Phase II trial of fenretinide [N-(4-hydroxyphenyl) retinamide] in myelodysplasia: possible retinoid-induced disease acceleration.

https://escholarship.org/uc/item/6zt2j09s

Leukemia research, 13(4)

0145-2126

Garewal, H S
List, A
Meyskens, F
et al.

1989

Peer reviewed
PHASE II TRIAL OF FENRETINIDE [N-(4-HYDROXYPHENYL) RETINAMIDE] IN MYELODYSPLASIA: POSSIBLE RETINOID-INDUCED DISEASE ACCELERATION*

HARINDER S. GAREWAL,†§ ALAN LIST,‡ FRANK MEYSKENS,§ ANTONIO BUZAID,§ BERNARD GREENBERG† andSURESH KATAKKAR

Section of Hematology/Oncology, Veterans Administration Medical Centers, Tucson† and Phoenix‡, and University of Arizona Cancer Center§, Tucson, AZ, U.S.A.

(Received 7 November 1988. Accepted 30 November 1988)

Abstract—To determine the activity of fenretinide in patients with myelodysplastic syndromes, 15 patients were treated (300 mg/d starting dose, escalated to 400 mg/d) for a 12-week course. No responses were observed in 14 evaluable patients. Exacerbation of thrombocytopenia occurred in one patient with chronic myelomonocytic leukemia, who succumbed to an intracerebral hemorrhage after 3 weeks of treatment. Two patients with long-standing stable sideroblastic anemia experienced interval leukemic progression. In one patient, clinical features of chronic myelomonocytic leukemia appeared, characterized by a striking rise in peripheral monocyte count (0.49 × 10⁹/1 to 10.8 × 10⁹/1) and hepatosplenomegaly, which resolved promptly after cessation of treatment. The second patient experienced evolution into acute myelomonocytic leukemia with cytogenetic progression. The drug was well tolerated with no patient having to discontinue treatment because of toxicity. We conclude that fenretinide lacks clinical efficacy in the treatment of myelodysplasia and in some patients may enhance leukemic progression.

Key words: Retinoids, myelodysplasia, fenretinide.

INTRODUCTION

The myelodysplastic syndromes (MDS) are a heterogeneous group of blood cell disorders characterized by ineffective hematopoiesis and refractory cytopenias [1–3]. MDS are not uncommon disorders. Although their true incidence has not been well established, MDS have been reported to be six times as common as acute myelogenous leukemia [4]. Although the natural history of these disorders varies, the majority of patients ultimately succumb to bleeding or infectious complications, or transformation to acute leukemia. Management of these patients is generally supportive because of the lack of effective treatment modalities [4, 5]. Treatment with cytotoxic chemotherapy may achieve response in a minority of patients, but toxicity is formidable and remissions are of short duration [5–8].

Recent investigations have explored the use of retinoids in MDS. In-vitro studies have shown that several retinoid analogues have potent effects on hematopoiesis [9]. Isotretinoin, 13-cis-retinoic acid, a stereoisomer of retinoic acid, has been shown to inhibit leukemic cell growth in vitro [10], induce terminal differentiation of human leukemia cell lines [11, 12], and stimulate growth of normal erythroid and myeloid progenitors [13, 14]. Clinical trials employing isotretinoin in MDS have demonstrated only modest activity with improvement in at least one hematologic parameter in about a third of patients treated [15–19]. However, the dosage required to achieve response is high (1–2 mg/kg/day) and is associated with considerable dermatologic and hepatic toxicity which limits the clinical utility of this agent.

Fenretinide [N-(4-hydroxyphenyl) retinamide] is a synthetic amide derivative of retinoic acid with a markedly attenuated toxicity profile [20]. To evaluate the therapeutic activity of this agent in MDS, we treated 15 patients with fenretinide for 12 weeks and assessed toxicity and hematologic response.
MATERIALS AND METHODS

Patients with an established diagnosis of MDS seen at the Tucson and Phoenix Veterans Administration Medical Centers or at the University of Arizona Cancer Center between August 1986 and September 1987 were entered into the study. Eligible patients included those with a French–American–British (FAB) subtype of MDS [1] other than refractory anemia with excess blasts in transformation (RAEB-T). All patients had a life expectancy >2 months; no evidence of active infection; adequate liver function (bilirubin <2 mg/dl with normal prothrombin time); bone marrow aspiration with cytogenetic studies within one month of entry; and one or more of the following: hemoglobin <10.0 g/dl, absolute granulocyte count <1.0 × 10⁹/l, and/or a platelet count <125 × 10⁹/l.

