Randomized Study of 13-cis Retinoic Acid v Placebo in the Myelodysplastic Disorders

By H. Phillip Koeffler, Daniel Heitjan, Roland Mertelsmann, Jonathan E. Kolitz, Philip Schulman, Loretta Itri, Patricia Gunter, and Emmanuel Bessa

A double-blind, placebo-controlled randomized trial of 13-cis retinoic acid was performed to determine if the drug has a therapeutic effect in patients with myelodysplastic syndromes (MDS). Sixty-eight evaluable patients with MDS were randomized to receive a single, daily oral dose of either 13-cis retinoic acid (13-CRA, 100 mg/m²) or matching placebo. Treatment was continued, when possible, for a period of 6 months. Determination of response to treatment was based on clinical course, repeat bone marrow biopsies, and aspirates and blood counts (CBC) with WBC differential, platelet, and reticulocyte numbers at specified intervals. No significant difference was noted between the two treatment groups in response to test drug (P = .66). One patient (3%) in the 13-CRA group and two patients (6%) in the placebo group had a minor response. Approximately 30% of patients in both groups had progression of their disease, and progression-free survival was nearly identical. Greater than 90% of the patients receiving 13-CRA developed mild or moderate skin toxicity that was reversible with decreasing or discontinuing the drug. Our study did not find that 13-CRA exerts a beneficial therapeutic effect in patients with MDS.

MATERIALS AND METHODS

Control Methods and Drug Treatment Plan

Assignment of test medication was determined according to a set of computer-generated random numbers. Both 13-CRA and placebo were dispensed as identically appearing 40-mg gelatin capsules. Both patients and investigators and members of their staff were blinded as to knowledge of test medication. The 13-CRA or placebo was dispensed by pharmacists who had access to the randomized treatment codes. The tablets were placed in a compartmentalized container with a space for each day of the week.

A single, daily, oral dose of either 13-CRA (100 mg/m²) or placebo was administered. When possible, the patients were treated...
for a period of 6 months. Patients demonstrating a progression of their disease to acute leukemia or a worsening of neutropenia, anemia, or thrombocytopenia determined by the principal investigator to be significantly severe had their treatment discontinued and were removed from study. If severe toxicity developed, the administration of the test medication was terminated and restarted at a dose approximating one-half (50 mg/m²) the original dose after recovery from toxicity. If disabling toxicity developed at the lower dose level, treatment was again stopped and restarted at one-half the previous dose.

Parameters Measured

The patients were observed in the clinic every week for the first 3 weeks and then every 3 weeks for the remainder of the study. At each visit, a physical examination was performed and an interval history was recorded. A CBC with differential, platelet, and reticulocyte count was performed at each visit. A bone marrow biopsy and aspirate for routine staining and differential count was performed every 3 months during the treatment period.

Grading of Toxicity

We used previously published criteria for grading adverse experiences, which are divided into three categories: mild toxicity, disabling, but not disabling; moderate toxicity, disabling, but hospitalization not necessary; and severe toxicity, disabling, may require hospitalization.

Definitions for Evaluation of Progression of Disease

The following parameters were included in determining response to therapy: (a) bone marrow blasts (percentage of nucleated cells), (b) peripheral blood blasts (percentage of nucleated cells), (c) WBC count per microliter of blood, (d) blood neutrophils per microliter of blood, (e) blood monocytes per microliter of blood, and (f) blood platelets per microliter of blood. Normal ranges for these parameters were: WBC 4,300 to 10,000/μL, blood neutrophils 1,800 to 7,200/μL, blood monocytes 200 to 950/μL, blood platelets 140,000 to 440,000/μL, bone marrow blasts <1%, peripheral blood blasts 0.

