

# Pharmacologic Doses of Recombinant Human Erythropoietin in the Treatment of Myelodysplastic Syndromes

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Twenty patients with myelodysplastic syndromes (MDS) entered a randomized, placebo-controlled, double-blind trial designed to evaluate the efficacy and toxicity of high doses of recombinant human erythropoietin (rhEPO). Patients completing the trial were eligible to receive rhEPO as part of an open-label study. Eighteen patients were transfusion dependent; 10 had refractory anemia (RA), and 10 had refractory anemia with ringed sideroblasts (RARS). A response to rhEPO was defined as an increase in hematocrit of 4 percentage points or more over baseline, or the elimination of all transfusions with the hematocrit stable at the baseline level. In the double-blind trial, 1 patient (12.5%) receiving rhEPO responded, as compared with no responses in the placebo

group. Overall, responses occurred in 4 of 17 patients (24%) receiving rhEPO at a dose of 1,200 to 1,600 U/kg intravenously (IV) twice weekly. Changes in granulocyte or platelet counts were not observed. Despite the administration of high doses of rhEPO, toxicity attributable to rhEPO was not observed in either the double-blind or open-label study. Response to rhEPO was not significantly related to age, gender, type of MDS, time since diagnosis, time since initiation of transfusion therapy, or baseline serum EPO. These studies indicate that rhEPO can be administered safely in very high doses to patients with MDS and that 24% of these patients will respond with increased erythropoiesis.

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**T**HE MYELODYSPLASTIC syndromes (MDS) are clonal disorders of hematopoiesis in which normal bone marrow (BM) activity is replaced by disordered production of RBC, WBC, and platelets. Anemia is often the initial finding in this disorder, and most patients eventually become transfusion dependent. Although many patients with MDS progress to acute leukemia, others die of infection due to neutropenia. Because of the variable clinical course and lack of effective primary therapy, most of these patients are treated solely with supportive therapy, including transfusions, rather than chemotherapy.<sup>1</sup>

Erythropoietin (EPO) deficiency is not the basis of anemia in MDS because EPO levels are generally increased in this condition, although in some patients the degree of increase may be quite low for the degree of anemia.<sup>2,3</sup> Occasional patients with MDS have responded to androgens.<sup>4</sup> Because androgens may act by augmenting the amount of EPO,<sup>5</sup> recombinant human EPO (rhEPO), especially in pharmacologic doses, might be an effective means of treating patients with MDS. We hypothesized that residual normal stem cells, or perhaps even the abnormal clone of MDS stem cells, might respond to pharmacologic doses of rhEPO with enhanced effective erythropoiesis. The relative safety of rhEPO in patients with renal failure<sup>6-8</sup>

and rheumatoid arthritis<sup>9</sup> provided further justification for studying dose escalation of rhEPO in patients with MDS.

## PATIENTS AND METHODS

Between January 1989 and July 1990, 20 patients with MDS were randomized to receive either rhEPO 800 U/kg or a comparable volume of placebo, intravenously (IV), twice weekly, (biw) for an initial 4 weeks. In the absence of a suitable response, the dose was increased in increments of 400 U/kg at 4-week intervals to a maximum dose of 1,600 U/kg biw. After completing 12 weeks under double-blind study conditions, all patients were eligible to receive rhEPO under open-label study conditions for 12 to 24 weeks. Patients entered the open label at the rhEPO dose level at which they had completed the randomized trial, ie, 1,600 U/kg biw. The rhEPO was provided by the R. W. Johnson Pharmaceutical Research Institute, Raritan, NJ. Because BM biopsies routinely showed increased iron in this group of transfusion-dependent patients, and because of the risk of hemochromatosis, iron was not routinely administered to these patients whose median serum ferritin level was 1,815 ng/mL.

