Recombinant Human Erythropoietin in Transfusion-Dependent Anemic Patients With Multiple Myeloma and Non-Hodgkin's Lymphoma—A Randomized Multicenter Study

By Anders Österborg, Marc A. Boogaerts, Renato Cimino, Ursula Essers, Jerzy Holowiecki, Gunner Jullienson, Gerald Jäger, Albert Najman, and Dietrich Peest for the European Study Group of Erythropoietin (Epoetin Beta)

Treatment in Multiple Myeloma and Non-Hodgkin's Lymphoma

One hundred twenty-one anemic, transfusion-dependent patients with multiple myeloma (MM) or low-grade non-Hodgkin's lymphoma (NHL) were randomly allocated to receive (a) recombinant human erythropoietin (rhEPO) 10,000 U/d subcutaneously 7 days a week (fixed dose group) (n = 38), or (b) rhEPO 2,000 U/d subcutaneously for 8 weeks followed by step-wise escalation of the rhEPO dose (titration group) (n = 44), or (c) no rhEPO therapy (control group) (n = 39). The total treatment period was 24 weeks. There were no differences between the three groups with regard to baseline clinical, demographic, or health status measures. The cumulative response frequency, defined as elimination of transfusion need in combination with an increase in the hemoglobin concentration by >20 g/L, was 60% in both rhEPO treatment groups and 24% in the control group (P = .01 and .02, respectively, log rank test). For patients in the titration group the response rate on the first dose level (2,000 U/d) was only 14%. Cox's univariate regression analysis revealed that an inadequately low endogenous erythropoietin concentration in relation to the degree of anemia and a baseline platelet concentration ≥100 × 10^9/L were significant predictors for response to rhEPO therapy (P < .01). Multivariate regression analysis showed that relative erythropoietin concentration was the most important factor and the platelet count had no additional influence on response. Treatment with rhEPO was well tolerated. We conclude that treatment with rhEPO may be indicated in anemic MM and NHL patients with a relative erythropoietin deficiency. An initial dose of 5,000 U/d subcutaneously may be recommended.

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AMENIA OCCURS in most patients with multiple myeloma (MM) and low-grade non-Hodgkin's lymphoma (NHL) in the course of their disease. Impairment of normal hematopoiesis by malignant cells, autoimmune hemolysis, renal impairment, and myelosuppressive effects of chemotherapy may contribute to this type of anemia. Anemia of chronic disease (ACD), which is characterized by bone marrow (BM) erythroid hypoplasia, shortening of red cell survival, and a deficient production of erythropoietin compared with the degree of anemia, may also contribute. In the past, transfusion was the only available therapy. The development of recombinant human erythropoietin (rhEPO) provided a new therapeutic modality. Beneficial effects of erythropoietin have been shown both in patients with chronic renal failure and patients with different malignancies. The first pilot study on the use of rhEPO in patients with MM was performed by Ludwig et al, who observed an increase in the hemoglobin concentration by ≥20 g/L in 11 of 13 patients. Similar results have been reported in a small group of low-grade NHL patients. Based on these results, a randomized, multicenter trial was begun in March 1991 to analyze the therapeutic effect of rhEPO, to define the optimal dose of rhEPO, and to identify prognostic factors for response to rhEPO treatment in anemic, transfusion-dependent patients with MM or low-grade NHL. We report the final analysis below.

MATERIALS AND METHODS

Patients

Patients meeting the following inclusion criteria were eligible for the study: diagnosis of MM or low-grade NHL, age ≥18 years, WHO performance status ≤2, life expectancy >2 months, no acute or chronic bleeding within 3 months before randomization, hemoglobin concentration <100 g/L, and transfusion requirement ≥2 U (500 mL) during the last 3 months before randomization. Exclusion criteria were therapy-resistant hypertension; acute infection; severe liver disease (serum ALAT >1.3 μkat/L); platelet count <20 × 10^9/L; vitamin B12, folic acid, or iron deficiency; hemolytic anemia (haptoglobin <0.5 g/L or positive Coombs' test); or epilepsy.

The Kiel classification was used for patients with low-grade NHL. Staging was performed according to Durie and Salmon for patients with MM and according to the Ann Arbor classification for NHL patients. The Rai staging system was used for patients with chronic lymphocytic leukemia (CLL).