The response criteria were as follows: (a) complete response (CR), improvement to within a normal range of all hematologic parameters listed above for a period of at least 4 weeks; (b) partial response (PR), improvement of at least 50% for each parameter listed above for at least 4 weeks but not sufficient to constitute a CR; (c) minor response, improvement of 50% in at least one hematologic parameter for at least 4 weeks without worsening of ≥50% in any of the others; (d) stable disease, no changes of hematopoietic parameters of ≥50% for 4 weeks in either direction or 50% improvement in at least one parameter for 4 weeks accompanied by worsening of ≥50% in at least one other parameter for 4 weeks; (e) progressive disease, progression to leukemia, death from a leukemic or preleukemic pathology or worsening of ≥50% for at least 4 weeks in a hematologic parameter without improvement of 50% or more in any other parameter. Responses were determined by a committee that included at least one member from a different institution.

Statistics

Comparison of treatment groups. Disease progression outcomes in the two groups were compared using the Wilcoxon rank-sum test. Product limit estimates of the progression-free survival time distributions were computed and compared by means of the log-rank test for right censored data.

Evaluating hematologic changes by regression. For each parameter, an average weekly change in the given hematologic parameter was assessed by regressing the values of that parameter v week on study. The individual slopes were then averaged within treatment groups using a weighting scheme to reflect the fact that not all slopes were equally precise. The treatment group averages were then compared in a test of whether the slopes were the same in both groups.

RESULTS

Baseline characteristics of the 68 patients entered on the study are listed in Table 1. Mean age of the patients was 64 years (range, 20 to 86 years) in the 13-CRA group and 65 years (range, 16 to 87 years) in the placebo group. Both groups were similar when evaluated by gender, race, Karnofsky performance score, and disease subtypes (P > .05). About 50% of the patients in each group had refractory anemia with excess myeloblasts (RAEB).

Figure 1 shows the mean ± SE of several of the hematopoietic parameters in the two groups from the time of randomization to the end of the study. No significant difference between the treatment groups in the mean values of the hematologic parameters was observed at any of the test times (P > .05). Likewise, over the course of study no difference was noted between the 13-CRA and placebo groups when a regression analysis was performed on the monocyte, neutrophil, WBC, platelet, and reticulocyte concentrations in the peripheral blood and on cellularity and percentage of blasts in the bone marrow.

No significant difference (P - .66) between treatment groups was noted when the proportions of responders were compared (Table 2). One patient (3%) in the 13-CRA group and two patients (6%) in the placebo group had a minor response. The patient receiving 13-CRA had a transient (5 weeks) improvement in neutrophil count, and two patients receiving placebo had a 10- to 12-week improvement in WBC, platelets, and monocytes. Thirty-one percent in the 13-CRA group and 27% in the placebo group had pro-

Table 1. Entry Characteristics of 68 Eligible Study Participants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (n = 33)</th>
<th>13-CRA (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean yr)</td>
<td>65</td>
<td>64</td>
</tr>
<tr>
<td>Male (%)</td>
<td>58</td>
<td>60</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>88</td>
<td>91</td>
</tr>
<tr>
<td>Black</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Karnofsky performance score (mean)</td>
<td>89</td>
<td>93</td>
</tr>
<tr>
<td>Randomization diagnosis* (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>RARS</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>CMML</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>RAEB</td>
<td>52</td>
<td>54</td>
</tr>
<tr>
<td>RAEB-TR</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Treatment-related MDS† (%)</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

* MDS is composed of five syndromes: RA, refractory anemia; RARS, refractory anemia with ring sideroblasts; CMML, chronic myelomonocytic leukemia; RAEB, refractory anemia with excess myeloblasts; and RAEB-TR, refractory anemia with excess myeloblasts in transformation.
† This MDS develops after antecedent therapy, usually chemotherapy, for another disease. This syndrome has a dire prognosis.
Fig 1. Effect of 13-CRA on parameters of hematopoiesis. Results represent the mean ± SE of peripheral blood neutrophil (left, upper panel), platelets (right, upper panel), and monocyte (left, lower panel), and mean percentage of blast cells in the bone marrow (right, lower panel). Group of patients receiving 13-CRA (O—○); group receiving placebo (■—■). No significant difference (P > .05) was observed between the 13-CRA and placebo groups on any parameter.

