1.9	80	AN (17/2)	—
13	M/30	Second relapse	2	73	AN+ (19/6)	+
15	F/23	Second relapse	0.7	65	AN+ (16/1)	+
14	M/19	Third relapse	4.6	100	AN+ (23/1)	+

Abbreviations of karyotypes: NN, normal; AN, metaphases with t(15;17) and normal metaphases; AA, t(15;17) in all metaphases; +, additional changes (clonal or nonclonal).

Numbers in parentheses show ratios of abnormal/normal metaphases.

Table 2. Results and Follow-Up After All-Trans RA Treatment

Patient	CR (d)	PR (d)	Failure	Death (d)	Hyper- leukocytosis (WBC $10^9/L$ )	Maintenance	CR Duration (mo)
1	+30					6 MP/MTX	13+
3				+6	+(73)	—	
17				+12	+(32)	—	
22	+30					6 MP/MTX	2
5				+8	+(80)	—	
9	+30					6 MP/MTX	8+
4	+30					Mitoguazone/Ara-C	7
6	+60					6 MP/MTX	8
7	+40					6 MP/MTX	5
8	+60					6 MP/MTX	7
10	+40					All-trans RA	7
11	+60				+(35)	6 MP/MTX	7+
16	+90					All-trans RA	3
18		+60				—	
19	+90					6 MP-MTX	4+
20	+30					6 MP-MTX	5+
21	+90					Mitoguazone/Ara-C	2
2	+60					6 MP/MTX	13
12		+60				—	
13		+60				—	
15		+60				—	
14			+			—	

Abbreviations: 6 MP, 6-mercaptopurine; MTX, methotrexate; Ara-C, cytosine arabinoside.

**CR.** CR was obtained in 14 patients after all-trans RA treatment: in 2 previously untreated patients, in 1 patient after failure of induction chemotherapy, in 10 patients in first relapse, and in 1 in second relapse. The earliest feature of the response was normalization of the DIC. No patient had an exacerbation of DIC. Fibrinogen level was normalized between the second and the nineteenth day (median day 8), and the FDP disappeared between the third and fourteenth day (median day 4). With regard to correction of cytopenia, the mean time of normalization was day 30 for thrombocytopenia, day 50 for neutropenia, and day 60 for anemia.

Eight patients needed no transfusion. In two patients the last transfusion was necessary on day 15, and in four patients the last transfusion was performed between day 30 and day 40. A normal BM was obtained between day 30 and 90. Most often, cytologic and cytogenetic remissions were noted at the same time; however, in four patients cytogenetic studies were normal while cytologic examination showed some abnormal cells. After treatment, karyotype was normal in 11 of 14 complete responders (technical failure in three patients).

The duration of initial hospitalization was very short for patients who achieved CR: 3 to 20 days (median 8 days). Only two patients were rehospitalized for a fever of unknown origin.

**Early deaths.** Three patients died at days 6, 8, and 12 after beginning of treatment. One patient, aged 81 years, who had a hyperleukocytic M3 variant, died of acute respiratory failure. One patient, aged 36 years, who failed after intensive chemotherapy, died at day 8 of cardiac and respiratory failure. One patient, aged 78 years, died on day 12 of intracranial hypertension. All these patients had a striking increase in their WBC count during treatment (WBC counts of 33, 0.9, and  $2.3 \times 10^9/L$  before treatment and 73, 80, and  $32 \times 10^9/L$ , respectively, on day of death). The