One hundred fifty patients were enrolled. Six of these were withdrawn during the pretreatment phase. Two patients had a hemoglobin concentration <100 g/L, one had hemolytic anemia, two were withdrawn because of personal reasons, and in one case the informed consent was taken back. One hundred forty-four patients were analyzed for safety. Twenty-three patients had to be excluded from efficacy analysis. Thirteen of these 23 patients had been in the treatment phase for less than 4 weeks, 8 had a transfusion requirement of <2 U before entering the study, and 2 patients were excluded because of iron deficiency. Thus, a total of 121 patients were evaluable; 65 had MM and 56 had NHL. Twenty-six of the NHL patients...
had CLL, 13 had immunocytoma, 7 had Waldenström’s macroglobulinemia, and in 10 patients NHL subtype data were missing. Pretreatment characteristics are shown in Table 1. No significant differences were noted between the three groups with regard to clinical characteristics and major prognostic factors.

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Dose Titration</th>
<th>Fixed Dose</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>44</td>
<td>38</td>
<td>39</td>
</tr>
<tr>
<td>Median age (yr) (range)</td>
<td>65 (38-82)</td>
<td>66 (43-84)</td>
<td>64 (36-83)</td>
</tr>
</tbody>
</table>

NHL patients had advanced disease (Durie and Salmon stage III and Ann Arbor/Rai stage IV, respectively) at study entry.

Seventy-eight of the patients (64%) had one or more active concomitant diseases at the start of the study. There was a higher proportion of patients suffering from chronic obstructive lung diseases in the fixed dose group (16%) than in the titration group (4%) and the control group (3%). Heart disease was more common in the titration group (49%) than in the fixed dose group (23%) and the control group (29%).

Study Design and Randomization

Twenty-eight European centers participated in the study. The protocol of the study was approved by each institution’s Ethics Committee. Patients with informed consent were reported by facsimile or telephone call to a central site, and after stratification according to diagnosis (MM or NHL) and presence or absence of concomitant chemotherapy were randomized into three arms: fixed rhEPO dose group, escalating rhEPO dose group, and control group.

Treatment Plan

Eligible patients were randomly allocated to one of the following three treatment groups.

Fixed dose group. rhEPO (epoetin beta, Boehringer Mannheim GmbH, Mannheim, Germany) 10,000 U subcutaneously (SC) per day, 7 days a week, until the hematocrit value had reached 35% of normal after elimination of the transfusion need.

Dose titration group. rhEPO (epoetin beta, Boehringer Mannheim GmbH) 2,000 U SC per day, 7 days a week, for 8 weeks. After 8 weeks the daily dose was increased to 5,000 U SC if the hematocrit concentration had not reached 40% of normal after elimination of the need for transfusions. After 12 weeks, the daily dose was increased to 10,000 U SC if the hematocrit had not reached 45% of normal after elimination of the need for transfusions.

Control group. No rhEPO therapy.

Dose reductions were performed primarily by changing the frequency of administrations of rhEPO rather than reducing the individual dose. After reaching a hematocrit concentration of 110 to 130 g/L without transfusions, the number of administrations was reduced to 5 or even 3 times a week. If the hematocrit concentration exceeded 130 g/L in women and 140 g/L in men, the rhEPO administration was withheld until the hematocrit concentration fell to at least 100 g/L. Treatment was then restarted with a reduced frequency of administrations. Further dose modification could be undertaken individually by the investigator in order to maintain the hematocrit concentration at a level between 110 and 130 g/L. If the transfusion need was not eliminated after 12 weeks of therapy with 10,000 U/d of rhEPO, the patient was withdrawn from the study as a nonresponder.

The total treatment period was 24 weeks.

Pretreatment Evaluation

The initial evaluation included medical history, physical examination, documentation of transfusions and concomitant medication during the last 3 months, hematocrit concentration, packed red cell volume, red cell count, reticulocyte count, white blood cell count (WBC) with differential, platelet count, electrolytes, urea, creatinine, serum iron, transferrin and transferrin saturation, ferritin, serum liver enzymes, electrophoresis of plasma, prothrombin time, partial thromboplastin time, and serum erythropoietin concentration.

