Response to Recombinant Human Erythropoietin in Patients with Myelodysplastic Syndromes

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ABSTRACT

Recombinant human erythropoietin (rhEPO) at pharmacological doses was used to improve anemia and reduce the transfusional requirements of 43 patients with myelodysplastic syndrome (MDS). rhEPO was given by s.c. injection three times per week for 12 weeks. The EPO dose was started at 150 IU/kg and was increased to 300 IU/kg if after 6 weeks there was no or suboptimal erythroid response. Responses were defined as being a complete response (CR), partial response (PR), or no response (NR). A CR was considered a rise in transfused hemoglobin concentrations of at least 2 g/dl or a 100% decrease in RBC transfusion requirements over the treatment period. A PR was defined as an increase in transfused hemoglobin values of 1–2 g/dl or a decrease in RBC transfusion requirements equal to or greater than 50%. NR was defined as responses less than a PR. Patients who responded to therapy were continued on rhEPO at the same dose for 6 additional months. An objective response (CR and PR) was observed in 7 of 42 (16.7%) assessable cases after 6 weeks of treatment at the dose of 150 IU/kg. Dose escalation (300 IU/kg) in nonresponders resulted in another six patients attaining a rise in hemoglobin concentrations. The final response rate was 13 of 41 (31.7%); 4 patients became transfusion independent. Therapy was tolerated well, with no relevant side effects. MDS progression was seen in one case. An elevated bone marrow erythroid infiltration (erythroid index) and detectable pretreatment circulating erythroid progenitors (burst-forming units-erythroid) were the best predictors of hemoglobin response when we controlled for other variables. These data suggest that rhEPO has a role in the treatment of certain patients with MDS, particularly in those with a high erythroid index and detectable circulating erythroid burst-forming units.

INTRODUCTION

The MDSs are a group of clonal stem cell disorders characterized by abnormal bone marrow proliferation, differentiation, and maturation, leading to ineffective hematopoiesis. Peripheral cytopenias and functional defects, as well as a high likelihood of leukemic transformation, are the clinical hallmarks of MDSs. In the absence of effective treatment, many patients receive supportive therapy only, the mainstay of which has been blood transfusions. Due to limits and risks of transfusion therapy (namely immunization, transmission of viral diseases, and iron overload), there is a strong necessity for alternative approaches to relieve anemia in these disorders. In vitro studies of bone marrow progenitors from myelodysplastic patients grown in semisolid cultures have suggested that high concentrations of rhEPO can overcome the decreased responsiveness of these cells to physiological doses of EPO (1). Furthermore, some patients with MDS have an inadequate endogenous EPO response relative to the degree of anemia that may benefit from the administration of pharmacological doses of rhEPO (2–4). On these grounds, several trials have been designed to evaluate the efficacy of rhEPO in the enhancement of erythropoiesis in MDS (reviewed in Ref. 5). We herein report the results of a phase II study in which we evaluated the efficacy of high doses of rhEPO to improve anemia and/or reduce the transfusional requirements of patients with MDS. Special emphasis was placed on the identification of those categories of patients who are most likely to benefit from rhEPO treatment because thus far no consensus has been reached about a decision model for the use of this growth factor in MDS.

PATIENTS AND METHODS

From September 1992 to October 1995, 43 patients with MDS were entered into the study after informed consent had been obtained. MDS was classified according to the FAB Group criteria (6) as either RA, RARS, RAEB, CMMML, or RAEB-T. Patients’ clinical and hematological characteristics on entry into the study are reported in Table 1. At enrollment, 23 patients were transfusion dependent, requiring a median of 5 units of
Response to rhEPO in Patients with MDSs

Central nervous system tox. Exclusion criteria were clinically significant heart and treatment or administration of other hematopoietic growth factors for at least 2 months before entry, without cytostatic B12, and folate deficiency. All patients had to present stable Cooperative Oncology Group scale (7); hemoglobin levels duration; a performance status 2 according to the Eastern Cooperatively established diagnosis of MDS of at least 6 months outpatient conditions. Patients were questioned weekly given s.c. 3 times/week for 12 weeks. The EN) dose was started at the medical centers; subsequent therapy was administered under control of possible adverse events. Treatment had to be discontinued if severe side effects occurred, or at the patient's request. Supportive care was given throughout the study as clinically indicated.