To be eligible for the study, patients had to meet the following criteria: MDS with less than 5% blasts on BM examination (changed to <10% during the study), performance score of grade 0, 1, 2, or 3, life expectancy more than 6 months, age more than 18 years, clinically stable more than 1 month, hematocrit less than 32%, neutrophils greater than 500/ $\mu$ L, platelets greater than 20,000/ $\mu$ L, creatinine less than 2 mg/dL, calcium less than 12 mg/dL, and negative Coombs test. Patients were ineligible if they had any of the following: hematologic disease in addition to MDS; clinically significant pulmonary, cardiac, endocrine, neurologic, gastrointestinal, or genitourinary disease unrelated to MDS; tumor involvement of the CNS; a history of seizures, uncontrolled hypertension with a diastolic blood pressure (DBP) more than 100 mm Hg, iron deficiency anemia, drug or alcohol abuse within 2 years; or positive test for hepatitis antigen or human immunodeficiency virus (HIV) antibody. Patients were ineligible if they had received androgens or experimental cytokines within 2 months. Patients receiving maintenance doses of corticosteroids were allowed to enter the study if they had been hematologically stable for 1 month. All patients signed an informed consent approved by our Institutional Review Board.

Baseline evaluation included a complete history and physical examination, including documentation of transfusion history, and a 12-lead electrocardiogram. Clinical laboratory tests included complete blood counts with WBC differential and reticulocyte count, urinalysis, serum electrolytes, liver chemistry tests, blood urea nitrogen, creatinine, glucose, calcium, phosphorous, total protein,

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cholesterol, uric acid, serum iron, iron binding capacity, serum ferritin, serum folate, serum B<sub>12</sub>, and serum EPO. A BM aspiration and biopsy with cytogenetic studies were obtained unless a study had been performed within 6 months, during which time the patient had been hematologically stable.

During the study, vital signs and complete blood counts including reticulocytes were monitored weekly. Serum chemistry tests, urinalysis, and BM examinations were obtained at the end of the double-blind phase and again at the end of the open-label study. Patients were examined at Vanderbilt University Hospital at least every 2 weeks for the first 16 weeks, with intervening therapy administered by visiting nurses or local physicians. After 16 weeks, patients were examined at Vanderbilt at least every 4 weeks.

With regard to evaluation of the response to therapy, 18 of the 20 patients in the study were transfusion dependent. Thus, defining the true "baseline" hematocrit for each patient was not possible, because these patients were being supported, by transfusion, at a level above the baseline that their own BM could maintain. Nevertheless, for purposes of this study, the baseline level for patients receiving transfusions was defined as the mean of two posttransfusion hematocrits obtained in the 6-week period before study entry. A response to rhEPO was defined as an increase in hematocrit of 4 percentage points or more over baseline, independent of transfusions, or elimination of all transfusions with the hematocrit maintained at baseline level.

## RESULTS

Characteristics of the rhEPO patients and the placebo control patients in the randomized double-blind study are shown in Table 1. The two groups did not differ with respect to age, gender, specific diagnosis, or transfusion history. Patients in the control group had a longer interval between diagnosis and entry into the trial, but this difference was not statistically significant. There was a trend for abnormal cytogenetics to be observed more frequently in the control group, but this was not statistically significant ( $P = .22$ , Fisher exact test).

Toxicity in the double-blind trial was minimal (Table 2). One neutropenic patient discontinued rhEPO because of chills and fever for which no etiology could be found. A patient who had received placebo died of progressive congestive heart failure after 12 weeks. Progression to acute nonlymphocytic leukemia (ANLL) occurred in one patient

**Table 2. Toxicity in Double-Blind Trial**

Toxicity	rhEPO	Control
Death (congestive heart failure)	0	1
Chills and fever	1	0
Progression to leukemia	1	1
Hypertension	0	0
Seizures	0	0

in each group. Hypertension and seizures were not observed in either the double-blind or the open-label study although over the course of the entire study, rhEPO was administered to 17 patients at a dose of 1,200 to 1,600 U/kg biw for at least 4 weeks. (Only 17 patients received rhEPO because the control patient who died and the control patient who progressed to ANLL did not enter the open-label study. One other control patient declined participation in the open-label study.)