Fenretinide was supplied by McNeil Pharmaceutical in 100 mg gelatin capsules. Treatment was initiated at 300 mg as a daily oral dose and increased after four weeks to 400 mg per day if there was no or only mild toxicity (less than level II). A 50% reduction in fenretinide dose was permitted for patients experiencing moderate to severe toxicity (three level II toxicities or greater). Fenretinide toxicity and side effects were assessed according to our previously published retinoid toxicity scale [21]. With the exception of red blood cell transfusion as needed, patients received fenretinide as their only therapy.

Patients were evaluated at 4-week intervals with a history and physical examination, complete blood count with differential, urinalysis, serum creatinine, BUN, uric acid, alkaline phosphatase, SGOT, SGPT, bilirubin, cholesterol, albumin, calcium, phosphate, lactate dehydrogenase, prothrombin time and electrolytes. A bone marrow aspirate with cytogenetic analysis was planned after 12 weeks of treatment. The upper end of the treatment course. One patient reported a slight change in visual acuity on the last day of treatment. No objective changes could be demonstrated and the subjective symptom resolved within 24 hr. No patient discontinued treatment or required a reduction in drug dosage for these complaints.

Response criteria

Twelve weeks of treatment was required before assessment of response. A complete response (CR) was defined as return of the peripheral blood cell counts to normal and a bone marrow aspiration revealing normal erythroid, granulocytic and megakaryocytic maturation accompanied by a lack of ring sideroblasts for >1 month. A partial response (PR) was defined by any one or more of the following for >1 month: a >50% decrease from baseline in red cell transfusion requirements, increase in hemoglobin level of >2 g/100 ml without red cell support, >50% increase from baseline in absolute granulocyte count, >50% increase from baseline in platelet count, or >50% decrease from baseline in bone marrow myeloblasts if initially they were >10%. Stable disease was defined as no significant change in red cell transfusion requirements, peripheral blood cell counts, bone marrow abnormalities, or symptoms for >1 month.

RESULTS

Fifteen patients were enrolled in the study and 14 were evaluable for toxicity or response. Patient characteristics are shown in Table 1. The only invaluable patient succumbed to infectious complications after three weeks of therapy. Two patients had received prior antineoplastic therapy for a malignancy antedating the onset of MDS by >5 yr: one patient received adjuvant chemotherapy (cyclophosphamide, methotrexate, fluorouracil) for stage II breast cancer, and one patient received external beam irradiation after resection of a stage II squamous cell carcinoma of the oropharynx.

Fenretinide was well-tolerated, with no patients experiencing significant hepatic or dermatologic toxicity. Two patients reported very mild symptoms of dry skin and one patient reported dry eyes, both towards the end of the treatment course. One patient experienced life-threatening thrombocytopenia. Details regarding these are presented below:

Table 1. Patient profile

<table>
<thead>
<tr>
<th>Total number</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number evaluable</td>
<td>14</td>
</tr>
<tr>
<td>Median age (range):</td>
<td>69 (54–80) yr</td>
</tr>
<tr>
<td>MDS Type</td>
<td></td>
</tr>
<tr>
<td>RARS</td>
<td>6</td>
</tr>
<tr>
<td>RA</td>
<td>7</td>
</tr>
<tr>
<td>RAEB</td>
<td>1</td>
</tr>
<tr>
<td>CMML</td>
<td>1</td>
</tr>
<tr>
<td>Previous MDS therapy</td>
<td></td>
</tr>
<tr>
<td>Red cell transfusions</td>
<td>4</td>
</tr>
<tr>
<td>Pyridoxine and folate</td>
<td>3</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>1</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>1</td>
</tr>
<tr>
<td>No therapy</td>
<td>6</td>
</tr>
</tbody>
</table>

Patient 1

Seventy-six year old male with CMML diagnosed 3 months prior to beginning therapy. Initial platelet count was 42 × 10⁹/l. Three weeks into treatment he developed epistaxis followed soon thereafter by an intracerebral bleed leading to his death. His platelet count had dropped to 3 × 10⁹/l. A repeat bone mar-
Patient 2
Fifty-four year old male with a 2-yr history of stable RARS requiring no blood product support. Cytogenetic analysis showed trisomy 8 (+8) in 90% of marrow metaphases. Towards the end of 12 weeks of fenretinide treatment, his white blood count rose from $2.6 \times 10^9/l$ to $25.8 \times 10^9/l$. The latter was associated with 41% monocytes (absolute monocyte count $10.8 \times 10^9/l$) along with the development of palpable hepatic and splenic enlargement. His hemoglobin decreased from 10.3 to 7.4 g/dl and red blood cell support was required. One month after cessation of fenretinide all hematologic parameters returned to baseline with complete resolution of hepatosplenomegaly. The patient continues to be stable with no further transfusions being necessary.