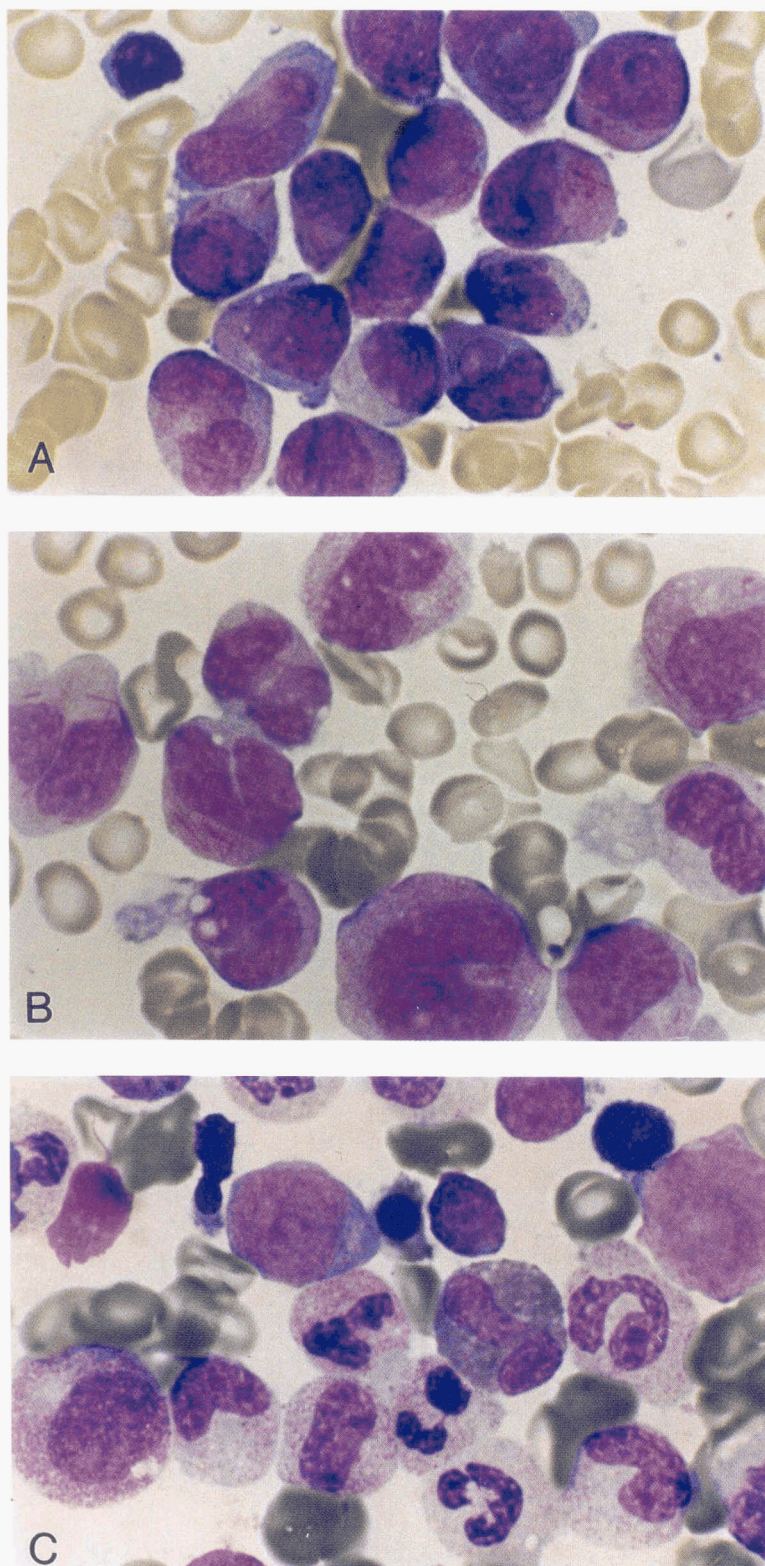
WBC counts at that time had the characteristics of maturing cells and not of abnormal promyelocytes; the DIC features initially present in these three patients had disappeared and were absent at time of death.

**Failure.** Four patients (three treated in second relapse and one in first relapse) had a transient improvement with normalization of neutropenia ( $PMN > 1.5 \times 10^9/L$ ) on days 15, 16, 60, and 60, with normalization of thrombocytopenia in one patient. In three patients, a normal cytogenetic study was obtained on days 30, 45, and 45, respectively; however, the disease was progressive again in three patients at day 80 and at day 120 in the fourth patient.