In the double-blind trial, one response to rhEPO was observed. This response rate, 12.5%, was not significantly different than the null response rate in the placebo controls. Thirteen patients entered the open-label phase of the study. Three of these 13 patients (23%) responded; 2 had initially received placebo, and 1 had received rhEPO in the randomized trial. Overall, when the randomized double-blind phase of the study and the open-label phase of the study are combined, 17 subjects received rhEPO; 4 of these 17 patients (24%) responded. No effects on granulocytes or platelets were noted during this trial.

To determine whether we could establish a means of predicting a response to rhEPO, we compared responders and nonresponders to rhEPO. As shown in Table 3, responders and nonresponders did not differ significantly with respect to age, gender, or diagnosis. There was a trend for responders to have a shorter history of transfusion therapy and to have received fewer transfusions in the 3 months before study entry, but these trends were not statistically significant. Baseline EPO levels were not useful in predicting a response in this series because the median baseline value was 550 mU/mL in responders as compared with 190 mU/mL in nonresponders (Fig 1). Nevertheless, no responses were noted in patients with an EPO level greater than 1,030 mU/mL.

Clinical information for individual patients is shown in Table 4. Two of the responses observed in this study are shown in Figs 2 and 3 and details of these cases are presented below.

*Case 1.* L. H., a 68-year-old woman, was first noted to have a macrocytic anemia 3 years before she entered this study (Fig 2). Baseline physical examination was normal except for a grade I/VI systolic ejection murmur and evidence of previous cataract surgery. At baseline, the hematocrit was 26%; the WBC was 2,800/ $\mu$ L with 54% granulocytes, 33% lymphocytes, and 13% monocytes; the platelet count was 357,000/ $\mu$ L; and the reticulocyte count was 2.7%. Her peripheral smear showed macrocytes and ovalocytes. Her BM aspiration and biopsy showed 50% cellularity with mild megaloblastic features. Ring sideroblasts were not seen, but marrow iron stores were de-

**Table 1. Characteristics of Patient Groups**

Parameter	rhEPO	Control
n	8	12
No. receiving transfusion therapy	7	11
Age		
Median	64	68
Range	42-83	34-87
M/F	4/4	5/7
Diagnosis		
RA	4	6
RARS	4	6
Cytogenetics		
Normal	3	2
Abnormal	1	7
Not obtained	4	3
Months since diagnosis (median)	14	25
Months since start of transfusion therapy (median)	6	10

**Table 3. Comparison of Responders and Nonresponders to rhEPO**

Parameter	Responders (n = 4)	Nonresponders (n = 13)	P-Value
Age			
Range	34-83	34-81	
Median	71	66	> .10*
M/F	1/3	6/7	.60†
Diagnosis			
RA	3	5	
RARS	1	8	.29†
Months since diagnosis			
Range	12-83	1-112	
Median	28	15	> .10*
Mean	38	29	
Months since start of transfusion therapy			
Range	0-83	0-67	
Median	10	6	> .10*
Mean	26	18	
Transfusions in 3 months prior to study			
Range	0-6	0-15	
Median	1	8	> .10*
Mean	3	8	
Serum EPO			
Range	16-1,030	42-10,902	
Median	550	190	> .10*
Mean	536	1,595	

\*Wilcoxon rank-sum test.