The presence of a relative erythropoietin deficiency (in relation to the degree of anemia) was analyzed in each patient by calculation of the ratio between observed (O) and predicted (P) logarithm of the baseline serum erythropoietin (EPO) concentration. The formula
be given if the hemoglobin concentration dropped below 100 g/L, but were not allowed if the hemoglobin value exceeded 100 g/L.

**Indications for Blood Transfusion**

During the prestudy and study period, blood transfusions could be given if the hemoglobin concentration dropped below 100 g/L. However, patients did not fulfill the response criteria (no need for transfusion and increase in hemoglobin concentration by >20 g/L) for transfusion and increase in hemoglobin concentration by >20 g/L were not allowed if the hemoglobin value exceeded 100 g/L.

**Progression of Underlying Disease**

In patients with myeloma, progression was denoted if any of the following criteria were fulfilled: >25% increase in the M component, serum calcium, or the serum creatinine concentration; >25% increase in Bence-Jones protein excretion; >25% increase in the number of bone marrow plasma cells; and an increase in or development of new bone lesions.

In patients with NHL, progression was denoted if one or more of the following criteria were met: >50% increase in the size of lymph nodes or occurrence of new nodes; >50% increase in the size of the spleen; >50% increase in the number of circulating lymphocytes; and occurrence of or worsening of B symptoms.

**Statistical Analyses**

Time to response was defined as time from randomization until date of registered response. Differences in time to response between groups were analyzed by survival time method using the log rank test. Response rates were estimated by the method of Kaplan Meier. Univariate and multivariate life table analyses were performed by Cox’s regression model.

Differences in binary data were tested using the chi-square statistic or the Fisher’s exact test. Student’s t-test was used to test differences between means of groups and medians were compared by the Wilcoxon rank sum test.

**RESULTS**

**Time to Response**

The time to response is shown in Fig 1. At the end of the study, 60% of the patients in each rhEPO group and 24% in the control group fulfilled the response criteria (no need for transfusion and increase in hemoglobin concentration by >20 g/L). The difference between each rhEPO group and the control group was statistically significant ($P < .02$) (Fig 1). No relevant differences were observed between the rhEPO treatment groups and the control group during the first 8 weeks. Thereafter the cumulative response rates differed markedly between the rhEPO treatment groups and the control group (Fig 1). Fourteen percent of the patients in the titration group responded to rhEPO therapy at the first dose level (2,000 U/d). After stepwise escalation to 5,000 and 10,000 U daily, the cumulative response rate increased to 42% and 60%, respectively.

Cox’s regression analysis was carried out to define influencing or prognostic factors for response to rhEPO therapy. Univariate analysis (Table 3) showed that only the O/P ratio of the baseline erythropoietin serum concentration and the platelet count were prognostic factors ($P < .01$). A multivari-

**Table 2. Baseline Laboratory Characteristics by Treatment Group**

<table>
<thead>
<tr>
<th></th>
<th>Dose Titration</th>
<th>Fixed Dose</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum erythropoietin (U/L) (median, range)</td>
<td>50 (6-4.044)</td>
<td>76 (1-1.404)</td>
<td>43 (1-1.000)</td>
</tr>
<tr>
<td>O/P ratio (median, range) of serum erythropoietin</td>
<td>0.80 (0.2-1.68)</td>
<td>0.95 (0.6-1.57)</td>
<td>0.64 (0.4-1.26)</td>
</tr>
<tr>
<td>Hemoglobin concentration* (g/L) (median, range)</td>
<td>80 (65-103)</td>
<td>80 (62-101)</td>
<td>81 (52-98)</td>
</tr>
<tr>
<td>Packed red cell volume* (median, range)</td>
<td>26.3 (19.2-34.5)</td>
<td>26.4 (13.2-36.1)</td>
<td>26.1 (18.1-32.1)</td>
</tr>
<tr>
<td>Erythrocytes* (10^{12}/L) (median, range)</td>
<td>2.77 (2.05-3.90)</td>
<td>2.76 (1.20-3.80)</td>
<td>2.75 (2.00-3.65)</td>
</tr>
</tbody>
</table>

* Median pretransfusion value during the 3 months before randomization.