Study Design. rhEPO (Eprex; Cilag, Milan, Italy) was given s.c. 3 times/week for 12 weeks. The EPO dose was started at 150 IU/kg and increased to 300 IU/kg if after 6 weeks there was no or suboptimal erythroid response. Patients who responded to therapy were continued on rhEPO at the same dose for 6 additional months. The first EPO injections were given at the medical centers; subsequent therapy was administered under outpatient conditions. Patients were questioned weekly concerning possible adverse events. Treatment had to be discontinued if severe side effects occurred, or at the patient's request. Supportive care was given throughout the study as clinically indicated.

Response Criteria. Responses were defined as being a CR, PR, or NR. A CR was considered a rise in untransfused hemoglobin concentrations of at least 2 g/dl or a 100% decrease in RBC transfusion requirements over the treatment period. A PR was defined as an increase in untransfused hemoglobin values of 1-2 g/dl or a decrease in RBC transfusion requirements ≥50%. NR was defined as less than a PR.

Study Parameters and Monitoring of Patients. Patients' evaluation before entry included a complete history, physical examinations, bone marrow biopsy and aspirate, analysis of karyotype, chest roentgenogram, electrocardiogram, and baseline laboratory tests that included a complete blood cell count with reticulocytes, serum EPO, vitamin B12 and RBC folate levels, erythroid progenitor cell assay (BFU-E), routine serum chemistry, coagulation tests, and urinalysis. Vital signs, complete blood cell count, and reticulocytes were monitored weekly. Serum EPO levels were determined using a commercially available enzyme-linked immunosassay (Quantikine IVD Erythropoietin; R&D Systems, Minneapolis, MN). Bone marrow aspirates were performed at study entry and at the end of the 12-week treatment. The degree of bone marrow erythroid hyperplasia was calculated on the basis of the bone marrow cellularity, measured on biopitic histological slides, and differential bone marrow counts evaluated on bone marrow films, according to the following formula (EI):

\[
\text{Bone marrow cellularity} \times \% \text{ of erythroblasts} = \frac{\text{Bone marrow cellularity}}{100}
\]

Karyotyping was carried out at study entry and on conclusion of the treatment period with standard techniques, as described previously (8). For cultures of erythroid progenitor cells, hematopoietic rhEPO was assayed in viscous medium using a modification of the method of Iscove et al. (9). Briefly, 2 x 10⁵ peripheral blood mononuclear cells were plated in triplicate in 35-mm Petri dishes with 1-ml aliquots of 0.9% methylcellulose viscous Iscove's modified Dulbecco's medium (Life Technologies, Inc., Grand Island, NY) supplemented with 30% human AB serum, 10% BSA (Fraction V; Sigma Chemical Co., St. Louis, MO), 1 x 10⁻⁴ M 2-mercaptoethanol (Sigma), and 2 units of rhEPO (Cilag). After incubation for 14 days at 37°C in a humidified atmosphere supplemented with 5% CO₂, the cultures were scored for BFU-E (defined as bursts of colonies consisting of hematopoietic cells) with an inverted microscope.

Statistical Analysis. Statistical evaluation was performed with the STATISTICA for Windows (StatSoft, Inc.; Tulsa, OK) software package on an IBM computer. Results are summarized as mean ± SD or as median and range. Student's t test and ANOVA were used to compare continuous variables between different groups of patients. The χ² test was used to compare qualitative or noncontinuous variables. A P of 0.05 or less was designated as statistically significant. All Ps are two-tailed. Correlations of variables with other variables were calculated by Spearman's rank correlation coefficient. For the multivariate analysis, clinical and laboratory parameters were entered into a forward stepwise logistic regression model to determine predictors of response.
Table 2  Response to erythropoietin treatment as related to clinical and biological characteristics

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<th>Case no.</th>
<th>Age/sex</th>
<th>FAB type</th>
<th>Hemoglobin level (g/dl)</th>
<th>Baseline EPO level (mIU/ml)</th>
<th>BFU-E (per 2 × 10³ cells)</th>
<th>Karyotype</th>
<th>Transfusion requirements (units/month)</th>
<th>Type of response</th>
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</table>

* M, male; F, female; NA, not assessable; ND, not done; IM, insufficient number of mitoses.
determine the most appropriate combination of covariates for predicting response to rhEPO therapy.