Fig 2. Effect of 13-CRA on parameters of hematopoiesis. Results represent the mean ± SE of peripheral blood neutrophil (left, upper panel), platelets (right, upper panel), and monocyte (left, lower panel), and mean percentage of blast cells in the bone marrow (right, lower panel). Group of patients receiving 13-CRA (O—○); group receiving placebo (■—■). No significant difference (P > .05) was observed between the 13-CRA and placebo groups on any parameter.

Table 2. Responses to Treatment Regimen

<table>
<thead>
<tr>
<th>Response</th>
<th>Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 33)</td>
</tr>
<tr>
<td>Disease progression*</td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>0</td>
</tr>
<tr>
<td>Minor response</td>
<td>6</td>
</tr>
<tr>
<td>Stable disease</td>
<td>67</td>
</tr>
<tr>
<td>Progression</td>
<td>27</td>
</tr>
</tbody>
</table>

*Total does not equal 100% because of rounding error.

Table 3. Final Status of 68 Eligible Participants

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Placebo (n = 33)</th>
<th>13-CRA (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>Completed 6 months of study</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>Removed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cited ineffectiveness</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Cited toxicity</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>Nonrelated intercurrent disease</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Disease progression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Other</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Physician error</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Died</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Secondary causes</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>9</td>
<td>3</td>
</tr>
</tbody>
</table>

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Fig 2. Comparison of progression-free survival curves. Progression is defined as progression to AML or deterioration of hematopoietic parameters sufficient to warrant removal from the test medication. Group of patients receiving 13-CRA ( — — — — ); group receiving placebo ( · · · · · · · ). The curves were not significantly different, \( P = .89 \) by log-rank test.

progression-free survival between the 13-CRA and placebo groups (\( P = .89 \)).

Toxicity

Among the 35 13-CRA patients, 94% (33 patients) experienced toxicities; in the placebo group, 36% experienced toxicities (Table 4). This difference is significant at \( P < .001 \). Dry skin and cheilitis of mild or moderate severity were the most frequent abnormalities. Approximately 30% of the 13-CRA group also reported mild or moderate lethargy while on therapy. The mean dose of 13-CRA initially was 100 mg/m\(^2\)/d PO, but decreased to a nadir of 86 mg/m\(^2\) (range, 42 to 100 mg/m\(^2\)) by week 12 of treatment and remained near this level throughout the remainder of the study. Although no patient receiving 13-CRA had severe side effects that required hospital care, seven patients stopped the study because of intolerance to test drug. Generally, the toxicities in the placebo group were mild and not well defined, being most often dry skin (Table 4); however, two patients stopped the placebo because of perceived toxicity. All side effects were reversible on discontinuation of test drug.

DISCUSSION

Sixty-eight patients with MDS were randomized and treated in a double-blind, placebo-controlled fashion. A comparable proportion of age, gender, Karnofsky score, and disease subtype was present in each treatment arm. The physician was usually able to infer which treatment the patient was receiving by the fourth to the seventh week of therapy due to the frequent occurrence of cutaneous toxicity. No significant difference (\( P = .66 \)) was observed between responses in patients receiving 13-CRA as compared with those receiving placebo. Analysis of each of the hematologic values showed no statistical difference when either the mean of each treatment group was compared at each time point or the slopes of the values of the individual patients were compared against the slopes of the mean values from the other treatment arm. The hematopoietic values included WBC, neutrophil, monocyte, platelet, and reticulocyte concentrations in the peripheral blood, and cellularity and percentage of blast cells in the bone marrow. Only one patient in the 13-CRA group and two patients in the placebo group had a minor response. Eleven and nine patients from the 13-CRA and placebo groups, respectively, had progressive disease. A similar number of patients in each arm of the study stopped treatment because of the development of AML or severe problems due to neutropenia or thrombocytopenia.