One patient, in third relapse, who had received three intensive courses of chemotherapy during the previous 3 years, failed treatment with all-trans RA. In this patient, the blast cells before the beginning of treatment with all-trans RA were poorly differentiated and  $t(15;17)$  was present in the metaphases. This patient was the only one whose blast cells did not differentiate in vitro with all-trans RA.<sup>18</sup>

### Morphologic Results

Figure 1 shows variable features observed during treatment. This diversity resulted mainly from the variability in blast infiltration and in the granular content of blast cells. Three major features were observed in all the cases, however. First, the BM cellularity of each patient remained the same during the treatment. Second, morphologic changes of blast cells were observed. These cytoplasmic and nuclear changes led to maturing cells with more or less normal morphologic aspects. Auer rods were sometimes present in mature cells, confirming the differentiation process of the blast cells. Third, concomitant with the blast maturation, normal cells (either erythroblasts, megakaryoblasts, or myeloid cells) emerged. The rate of normal and abnormal maturing cells



**Fig 1.** BM smears. May-Grünwald-Giemsa stain (patient 16). (A) At relapse: FAB M3 hypergranular form with typical faggot cells. (B) At day 30: Normocellular BM with blast cells and maturing cells. Some of the maturing cells contain Auer rods. (C) At day 60: Except for a few atypical blast cells (arrow), the BM appearance is normal.

changed during treatment and led progressively to a normal BM.

#### *Cytogenetic Results*

Cytogenetic results were in accordance with cytologic results with an appearance of or increase in normal

metaphases with time. A normal karyotype was observed in patients in CR and in three patients in partial response.

#### *Adverse Effects*

Dryness of skin, lips, and mucosa were observed to varying degrees in all patients. Severe bone pain was noted in 11

patients between day 15 and day 60. The pain occurred in the head, neck, rachis, shoulders, knees, or tibias. Bone pains were controlled by oral analgesics and, in spite of the pursuit of all-trans RA, bone pain did not reappear.

Triglycerids increased (to two to three times normal level) in 11 patients and SGPT (to 2 to 10 times normal level) in nine patients. These two biologic phenomena resolved spontaneously after treatment was ended.

#### Follow-Up of Patients in CR

At the end of 3-month therapy with all-trans RA, the 14 patients in CR received the following maintenance treatment: 10 patients were treated with 6-mercaptopurine (100 mg/m<sup>2</sup> per day) and methotrexate (12 mg/m<sup>2</sup> each week); two patients were treated with mitoguazone (200 mg/m<sup>2</sup> each week) and cytosine arabinoside (100 mg/m<sup>2</sup> each week); and two patients who refused chemotherapy were treated with all-trans RA (45 mg/m<sup>2</sup> per day).

Nine patients relapsed whatever the maintenance treatment (median duration of CR 7 months). Five patients are still in CR (median duration of CR 7 months, range 4 to 13 months).

#### DISCUSSION

This study shows a major efficacy of all-trans RA in treatment of M3 leukemia. We treated 22 patients; 16 were treated in relapse. Fourteen CRs and four transient responses were observed. These results confirm the first data reported on the treatment of M3 patients with all-trans RA by Huang et al.<sup>12</sup> Among the 24 patients, a CR was achieved in 23 patients with all-trans RA alone and was achieved in the last patient by addition of low-dose cytosine arabinoside. The difference in the percentage of CRs in both studies may be attributable to the fact that our patients had been more heavily pretreated than the Chinese patients.

Together, these two first studies of treatment of M3 leukemia with all-trans RA provide strong evidence (a) that all-trans RA may be an alternative therapy for this subgroup of leukemia and (b) that all-trans RA is more potent than its naturally occurring isomer, 13-cis RA.

Clinical and biologic features noted during treatment with all-trans RA are different from those usually observed during conventional antileukemic chemotherapy.

CR was always obtained without any signs of BM hypoplasia, and an increase in the leukocyte count in PB was observed with a maximum peak on day 15 (Fig 2).

The most striking effect of the treatment was not only the absence of an exacerbation of DIC, but also a correction of the coagulation abnormalities within the first weeks.