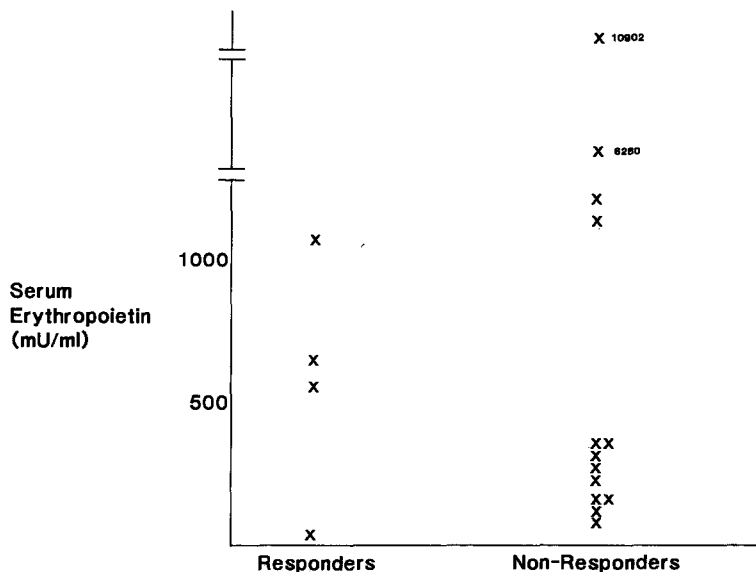
†Fisher's exact test.

Abbreviations: RA, refractory anemia; RARS, RA with ring sideroblasts.

creased. Cytogenetic studies were normal. RBC folate was increased (888 ng/mL), as was serum vitamin B<sub>12</sub> (627 pg/mL). Serum iron was 170 µg/dL, total iron binding capacity was 225 µg/dL, and serum ferritin was 189 ng/mL. Serum EPO was 1,030 mU/mL. The patient was believed to have an MDS (refractory anemia, RA).

The patient had first received packed RBC transfusions 16 months before entering the study, but had received only 2 U packed RBC in the 3 months before entering the study. The patient received ferrous sulfate 325 mg three times

daily (tid) for 1 month before entering the study; during this time, her hematocrit was unchanged. The patient entered the double-blind randomized trial and was started on rhEPO 800 U/kg biw. After 4 weeks, the hematocrit had increased minimally to 28%; the WBC and differential were essentially unchanged. At that time, the rhEPO dose was increased to 1,200 U/kg biw. In the next 6 weeks, the hematocrit rose slowly, peaking at 36%. The maximum reticulocyte count observed during this period was 2.9%. After receiving rhEPO at a dose of 1,200 U/kg biw for 6



**Fig 1. Erythropoietin (EPO) levels in responders and nonresponders to rhEPO.**

Table 4. Clinical Features and Response in rhEPO Trial

Case	Age/Sex	DX	Cytogenetics	Months Since DX	Months Start of Transfusions	Transfusions in 3 mo Prestudy	EPO Level	Base-line HCT	Randomized Study				Open Label		Comment	
									Final HCT	Transfusion	Response	Treatment	Final HCT	Transfusion		Response
1	44/M	RARS		15	15	15	6280	29	25	19	NR	rhEPO	25	18	NR	
2	75/M	RARS	Abn	29	17	12	190	27	28	12	NR	Placebo	28	8	NR	
3	68/F	RA	NI	36	14	0	1030	25	36	0	R	rhEPO	Did not enter		Withdrew	
4	34/M	RA	Abn	4	4	4	10902	21	21	4	NR	Placebo	23	6	NR	
5	66/M	RARS	NI	69	66	10	164	26	26	12	NR	rhEPO	26	12	NR	
6	70/F	RARS		67	67	15	203	30	31	13	NR	Placebo	26	16	NR	
7	74/F	RARS	Abn	35	21	8	139	30	31	10	NR	Placebo	Did not enter		Died after week 12	
8	81/F	RARS	Abn	18	4	6	59	28	26	6	NR	rhEPO	Did not enter		Withdrew	
9	83/M	RA	NI	12	5	2	515	29	25	0	NR	rhEPO	32	0	R	
10	34/F	RA		20	0	0	585	28	29	0	NR	Placebo	39	0	R	
11	65/F	RARS	NI	45	42	0	96	31	34	0	NR	Placebo	33	0	NR	
12	73/F	RARS	Abn	83	83	8	16	26	25	8	NR	Placebo	30	2	R	
13	87/M	RA	Abn	11	11	20	102	23	18	20	NR	Placebo	Did not enter		Acute leukemia	
14	62/F	RA		6	6	8	1250	30	30	8	NR	rhEPO	29	8	NR	
15	66/F	RA	Abn	7	4	9	151	27	26	9	NR	Placebo	28	8	NR	
16	60/M	RARS	Abn	112	6	6	1125	21	23	10	NR	Placebo	19	8	NR	
17	66/M	RA		10	10	6	42	31	28	6	NR	Placebo	Did not enter		Withdrew	
18	42/F	RA		4	4	2	90	29	31	0	NR	rhEPO	Did not enter		Chills in randomized trial	
19	69/F	RA	NI	4	4	11	204	25	27	9	NR	Placebo	27	5	NR	
20	61/M	RARS		1	0	0	70	32	25	0	NR	rhEPO	Did not enter		NR	Acute leukamia