**Preparation Laboratory Characteristics**

The baseline values of hematologic variables are shown in Table 2. There were no differences between the treatment groups or between MM and NHL patients with regard to pretreatment hemoglobin concentration, packed red cell volume, red cell count, reticulocyte count, transferrin saturation, or serum ferritin concentration. The highest median serum erythropoietin concentration was found in the fixed dose group. The median O/P ratio of serum erythropoietin was found to be lower in the control group compared with the rhEPO treatment groups (Table 2). Sixty-eight percent of the patients in the control group had a low O/P ratio (<0.9) compared with 38% in the fixed dose group ($P = .02$).

**Follow-Up**

Every week the following tests were performed: hemoglobin concentration, packed red cell volume, red cell count, and reticulocyte count. The following investigations were performed every 4 weeks: medical history and physical examination, WBC with differential, platelet count, electrolytes, urea, creatinine, serum iron, transferrin and transferrin saturation, ferritin, and serum liver enzymes. Erythropoiesis of plasma, prothrombin time, partial thromboplastin time, and serum erythropoietin concentration were analyzed every 8 weeks. Blood transfusions were recorded continuously during the study period.

**Objectives and Criteria for Response**

The primary study objective was to investigate the efficacy of different doses of rhEPO in reducing or eliminating the need for blood transfusions. The secondary objective was the safety of rhEPO therapy. Response was defined as independence from erythrocyte transfusions during an 8 week period and an increase in hemoglobin concentration by >20 g/L (mean over 4 weeks) compared with the baseline hemoglobin value (median 100 g/L) for patients with a packed red cell volume >38%. O/P ratio values <1.0 indicate an inadequate endogenous erythropoietin concentration with respect to the degree of anemia.

**Progression**

In patients with myeloma, progression was denoted if any of the following criteria were fulfilled: >25% increase in the M component, serum calcium, or the serum creatinine concentration; >25% increase in Bence-Jones protein excretion; >25% increase in the number of bone marrow plasma cells; and an increase in or development of new bone lesions.

In patients with NHL, progression was denoted if one or more of the following criteria were met: >50% increase in the size of lymph nodes or occurrence of new nodes; >50% increase in the size of the spleen; >50% increase in the number of circulating lymphocytes; and occurrence of or worsening of B symptoms.

**Statistical Analyses**

Time to response was defined as time from randomization until date of registered response. Differences in time to response between groups were analyzed by survival time method using the log rank test. Response rates were estimated by the method of Kaplan Meier. Univariate and multivariate life table analyses were performed by Cox’s regression model.

Differences in binary data were tested using the chi-square statistic or the Fisher’s exact test. Student’s t-test was used to test differences between means of groups and medians were compared by the Wilcoxon rank sum test.

**RESULTS**

**Time to Response**

The time to response is shown in Fig 1. At the end of the study, 60% of the patients in each rhEPO group and 24% in the control group fulfilled the response criteria (no need for transfusion and increase in hemoglobin concentration by >20 g/L). The difference between each rhEPO group and the control group was statistically significant ($P < .02$) (Fig 1). No relevant differences were observed between the rhEPO treatment groups and the control group during the first 8 weeks. Thereafter the cumulative response rates differed markedly between the rhEPO treatment groups and the control group (Fig 1). Fourteen percent of the patients in the titration group responded to rhEPO therapy at the first dose level (2,000 U/d). After stepwise escalation to 5,000 and 10,000 U daily, the cumulative response rate increased to 42% and 60%, respectively.

Cox’s regression analysis was carried out to define influencing or prognostic factors for response to rhEPO therapy. Univariate analysis (Table 3) showed that only the O/P ratio of the baseline erythropoietin serum concentration and the platelet count were prognostic factors ($P < .01$). A multivari-
Hematopoietic Effects and Transfusion Need

Comparing the baseline and the last value of the study, the absolute change in the median hemoglobin concentration was +21 g/L in the fixed dose group, +15 g/L in the titration group, and +5 g/L in the control group. The differences were not statistically significant (Wilcoxon rank sum test). Similar results were observed with regard to the packed red cell volume and the red cell count (data not shown). No significant differences between baseline and the last value of the study were observed for serum iron concentration, transferrin saturation, and serum ferritin concentration. During the study 32%, 35%, and 18% of the patients in the titration, fixed dose, and control group, respectively, presented with transferrin saturation <15%. The median neutrophil and platelet counts remained unchanged in all groups during the study.