The initial phase I study of administration of 13-CRA (20 to 120 mg/m\(^2\)/d) to MDS patients showed that peripheral blood counts and/or bone marrow morphology improved in five of 15 patients within 3 to 8 weeks of initiating 13-CRA therapy.\(^2\) Another recent study of 15 patients with MDS showed that \( \sim 50\% \) of patients had a \( > 20\% \) increase in their peripheral blood granulocyte counts.\(^2\) No change in marrow morphology or karyotype was noted during the 8-week course of 13-CRA (2.5 to 4 mg/kg/d PO). One patient in the

<table>
<thead>
<tr>
<th>Table 4. Possible Side Effects of Study Medication (%)</th>
</tr>
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<tbody>
<tr>
<td><strong>Treatment Group</strong></td>
</tr>
<tr>
<td><strong>Toxicity</strong></td>
</tr>
<tr>
<td>Skin and mucous membrane</td>
</tr>
<tr>
<td>Dry skin</td>
</tr>
<tr>
<td>Cheilitis</td>
</tr>
<tr>
<td>Pruritis</td>
</tr>
<tr>
<td>Conjunctivitis</td>
</tr>
<tr>
<td>Epistaxis</td>
</tr>
<tr>
<td>Other toxicity</td>
</tr>
<tr>
<td>Lethargy</td>
</tr>
<tr>
<td>Joint pain</td>
</tr>
<tr>
<td>Alopecia</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Anorexia</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Any toxicity</td>
</tr>
</tbody>
</table>

*Definition of toxicities given in the Materials and Methods section.
study who probably had refractory anemia by the FAB classification of MDS had a dramatic response, with the granulocyte count increasing from 400 to 2,800 cells/µL blood with a disappearance of the abnormal karyotype. Another trial of 13-CRA (1.0 mg/kg/d) for patients with MDS showed that three of 18 patients had a response to the treatment.22 By the definitions used in our study, the responses were minor. The authors believed that four of the patients developed a decreased platelet concentration in the blood as a result of the 13-CRA. A small trial showed that two of eight patients with MDS had an increase in their peripheral blood neutrophil counts (40% and 114%) while receiving 20 to 100 mg/m² 13-CRA.24 Recently, a randomized study showed that 13-CRA significantly improved survival of patients with refractory anemia.25 In that study, no improvement was observed in blood counts in the patients receiving 13-CRA. The study showed that 64% of the control patients died in <1 year as compared with 23% of the patients receiving 13-CRA. The median survival of refractory anemia patients is often reported to be ~5 years.26 Why this group of patients did so poorly in their study is not clear.

What considerations might explain the variation in our results with several of the above reports? Dosage and duration of administration of 13-CRA do not appear to be a variable. Most of the studies, including ours, administered similar doses of ~85 to 100 mg/m²/d 13-CRA. This dose should achieve serum concentrations of $10^{-7}$ to $5 \times 10^{-4}$ mol/L.22 These are concentrations that are able to inhibit proliferation and to induce differentiation of leukemic cells in vitro.11-15 Only 30% of patients in our trial completed 24 weeks of therapy. Another one-third discontinued treatment because of the development of AML or a serious complication associated with the disease. Nevertheless, almost all patients received the treatment for 8 weeks; this is the same amount of time required to see a positive response in the other trials.20-23 Only 1 to 2 weeks' time is required in vitro to induce differentiation of leukemic cells or to inhibit their clonal growth.11-15

The randomized trial by Clark et al25 showed that patients with refractory anemia who received 13-CRA had increased survival as compared with control patients. Our study contained only eight patients with refractory anemia, five of whom received 13-CRA. We found no difference in response between the two groups, but our study clearly had too few refractory anemia patients to either refute or corroborate the findings of Clark et al.25

Although in vitro studies,11-15 several case reports,16,20 and clinical studies21-25 suggest that 13-CRA may be effective therapy in select patients with MDS, our study suggests that this compound, when used alone, will probably play only a minor role in the management of most patients with MDS. Further studies of administration of 13-CRA to refractory anemia patients is warranted, and investigations to determine how to predict which patients may respond to 13-CRA are needed.

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REFERENCES


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