Abbreviations: DX, diagnosis; Abn, abnormal; NI, normal; R, response; NR, no response; other abbreviations as in Table 3.

weeks, the patient was hospitalized at her local hospital for pneumonia. (Her total granulocyte count 3 days earlier had been 1,612.) Despite recovering from the pneumonia, the patient chose not to continue on the study and received no further rhEPO.

**Case 2.** J. M., a 34-year-old woman, was first noted to be anemic 20 months before she entered the study (Fig 3). She had not required transfusions but had a hematocrit of 26% for 1 year before it decreased to 21%. The patient was then started on prednisone 40 mg/day, and the hematocrit increased to 30%. At that time, a slow tapering of pred-

nison was started and she was maintained on prednisone 30 mg every other day (qod) for 2 months before she entered the study. The baseline hematocrit was 28%, and her peripheral smear was macrocytic. The WBC was 6,000/ $\mu$ L with a normal differential; the platelet count was 244,000/ $\mu$ L. RBC folate was 8.7 ng/mL, and serum B<sub>12</sub> was 603 pg/mL. Serum iron and iron binding capacity were 132 and 203  $\mu$ g/dL, respectively. Serum ferritin was 136 ng/mL. Serum erythropoietin was 585 mU/mL. The BM was hypercellular with erythroid hypocellularity. Megakaryocytes were hypobulbated, and granulocyte maturation appeared normal. The marrow was compatible with MDS-RA.

The patient entered the double-blind study; during the 12 weeks of placebo administration, the hematocrit ranged between 25% and 31%. Because of the failure to respond, the placebo dose was increased incrementally to a volume equivalent to 1,600 U/kg biw. After 12 weeks, the patient entered the open-label study and received rhEPO at an initial dose of 1,600 U/kg biw. At the end of 4 weeks, the hematocrit had increased to 33%. The rhEPO dose was reduced to 1,200 U/kg biw; in the next 2 weeks, the hematocrit increased to 36%. The maximum reticulocyte count during this period was 10.4%. At that time, the dose of rhEPO was decreased to 800 U/kg biw, and the patient continued to maintain a hematocrit at a level between 37% and 39%. When the dose was later decreased to 400 U/kg biw, the hematocrit decreased to baseline levels.