RESULTS

Response to Treatment. Forty-one of forty-three patients completed the study and were evaluated for response. Of the two patients who interrupted the study, one (case 17) died of the consequences of a traumatic femur fracture on week 6 of treatment (he had not responded to the lower dose of rhEPO); the other (case 40) discontinued rhEPO therapy on week 3 when he was hospitalized for bacterial pneumonia, dying a few weeks later of heart failure. Changes in hemoglobin concentrations, transfusion requirements, and BFU-E before and after rhEPO treatment are summarized in Table 2. According to defined response criteria, on week 12 of rhEPO treatment 5 patients showed CR, 8 patients PR, and 28 patients NR. Of the five patients who attained a CR, 8 patients PR, and 28 patients NR. Of the five patients who attained a CR, 4 patients showed an optimal response at the dose of 150 IU/kg and were maintained with that dose, whereas the fifth patient achieved CR only at the higher dose. Three of the eight patients with PR had signs of response after the first 6 weeks of treatment but did not benefit from the higher dose of rhEPO; the other five patients showed PR only after being challenged with rhEPO at 300 IU/kg. Seven of the 13 responders who received rhEPO during the extension phase had a continued response. In all responders, the rise of hemoglobin concentration was associated with a significant increase in reticulocyte counts. Similarly, as shown in Fig. 1, the number of circulating BFU-Es consistently increased in all responders. The increase between baseline and peak BFU-E was significantly higher in responders than in nonresponders \( (P < 0.001) \), although a slight increase in the number of circulating BFU-Es was also observed in five nonresponders at the end of treatment. Two of these patients (patients 31 and 39) also showed an increase in reticulocyte counts. Because it was hoped that these patients might present a delayed response, they continued rhEPO treatment for another 12 weeks, but no response was observed. No significant changes in white blood cell and platelet counts were noted over the course of treatment (data not shown). A representative responding patient’s course (case 25) is shown in Fig. 2.

Examination of bone marrow aspirates on conclusion of the study (available in 39 of 41 cases), showed an increase in the percentage of erythroid cells in 4 of the 5 complete responders and in 5 of 7 partial responders. As assessed by bone marrow morphology, disease progression during therapy was observed in 1 patient (case 36), who showed an increase in bone marrow blasts from 7 to 18%. This patient eventually developed overt acute myeloid leukaemia 5 months later. The other patients showed an almost unchanged bone marrow morphology.

Analysis of karyotype at the end of treatment (available in 33 cases) did not show remarkable changes except for case 12, who had an abnormal karyotype at diagnosis but showed only normal metaphases in the post-EPO bone marrow, and case 36, who displayed metaphases with multiple complex abnormalities in addition to metaphases with the original monosomy of chromosome 7.

Side Effects. rhEPO treatment was well tolerated overall, and no relevant adverse effects were observed. A mild increase in arterial blood pressure, which was easily controlled by medical therapy, was seen in patient 12 after 8 weeks of treatment. Two other patients (patients 3 and 19) complained of painful erythema at the site of rhEPO injections; however, rhEPO administration was not interrupted.

Prognostic Factors. In univariate analysis, three pre-treatment variables turned out to be significantly different between responders (CR and PR) and nonresponders: the EI \( (P = 0.0000) \), BFU-E values \( (P = 0.0057) \), and serum EPO levels \( (P = 0.0471) \). Responders had a higher EI than patients who did not respond to rhEPO treatment \( (37.09 ± 13.40 \text{ versus } 18.35 ± 5.91) \). BFU-E values also were more elevated in cases who
achieved CR or PR than in those who did not benefit from therapy (8.40 ± 7.12 versus 3.08 ± 3.27); only one responder (case 33) presented undetectable BFU-E. Serum EPO levels were 225.5 ± 121.3 mIU/ml in responders versus 393.4 ± 256.4 mIU/ml in nonresponders.

No differences in serum iron, ferritin, vitamin B12, and folate levels were found between the two categories of patients. The FAB type did not hold a statistically significant prognostic value (P = 0.348), but no assessable case of CMML and RAEB-T attained a response. Age, sex, karyotype, transfusion requirements on entry of the study, pretreatment hemoglobin levels, reticulocyte count, and length of MDS duration before rhEPO therapy also did not predict treatment outcome.