The proportion of patients receiving transfusions during the prestudy period was 66%, 63%, and 71% in the titration,

<table>
<thead>
<tr>
<th>Table 3. Cox’s Univariate Regression Analysis of Factors on Time to Response</th>
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</thead>
<tbody>
<tr>
<td>Factor</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>O/P ratio of serum erythropoietin conc.*</td>
</tr>
<tr>
<td>Platelet*</td>
</tr>
<tr>
<td>Underlying disease (MM/NHL) (0/1)</td>
</tr>
<tr>
<td>Chemotherapy (no/yes) (0/1)</td>
</tr>
<tr>
<td>Neutrophil*</td>
</tr>
<tr>
<td>Serum creatinine conc.*</td>
</tr>
<tr>
<td>Transferrin saturation*</td>
</tr>
</tbody>
</table>

* Continuous variable, 0.1 U increment.
† Continuous variable, 50 U increment.
‡ Continuous variable, 1 U increment.
§ Continuous variable, 10 U increment.
ERYTHROPOIETIN THERAPY IN MYELOMA AND LYMPHOMA

Table 4. Response Rate in Relation to Treatment in Different Patient Subgroups

<table>
<thead>
<tr>
<th>Patient Subgroup</th>
<th>Dose Titration</th>
<th>Fixed Dose</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Responder/</td>
<td>Responder/</td>
<td>Responder/</td>
</tr>
<tr>
<td></td>
<td>Treated</td>
<td>Treated</td>
<td>Treated</td>
</tr>
<tr>
<td></td>
<td>Response Rate*</td>
<td>Response Rate*</td>
<td>Response Rate*</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>13/22</td>
<td>12/23</td>
<td>4/20</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>10/22</td>
<td>7/15</td>
<td>4/19</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>22/38</td>
<td>18/34</td>
<td>7/35</td>
</tr>
<tr>
<td>No</td>
<td>1/6</td>
<td>1/4</td>
<td>1/4</td>
</tr>
<tr>
<td>O/P ratio of serum erythropoietin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.9</td>
<td>15/21</td>
<td>6/10</td>
<td>3/15</td>
</tr>
<tr>
<td>≥0.9</td>
<td>1/10</td>
<td>5/16</td>
<td>1/6</td>
</tr>
<tr>
<td>Platelet count (10⁶/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td>7/21</td>
<td>7/18</td>
<td>2/22</td>
</tr>
<tr>
<td>≥100</td>
<td>15/22</td>
<td>12/20</td>
<td>6/17</td>
</tr>
</tbody>
</table>

* Kaplan Meier estimates.
† P < .05 compared with controls (log rank test).

fixed dose, and control group, respectively (median value during 4 weeks). The corresponding proportion for the first month of the study was 57% in the titration group, 55% in the fixed dose group, and 61% in the control group. During months 2 to 6 the percentage of transfused patients was 64% in the titration group, 58% in the fixed dose group, and 82% in the control group. The difference between each rhEPO group and the control group was statistically significant (P < .05, log rank test). Four of 32 transfused patients in the control group, 4 of 22 in the fixed dose group, and 9 of 28 patients in the titration group fulfilled the response criteria during the study. This explains the paradox response rate above 50% and the simultaneously high transfusion rate (>50%). The median packed red cell volume transfused every 4 weeks did not differ between the three groups during the 3 months before randomization. During the second and third months of the study period the median volume of transfused red cells was approximately 300 mL lower in the rhEPO treatment groups than in the control group, but the differences were not statistically significant, which was also the case at the end of the treatment period. In patients with an O/P ratio for serum erythropoietin of <0.9, the median volume of transfused packed red cells every 4 weeks was reduced by 24% in the titration group and reduced by 38% in the fixed dose group during the study period; however, the median transfusion volume in the control group remained unchanged (+7%). The differences were not statistically significant but the numbers of patients in each group were small.