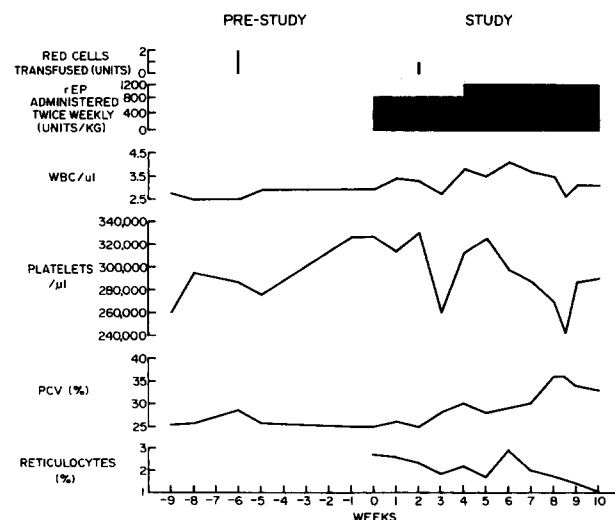
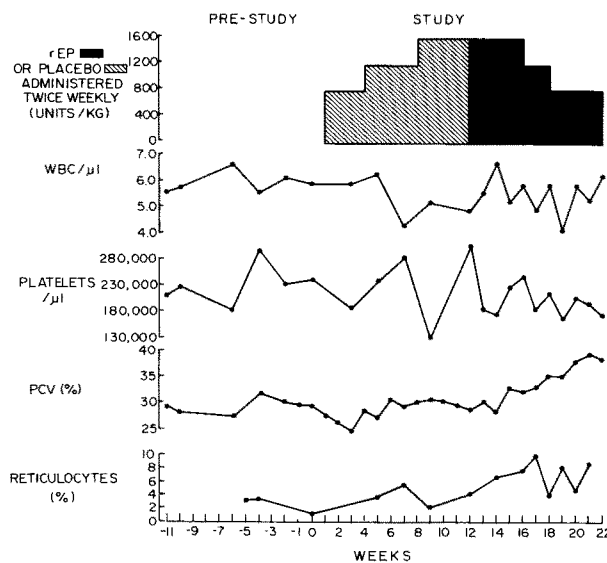


Fig 2. Response to rhEPO in case 1, a 68-year-old white woman with MDS (RA) for 3 years who responded to rhEPO with an increase in hematocrit level from 26% to 36%.

## DISCUSSION

We conducted a randomized, placebo-controlled double-blind trial and an open-label trial to evaluate the efficacy and toxicity of high doses of rhEPO in patients with MDS.



**Fig 3.** Response to rhEPO in case 2, a 34-year-old white woman with MDS (RA) for 20 months. She had no response to placebo but responded to rhEPO with an increase in hematocrit level from 28% to 36%.

Unlike renal failure, in which EPO deficiency is believed to be the cause of anemia, anemia in MDS is secondary to replacement of the BM by cells from a dysplastic clone. Therefore, instead of studying standard replacement dosages of rhEPO (50 to 100 U/kg twice weekly), we investigated whether pharmacologic doses of rhEPO (800 to 1,600 U/kg biw) would have a favorable effect in MDS. Although these doses might exceed the EPO receptor saturation point of normal erythroid progenitors, the dose-response curve for MDS progenitors is not known. Recent studies have suggested that daily administration of subcutaneous EPO may allow the total rhEPO dose to be decreased without a resultant decrease in efficacy.<sup>10,11</sup> Because these preliminary studies were not available when the present study was being designed, however, the drug was administered biw intravenously (IV).

Because of our concern that patients on the verge of evolution to acute nonlymphocytic leukemia would be unlikely to respond to rhEPO, we limited the trial to patients with less than 5% blasts in BM. Even though this was changed to less than 10% blasts during the course of the study, this criterion effectively limited the trial to two subsets of MDS, RA and RA with ring sideroblasts (RARS). There is no reason to believe, however, that patients with either RA with excess blasts (RAEB), or RA with excess blasts in transformation (RAEB-T) would have performed any better in this trial. In vitro studies have shown responses of CFU-E to rhEPO in RA and RARS, but poor responses in RAEB and RAEB-T.<sup>12</sup> Although we hoped to study both patients with and without transfusion requirements, the design of the study, which required biweekly IV injections all but limited the study to patients who were transfusion dependent because other patients, with less severe disease, essentially self-selected themselves out of

the study; patients who were well enough not to require transfusion therapy generally declined to participate in a study that would increase the frequency of their travel to receive medical care.

The trials demonstrated that high doses of rhEPO could be administered safely. Overall, in the open-label and double-blind trials, 17 patients received rhEPO at a dose of 1,200 to 1,600 U/kg biw without experiencing hypertension or seizures. These side effects, noted in initial trials of rhEPO, were probably secondary to rapid increases in the number of circulating RBC in patients in whom plasma volume and vascular tone were not well regulated owing to severe renal disease.<sup>7</sup> Although one patient with MDS receiving rhEPO progressed to ANLL, this phenomenon was also noted in one patient in the control group.