Regression analysis allowed us to demonstrate only an inverse relationship between serum EPO levels and circulating BFU-E values (r = -0.444; P = 0.012; Fig. 3).

Multivariate analysis (Tables 3 and 4) indicated El and BFU-E but not serum EPO as independent prognostic parameters. Attempts to define clear-cut values of these variables to be used to make treatment decisions led us to identify a subset of patients with a high likelihood of response. In fact, eight of the nine patients characterized by BFU-E > 0 and an El > 26.2 were responders (Table 2). Patients who did not fit the above criteria were all nonresponders, except for case 9, who had the highest BFU-E concentrations, and case 33, who had an El of 48.2.

**DISCUSSION**

In this study, rhEPO was administered to 43 MDS patients in a dose-escalating fashion. An objective response (CR and PR) was observed in 7 of 42 (16.7%) assessable cases after 6 weeks of treatment at the lower dosage (150 IU/kg). Increasing the dosage to 300 IU/kg resulted in 6 other patients attaining a rise in hemoglobin concentrations. The final response rate was 13 of 41 (31.7%); 4 patients became transfusion independent. Therapy was tolerated well, with no relevant side affects. MDS progression was seen in one case. Statistical analysis indicated bone marrow erythroid infiltration (El) and the number of circulating erythroid precursors as independent pretreatment variables associated with response to treatment. In particular, we found that eight of nine patients with detectable BFU-E and a high El (>26.2) were responders, and that the only two assessable responders of our series who did not meet these criteria had either BFU-E concentrations or an El far above the median values. Serum EPO levels were significantly more elevated in nonresponders but had a poor predictive value as compared to the El and BFU-E values.

The response rate in our series falls within the range of those reported in the literature. Data compiled from 15 separate trials of rhEPO, involving 308 patients with MDS, show an overall response rate of approximately 20%, with a range of 0–40% (5). In the largest trial carried out until now, a response to rhEPO treatment has been reported in 28 of 100 MDS patients (10). However, a comparison with single studies is difficult. The number of patients is often small, and they differ from each other in terms of patient selection, definition of response, dose of rhEPO, route of administration, and duration of treatment. The same arguments apply for prognostic factors. Thus far, no individual clinical trial has been sufficiently extensive to provide a basis for a decision model for the use of rhEPO. This would minimize the cost and improve the design of future studies. An accurate insight into the data has been provided by a recent meta-analysis by Hellström-Lindberg (11). Her evaluation included a total of 205 patients with MDS who had been treated with rhEPO. This analysis showed that the efficacy of rhEPO in MDS in general is low, with only 16% of cases presenting a significant response to treatment, and that the response rate were those with no transfusion requirement and FAB type other than RARS, irrespective of their serum level of EPO.

Information regarding the actual duration of rhEPO treatment in patients who do not respond initially is lacking. In most trials, patients discontinued rhEPO administration if they did not respond within 8–16 weeks from the start because later responses had not been reported. In our experience, two patients who had not presented clinical signs of response after 12 weeks, but did show an increase in BFU-E and reticulocyte counts, were challenged for 12 additional weeks because it was hoped that they might present a delayed response. However, no improvement in hemoglobin or transfusion requirements was observed during this extension phase, and it may be speculated that changes in laboratory parameters reflected an increase of pre-
Response to rhEPO in Patients with MDSs

Table 4

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum of squares</th>
<th>df</th>
<th>Mean square</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regression</td>
<td>4.834294</td>
<td>9</td>
<td>0.537144</td>
<td>7.329488</td>
<td>0.000111</td>
</tr>
<tr>
<td>Residual</td>
<td>1.465706</td>
<td>20</td>
<td>0.073285</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6.300000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In MDS. Besides, our multivariate analysis does not place this degree of importance on EPO levels, although it stresses the impact of the EI and BFU-E.

In conclusion, the results discussed above indicate that rhEPO is a safe, well-tolerated, and effective treatment for anemia in a substantial subset of MDS patients. Our data suggest that it is appropriate to assign rhEPO treatment to patients presenting both an elevated bone marrow erythroid infiltration (>26.2) and detectable circulating BFU-E, and also to those showing highly increased values of either parameters (relative to our suggested cutoff values). Challenging nonresponders with rhEPO for more than 3 months may not be warranted because clinical responses are usually not seen after that time.

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