Repeated morphologic studies showed a progressive maturation of blast cells with the presence of morphologically abnormal mature granulocytes. The presence of Auer rods in these maturing cells, including PMN, is strong evidence of differentiation. In vitro studies showed a good correlation between the in vivo and in vitro efficacy of all-trans RA (the only nonresponder had failed to respond to RA therapy).

Our clinical experience with RA therapy in M3 patients showed the following. First, we found a possible relationship between the history of M3 and the efficacy of RA. Indeed, 10 CRs were obtained in the 11 patients in first relapse, only one CR was obtained in the four patients treated in second relapse, and the only patient who failed was treated in third relapse. The role of a selection of a leukemic subclone owing to the subsequent relapses and chemotherapies is questionable. Thus, all-trans RA should probably be used early during the course of M3 leukemia.

Second, we noted a high degree of hyperleukocytosis ( $>30 \times 10^9/L$ ) during the two first weeks of treatment in four patients. Two of these patients were previously untreated, and one had an M3 variant form of the disease. All had an increased BM cellularity and a significant DIC before treatment with all-trans RA. Three of these patients died, and the role of hyperleukocytosis in the fatal evolution cannot be excluded. For this reason, we believe that all-trans RA must be used very carefully in patients with hyperleukocytosis at diagnosis and that very close follow-up is necessary during the first 2 weeks for all patients treated with all-trans RA, especially for patients with a high degree of BM cellularity and significant DIC.

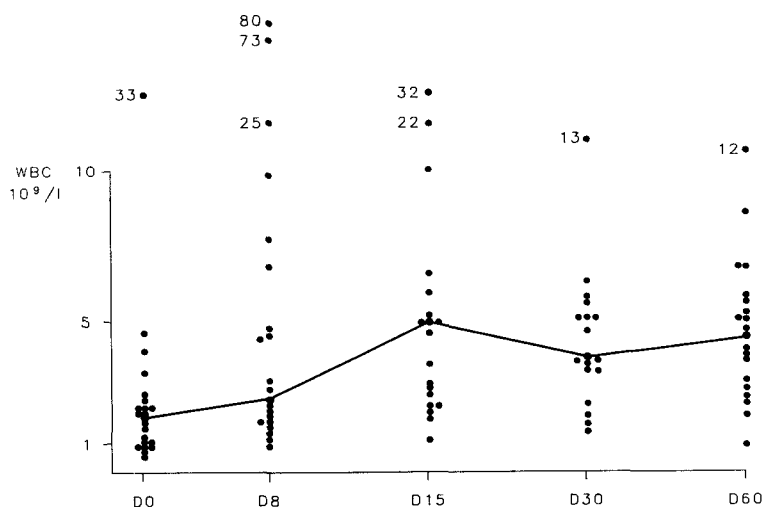


Fig 2. WBC count evolution during all-trans RA therapy (22 patients). Median (solid line).

Last, we question the place of RA in treatment of M3 leukemias. Our study has shown the following benefits of such treatment in first relapses of the disease: rapid correction of DIC, no induced aplasia, and treatment on an outpatient basis. The CRs, once obtained, are of short duration, however, whatever the maintenance therapy. Therefore, this therapy allows CR to be obtained without the inconvenience and hazardous period of aplasia but does not eradicate the leukemic clone. A more solid consolidation chemotherapy than the maintenance treatment chosen in our study appears to be necessary.

We also question whether all-trans RA may be beneficial in de novo M3 leukemias. Our own experience in four de novo cases was unfortunate in two cases. Although the number of cases is small, evidently extreme caution must be used in treating M3 leukemias with all-trans RA. An alternative would be to consider all-trans RA therapy as a novel therapy either alone or in combination chemotherapy in the consolidation regimens of CR M3 patients after conventional chemotherapy.

We conclude that all-trans RA appears to be a true novel therapy able to induce remission in this most severe form of

leukemia through a differentiation and not a cytotoxic effect. In many patients mainly in first relapse, remission is obtained with few transfusions, brief hospitalization, and minor side effects. This treatment appears to be a model of differentiation therapy of malignancy and deserves further study.

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