In this series of patients with MDS, 24% responded to rhEPO. This is consistent with previously reported small trials of rhEPO in MDS (Table 5).<sup>13,14</sup> Owing to differences in dose and schedule of administration, however, as well as differences in patient composition and definition of response, these studies are not truly comparable.

Only one patient responded in our placebo-controlled trial. Overall, only 4 of 17 patients receiving rhEPO responded, 3 with an increase in hematocrit of 4 percentage points or more over baseline, and the fourth by becoming transfusion independent. All responses initially occurred at a rhEPO dose of 1,600 U/kg biw; in one patient we were able to maintain the response as the dose was decreased to 800 U/kg. In the nonresponders, the transfusion requirements were unchanged. Thus, more liberal response criteria, such as a reduction in transfusion requirement by 25% or 50%, would not have changed the response rate in this series.

Before initiating the study, we were concerned about whether responses would involve the abnormal MDS clone or the residual normal cells. We were unable to shed any light on this issue because only one of the four responders had abnormal baseline cytogenetics and, in this patient, cytogenetic studies were not obtained on completion of the study. In one nonresponder with many abnormal erythroblasts (karyorrhexis, binucleate forms) before therapy, however, rhEPO produced a marked increase in the incidence of these abnormalities among the BM cells, suggesting that rhEPO was affecting the abnormal clone, but not excluding a possible effect on residual normal cells.

To determine which patients with MDS were most likely to respond to rhEPO, we compared the responders and

**Table 5. Responses to rhEPO in Clinical Trials in MDS**

Reference	Subset of MDS	Responses/ Patients	Dose Range
13	RA, RARS, RAEB, RAEB-T	2 of 8	12,000 U, tiw
14	RARS	0 of 2	50–500 U/kg tiw
This study	RA, RARS	4 of 17	800–1,600 U/kg, biw

Abbreviations: MDS, myelodysplastic syndrome; RAEB, RA with excess blasts; RAEB-T, RA with excess blasts in transformation; tiw, three times weekly; biw, twice weekly; other abbreviations as in Table 3.

nonresponders. In this small series, however, with only four responders, we were unable to demonstrate any difference between the two groups with respect to age, gender, diagnosis, time since diagnosis, or time since initiation of transfusion support. There was a trend for responders to have received fewer transfusions in the 3 months before study entry, but this trend was not statistically significant. Unlike studies in patients with AIDS,<sup>15</sup> baseline EPO levels did not predict the response to rhEPO in patients with MDS because the median baseline EPO value was 550 mU/mL in responders and 190 mU/mL in nonresponders. There was substantial overlap in EPO levels between responders and nonresponders, although responses were not noted in four patients with baseline serum EPO levels greater than 1,030 mU/mL.

The ability of patients with MDS to respond to pharmacologic doses of rhEPO may be more dependent on the state of the BM than on the baseline EPO level up to an exceedingly high level, and this marrow selectivity might

result from differences in the dose-response curve to rhEPO between the different abnormal clones, a variable percentage of residual normal progenitors, or both. Information on either of these variables might allow greater prediction of responses to rhEPO, but such information is not currently available.

In this series of patients with MDS, most of whom were transfusion dependent, 24% responded to rhEPO. rhEPO might be more effective earlier in the course of MDS, but it is disappointing that patients most in need of a beneficial response to rhEPO failed to show much response. Yet, in view of the minimal toxicity which we demonstrated with high doses of rhEPO in this series, pursuing further studies of rhEPO in MDS appears to be desirable. In such studies, rhEPO might be more effective if administered daily SC<sup>10,11</sup> and could be combined with other agents such as G-CSF or IL-3, which may enhance the effect of EPO by generating EPO-sensitive erythroid progenitor cells from earlier less active progenitors.<sup>16-19</sup>

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