during the study. SAE occurred in 50%, 64%, and 45% of the patients, respectively. The differences were related mainly to a higher incidence of infectious complications in the rhEPO treatment groups, but there was no rhEPO dose-dependency with regard to the incidence of infections. Nonserious hypertensive events occurred in five patients (10%) in the titration group, in four patients (8%) in the fixed dose group, and in one patient (2%) in the control group. A causal relationship to rhEPO therapy was considered possible in two of these patients. A nonfatal pulmonary embolism occurred in one patient with a hemoglobin concentration of 154 g/L and the SAE was classified as possibly related to rhEPO treatment. Skin reactions (erythema, itching) were reported in two patients. Epoetin beta therapy was withdrawn and the symptoms disappeared.

The number of patients with progression of underlying disease during the study was 48% in the titration group, 51% in the fixed dose group, and 45% in the control group (not significant). Eleven patients (23%) in the titration group, 15 patients (32%) in the fixed dose group, and 14 patients (29%)

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>AE (n = 48)</th>
<th>SAE (n = 47)</th>
<th>Controls (n = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>6</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Septicemia</td>
<td>—</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>—</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Bone pain</td>
<td>1</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Tumor progression</td>
<td>1</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>—</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Skin reactions</td>
<td>1</td>
<td>1</td>
<td>—</td>
</tr>
</tbody>
</table>

Toxicity

Treatment with rhEPO was well tolerated and most patients had no side-effects clearly related to rhEPO administration. The most important adverse events (AE) and serious adverse events (SAE) that occurred during the study period are summarized in Table 5. Eighty-three percent of the patients in the titration group, 85% in the fixed dose group, and 65% in the control group suffered from at least one AE
Moreover, the type of underlying disease (MM or NHL) was interpreting the insignificant differences in time to response between the groups with regard to reduction effects were noted in patients with a relative erythropoietin the results from the study by Abel. The most prominent lar in the three groups. The effect of rhEPO was more strik-

ing the control group died during the study period. The SAEs leading to death are shown in Table 6. More patients in the rhEPO treatment groups died from infections/septicemia but all events leading to death were classified as unrelated to rhEPO therapy.

DISCUSSION

The results of this randomized multicenter study showed that MM and NHL patients treated with rhEPO had a signifi-
gicantly higher rate of responding with hemoglobin incre-
ment and transfusion independence than patients allocated to the control group. The difference could be attributed to the rhEPO administration since (a) there were no differences between the groups with regard to reduction or progression of the underlying malignant disease during the study period, and (b) the intensity of concomitant chemotherapy was similar in the three groups. The effect of rhEPO was more striking in MM than in NHL patients. The reduced power of the latter subgroup analysis has, however, to be considered when interpreting the insignificant differences in time to response between rhEPO-treated NHL patients and the controls. Moreover, the type of underlying disease (MM or NHL) was not found to be of prognostic significance in the univariate regression analysis.

Patients not receiving chemotherapy responded poorly to rhEPO treatment compared with patients receiving concomi-
tant chemotherapy. It should, however, be noted that the number of patients in the nonchemotherapy subgroup was small, even though this observation is partially in line with the results from the study by Abels. The most prominent effects were noted in patients with a relative erythropoietin deficiency with respect to the degree of anemia (O/P ratio of serum erythropoietin <0.9). A very high response rate (89%) was found among patients with an O/P ratio <0.6. Nonresponse could be predicted with a high probability as the response rate among patients with an O/P ratio >1.2 was only 10%. In clinical practice it would be more useful to relate the (uncorrected) serum erythropoietin concentration to the probability of response. Using cutoff values of 50 U/L and 400 U/L, we found that a serum erythropoietin concentration <50 U/L was associated with a response rate of 76%, whereas a value >400 U/L strongly predicted nonre-
response (cumulative response rate 9%). The predictive value of the endogenous serum erythropoietin concentration has also been described in pilot studies in MM and NHL patients with myelodysplastic syndromes (MDS) where low serum levels of erythropoietin were associated with a high likelihood of response to rhEPO therapy. Thus, patients with MM receiving chemotherapy and with a relative eryth-
ropoietin deficiency may represent a subgroup with a very high likelihood of response to rhEPO treatment. Moreover, the response rate in patients without thrombocytopenia was higher compared with those who had platelets <100 × 10^9/L, indicating that a compromised BM function may negatively influence the probability of response to rhEPO therapy. Chemotherapy-induced stem cell damage may result in a reduc-
tion of the numbers of circulating erythropoietin progenitors, which may persist several months after the last chemother-
apy course. The compromised BM function may also result from tumor cell infiltration. In patients with MM, a heavy BM plasma cell load was associated with a poor in vitro response to rhEPO.

