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

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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 the 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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Seventy-three percent of the MM patients and 88% 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.

Fifty-nine percent of the patients (59% in the control group, 54% in the dose titration group, and 53% in the fixed dose group) had received chemotherapy during the last 4 weeks before study initiation. There were no relevant differences between groups with regard to type or intensity of chemotherapy before study entry. Eighty-eight percent of the patients received concomitant chemotherapy during the study. The chemotherapeutic regimens used included alkylating agents in 66% of the patients, 40% received vincristine, 36% received anthracyclines, and corticosteroids were used in 78% of the patients. Seventy-three percent of the MM patients and 81% of the 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 hemoglobin value had reached 110 g/L 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 hemoglobin concentration had not reached 110 g/L after elimination of the need for transfusions. After 12 weeks, the daily dose was increased to 10,000 U SC if the hemoglobin had not reached 110 g/L 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 hemoglobin 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 hemoglobin concentration exceeded 130 g/L in women and 140 g/L in men, the rhEPO administration was withheld until the hemoglobin concentration fell at least 10 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 hemoglobin 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 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, hemoglobin 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

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<th>Table 1. Patient Characteristics</th>
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determining the predicted log (EPO) was log$_{10}$ (EPO) = 4.746 – (0.093 \times \text{packed red cell volume}) for patients with a packed red cell volume \leq 38\%, and log$_{10}$ (EPO) = 1.381 – (0.005 \times \text{packed red cell volume}) 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.\textsuperscript{15}

**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.\textsuperscript{14} Response rates were estimated by the method of Kaplan Meier. Univariate and multivariate life table analyses were performed by Cox’s regression model.\textsuperscript{15}

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-
ate regression analysis including these two factors revealed that the platelet count had no significant additional influence on response besides that due to the O/P ratio.

The cumulative response frequencies in different subgroups of patients are shown in Table 4. The response rate in MM patients was significantly higher in the titration group than in controls ($P = .04$, log rank test), whereas the fixed dose group only approached significance ($P = .07$). No significant differences between treatment groups and controls were found for patients with NHL ($P = .19$ and $P = .12$, respectively), although the numerical value was higher in rhEPO-treated patients than in controls (52% and 54%, respectively, vs 28%). The reduced power of this subgroup analysis has to be taken into account.

Only two of ten patients without concomitant chemotherapy responded to rhEPO therapy. The response rate among 72 patients receiving chemotherapy was 63% (Kaplan Meier estimates), and the differences between rhEPO-treated patients and controls were statistically significant ($P = .02$ and $P = .01$, respectively, log rank test).

Several analyses with different cut off points for the O/P ratio of serum erythropoietin and comparing the two subgroups with respect to the time to response identified an O/P ratio of 0.9 as the most significant. The response rate in patients with an O/P ratio <0.9 was 79% and 60% in the titration and fixed dose groups, respectively. The difference in time to response between the titration group and the control group was statistically significant ($P = .04$), but the difference was merely caused by a very low response rate among the controls (11%) in this subgroup rather than to the response rate observed in the rhEPO-treated patients (50%).

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 3. Cox's Univariate Regression Analysis of Factors on Time to Response |
|------------------------|--------|--------|
| Factor                             | Hazard | P      |
| O/P ratio of serum erythropoietin conc.* | 0.84   | <.01   |
| Platelet**                        | 1.20   | <.01   |
| Underlying disease (MM/NHL) (0/1)  | 0.80   | .42    |
| Chemotherapy (no/yes) (0/1)        | 2.19   | .19    |
| Neutrophils*                       | 1.00   | .43    |
| Serum creatinine conc.†            | 0.99   | .92    |
| Transferrin saturation§             | 0.92   | .15    |

* Continuous variable, 0.1 U increment.  
† Continuous variable, 50 U increment.  
§ Continuous variable, 1 U increment.  
© Continuous variable, 10 U increment.
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 < 0.05, 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.

**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 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%)
in 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/sepsisemia 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 significantly higher rate of responding with hemoglobin increment 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 the groups with regard to reduction or progression of the underlying malignant disease during the study period, and 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 concomitant 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.5 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 nonresponse (cumulative response rate 9%). The predictive value of the endogenous serum erythropoietin concentration has also been described in pilot studies in MM an NHL and in patients with myelodysplastic syndromes (MDS) where low serum levels of erythropoietin were associated with a high likelihood of response to rhEPO therapy.16,18 Thus, patients with MM receiving chemotherapy and with a relative erythropoietin 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 reduction of the numbers of circulating erythroid progenitors, which may persist several months after the last chemotherapy course.19 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.20

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 concentration 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 patients (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.5,21,22 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 statistically 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.23,24 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/d, 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.24

| Table 6. Number of Patients With SAE Leading to Death in Relation to Treatment Group |
|----------------------------------------|-----------------|-----------------|-----------------|
| Type of Event                          | Dose Titration  | Fixed Dose      | Controls        |
|                                       | (n = 48)        | (n = 47)        | (n = 49)        |
| Heart failure                          | 4               | 1               | 2               |
| Hemorrhage                             | —               | 3               | 2               |
| Renal failure                          | 1               | 1               | 2               |
| Infections/sepsisemia                  | 4               | 5               | 2               |
| Tumor progression                      | 1               | 4               | 2               |
| Others                                 | 1               | 1               | 4               |

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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 therapy. 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. 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 chemotherapy and in patients with CLL.

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, as well as in patients with cancer. 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, 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. Gerhartz; Aachen, Germany, Praxis für Hämatologie/Onkologie, U. Essers; 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. Käser; Frankfurt, Germany, the Department of Hematology, Johann-Wolfgang-Goethe-Universität, D. Hoelzer; Erfangen, Germany, the Department of Hematology and Oncology, Med. Klinik III, M. Granatzki; Gothenburg, Sweden, the Department of Oncology, Sahlgrenska Hospital, K. Lanöys; Gutersloh, Germany, the Department of Medicine, Städtisches Krankenhaus, F. Bergman; Stockholm, Sweden, the Department of Oncology, Karolinska Hospital, H. Mellstedt, A. Østerborg; 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. Ö. Landeskrankenhaus, G. Jäger, H.-L. Seewann; Pessac, France, the Department of Hematology, Hôpital du Haut Lévêque, A. Broustet; Mannheim, Germany, the Department of Oncology, Klinikum Mannheim, W. Queisser; Huddinge, Sweden, the Department of Medicine, Huddinge University Hospital, G. Julliusson, M. Ohrling; 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 Hematology and Oncology, Krankenanstalten Gilde, F.K. Lindemann; Vienna, Austria, the Department of Medicine, Krankenhaus der Stadt Wien, M. Pecherstorfer; Naples, Italy, the Division of Hematology, Ospedale Cardarelli, R. Cimino; Upsalla, Sweden, the Department of Medicine, Academic Hospital, G. Birgégård; 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 Hematology, 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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