Patient 3
Seventy-eight year old man with a 7-yr history of stable RARS requiring regular transfusion support over the previous 4 yr. At the time of entry, 2% of the nucleated bone marrow elements were blasts and cytogenetic analysis showed monosomy 7 (-7) in 44% of metaphases. Circulating blast forms were not detected in his peripheral blood smear at any time prior to treatment. At the end of 12 weeks of treatment, 6% blasts were noted on the peripheral smear. A marrow aspirate showed 45% myelomonoblasts with monosomy 7 present in 90% of metaphases examined. Acute leukemic progression occurred during the ensuing weeks of observation. Induction chemotherapy was administered, but the patient succumbed to infectious complications.

DISCUSSION
The principle objective of this trial was to determine the therapeutic activity of fenretinide in patients with MDS. Although the drug was well-tolerated, no hematologic responses were observed. However, two patients had rapid progression of disease on therapy, and one patient experienced worsening thrombocytopenia. Clinical features of CMML developed in Patient 2, characterized by a striking rise in peripheral monocyte count ($0.49-10.6 \times 10^9/l$) and development of hepatosplenomegaly, which resolved promptly with cessation of treatment. Patient 3, however, experienced evolution to acute myelomonocytic leukemia with attendant cytogenetic progression.
Patients 2 and 3 had an initial diagnosis of RARS. RARS has a relatively low risk of leukemic transformation compared with other FAB subtypes [3]. The detection of karyotypic abnormal clones has been associated with adverse prognosis independent of FAB morphology. However, the presence of a single abnormality, in contrast to multiple cytogenetic anomalies, usually has only a modest impact on survival [22, 23]. In particular, trisomy 8, which was identified in Patient 2, has been associated with a favorable clinical course in patients with RARS [24]. Thus, both Patients 2 and 3 had a favorable MDS subtype and karyotype at the start of treatment.

The temporal association of disease progression with fenretinide administration in Patients 2 and 3 with a low-risk subtype of MDS suggests that this agent may have promoted expansion of an abnormal clone. Trisomy 8, present in Patient 2, has also been described with regular frequency in patients with CMML [25, 26]. It is conceivable that fenretinide may have facilitated growth of hematopoietic progenitors committed to monocytic differentiation in this patient. Nevertheless, in the absence of serial cytogenetic studies, we cannot prove that the hematologic changes observed resulted from expansion of the abnormal clone. This clearly occurred in Patient 3, however, who demonstrated a marked increase in the percentage of abnormal metaphases with monosomy 7.

Tobler et al. [9] have shown that structural variations in retinoic acid analogues account for distinct functional differences on hematopoietic progenitors in vitro. Retention of the terminal carboxyl group which is absent in amide derivatives appears essential for stimulation of normal hematopoiesis as well as inhibition of leukemic cell growth. Lawrence et al. [27] recently reported stimulation of leukemic cell growth in vitro in some patients with acute non-lymphocytic leukemia. Enhanced leukemic colony growth was noted in 28% of specimens and occurred primarily in leukemic cells of monocytic lineage. Interestingly, the leukemic cells of patients in this trial experiencing disease progression exhibited monocytic features.

Clinical evidence of disease acceleration by retinoids has not been reported in previous trials in MDS [15, 19]. In a randomized study comparing isotretinoin with placebo [28], leukemic progression occurred with equal frequency in both treatment groups and only in patients at greatest risk for this complication, i.e. FAB subtype RAEB or RAEB-T. However, marked increases in white blood cell counts have been noted in early Phase I trials of isotretinoin, e.g. Patients 2 and 4 in the trial reported by Gold et al. [15]. These may have represented disease progression similar to that seen with fenretinide in our study.

Retinoid treatment-associated thrombocytopenia, which occurred in Patient 1, has been observed in as many as one third of patients in some trials [16, 17, 19]. This is thought to arise from drug-induced suppression of thrombopoiesis, but objective evidence to support this notion is not available. Drug-induced thrombocytopenia was not observed in over 240 patients with non-hematologic malignancies treated with isotretinoin at our institution [29]. Therefore, at least some cases of thrombocytopenia in retinoid trials in MDS may be the result of stimulation of an abnormal clone leading to further suppression of normal hematopoiesis and resultant ineffective thrombopoiesis.

The results of this phase II study show that, although fenretinide was well-tolerated at the doses administered, a therapeutic benefit in patients with MDS was not apparent. More importantly, our findings of disease progression in two patients with RARS suggest that fenretinide may promote leukemic progression in some patients with MDS. Future trials of retinoids or other agents in MDS must recognize a potential for such agents to promote leukemic evolution. Clinical correlation with in-vitro bone marrow culture data may prove useful to identify patients at risk for stimulation of the abnormal clone.

REFERENCES

Fenretinide in myelodysplasia