It should be noted that 62% of our patients treated with the fixed rhEPO dose had a baseline O/P ratio of serum erythropoietin ≥0.9, whereas in the control group only 29% of the patients had an O/P ratio ≥0.9. Since the probability of a response to rhEPO was highest in patients with an O/ P ratio of <0.9, it cannot be excluded that this imbalance between the groups may underestimate the true difference in response rate between rhEPO-treated patients and controls. We suggest that the relative erythropoietin concentra-
tion should be stratified when randomizing patients in future trials on rhEPO therapy.

The proportion of patients receiving transfusions during month 2 to 6 was significantly lower in both rhEPO groups than in the control group. In contrast, no relevant differences were found in the median volume of transfused red cells between the three groups. Because only six responding pa-
tients (2 in each arm) became transfusion-dependent again during the study period, it was clearly not because of rapid relapses and short response durations. Similar results have been reported by others in randomized rhEPO studies. Notably, among rhEPO-treated patients with an O/P ratio ≤0.9, the median transfusion volume decreased considerably compared with the controls, but the number of patients in each subgroup was small and the difference was not statisti-
cally significant.

A functional or relative iron deficiency may occur in some patients during rhEPO treatment. Iron supplementation may, in such patients, be required to obtain a response to rhEPO therapy. During the study, one third of the rhEPO-treated patients presented with transferrin saturation below 15%, indicating at least functional iron deficiency. As iron was not administered to our patients, it cannot be excluded that the therapeutic effect of rhEPO in the present study could have been enhanced by a concurrent iron administration.

A clear dose-dependency for rhEPO was noted when only 14% of the patients in the titration group showed a response during 8 weeks of therapy with 2,000 U of rhEPO per day. After step-wise escalation to 5,000 and 10,000 U/day, the cumulative response rate increased considerably. This is in accordance with a previous pilot study of patients with solid tumors in which doses of 100 to 200 U/kg (administered 5 times a week) were optimal to induce a clinical response.
Because many of our patients in the fixed dose group were able to maintain their hemoglobin concentration between 110 and 130 g/L on a reduced rhEPO dose, an initial dose of 5,000 U daily may be recommended for practical use.

Even though more AEs were reported in the rhEPO treatment groups than in the control group it should be taken into account that only six AEs were assessed as related to rhEPO treatment. The higher numbers of reported AEs in the rhEPO treatment groups may have been influenced by the fact that patients treated with rhEPO had a larger number of concomitant (nonmalignant) diseases at the start of the study. Thus, we conclude that rhEPO can be administered safely to patients with MM and low-grade NHL.

The results of the present randomized study are in line with previous pilot studies on patients with MM and NHL.17,18,29 Because as much as 24% of the patients in the control arm fulfilled the response criteria, it is obvious from our results that it is of utmost importance to include a control arm in rhEPO trials to correct for factors other than rhEPO that may affect the hemoglobin concentration and the transfusion need, such as concomitant chemotherapy and regression or progression of BM tumor cell infiltration. Thus, further randomized controlled studies not only on cancer patients in general, but also on patients with specified tumors in particular, are warranted to define the clinical effects of rhEPO and to identify patient subgroups that may gain benefit from rhEPO treatment. To our knowledge, preliminary results from such studies have as yet been reported only in patients with ovarian carcinoma receiving platinum-based chemotherapy20 and in patients with CLL.21

This study did not contain cost-benefit and quality of life analyses. As reported by others, treatment with rhEPO may result in higher costs than blood transfusions, although it seems likely that the cost of blood and blood products will escalate in the future as new technologies and tests are added. On the other hand, rhEPO therapy has been reported to improve the quality of life in anemic dialysis-dependent patients,22 as well as in patients with cancer.6,27,30 To reduce the costs, it is important to identify the optimal dose of rhEPO. In this study, 2,000 U/d of rhEPO was clearly suboptimal, whereas 10,000 U/d seemed to be only marginally better than 5,000 U/d. Moreover, the identification of prognostic factors, either upfront as in the present study or after a short (2 weeks) rhEPO treatment period,31 may be extremely helpful to identify patients with a high probability of response to rhEPO, thereby avoiding expensive and ineffective treatment.

We conclude from the present study that rhEPO treatment is indicated in anemic, transfusion-dependent patients with MM and low-grade NHL with a relative erythropoietin deficiency with respect to the degree of anemia. An initial daily dose of 5,000 U SC may be recommended.

**APPENDIX**

The following medical centers and investigators included two or more evaluable patients in the European Study on recombinant human Erythropoietin (epoetin beta) in Multiple Myeloma and Non-Hodgkin’s Lymphoma: Munich, Germany, the Department of Medicine, Ludwig-Maximilians-Universität, H. Gerhardt; Aachen, Germany, Praxis für Hämatologie/Onkologie, U. Eiers; Hannover, Germany, the Department of Clinical Immunology and Blood Transfusion Medicine, Hannover Medical School, H. Deicher, D. Peest; Nürnberg, Germany, the Department of Medicine, Klinikum Nürnberg, G. Kaiser; Frankfurt, Germany, the Department of Haematology, Johann-Wolfgang-Goethe-Universität, D. Hoelzer; Erfangen, Germany, the Department of Haematology and Oncology, Med. Klinik III, M. Granatzki; Gothenburg, Sweden, the Department of Oncology, Sahlgrenska Hospital, K. Landys; Gitterwolm, Germany, the Department of Medicine, Städtisches Krankenhaus, F. Bergman; Stockholm, Sweden, the Department of Oncology, Karolinska Hospital, H. Mellstedt, A. Österborg; Paris, France, the Department of Hematology, Hôpital Saint-Antoine, A. Najman, F. Isnard, N. Cheron; Mainz, Germany, the Department of Medicine, Johannes-Gutenberg-Universität, H. Garam; Graz, Austria, the Department of Medicine, A. O. Landeskrankehaus, G. Jäger, H.-L. Seewann; Paris, France, the Department of Haematology, Hôpital du Haut Lévêque, A. Broust; Mannheim, Germany, the Department of Oncology, Klinikum Mannheim, W. Queisser; Huddinge, Sweden, the Department of Medicine, Huddinge University Hospital, G. Jüliusson, M. Ohring; Paris, France, the Hematology Laboratory, Hôpital du Val de Grâce, P. Auzanneau; Trier, Germany, Akademisches Lehrkrankenhaus, W. Weber; Modena, Italy, the Division of Medical Oncology, V. Silingardi; Jena, Germany, the Department of Medicine, Friedrich-Schiller-Universität, M. Stauch; Bielefeld, Germany, the Department of Haematology and Oncology, Krankenanstalten Gilde, F.K. Lindemann; Vienna, Austria, the Department of Medicine, Krankenhaus der Stadt Wien, M. Peschstorfer; Naples, Italy, the Division of Hematology, Ospedale Cardarelli, R. Cimino; Uppsala, Sweden, the Department of Medicine, Academic Hospital, G. Birgégär; Leuven, Belgium, the Department of Hematology, University Hospital Leuven, M.A. Boogaerts; Katowice, Poland, the Department of Haematology, Silesian Medical Academy. J. Holowiecki; Oviedo, Spain, the Department of Medical Oncology, Hospital Central de Asturias, A.J. Lacave; Reims, France, the Department of Haematology, Hôpital Robert Debré, A.M. Blaise.

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Recombinant human erythropoietin in transfusion-dependent anemic patients with multiple myeloma and non-Hodgkin's lymphoma--a randomized multicenter study. The European Study Group of Erythropoietin (Epoetin Beta) Treatment in Multiple Myeloma and Non-Hodgkin's Lymphoma

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