Once-weekly dosing of recombinant human erythropoietin alpha in patients with myelodysplastic syndromes unresponsive to conventional dosing

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Background: Once-weekly dosing of recombinant human erythropoietin (rhEPO) in patients with myelodysplastic syndromes (MDS) has not been investigated thoroughly. We performed a clinical trial to evaluate the effects of this new dosing regimen in patients with MDS who were unresponsive to the conventional three-times-weekly schedule.

Patients and methods: Forty-eight patients with low- or intermediate-risk MDS were enrolled in a 12-week study. rhEPO alpha (rhEPOα) was administered once-weekly by subcutaneous injection with a starting dose of 40 000 U fixed dose. The drug dosage was increased to 60 000 U fixed dose if after 6 weeks there was no or suboptimal erythroid response.

Results: Clinically significant responses were seen in 13 (27%) patients, with 11 improving their response after dose escalation of rhEPOα. Only one patient (case 23) maintains a response after a follow-up period of 14 months. All other patients had responses lasting between 10 and 43 weeks, with a median time to relapse of 20 weeks. Treatment was well tolerated, with no relevant adverse events. Response to therapy was associated with significantly higher concentrations of circulating erythroid blast-forming units and a decrease of the bone marrow fraction of apoptic CD34+ cells.

Conclusions: Once-weekly rhEPOα therapy results in an improvement of erythropoiesis in a subset of MDS patients who are unresponsive to conventional dosing, and may act by inhibiting apoptosis of erythroid precursors. These results warrant further investigation of this dosing regimen either alone or in combination with other agents.

Key words: apoptosis, erythropoietin, myelodysplastic syndrome, schedule

Introduction

Results of several trials have demonstrated clearly that recombinant human erythropoietin (rhEPO) can increase hemoglobin concentration and reduce red blood cell transfusion requirements in selected patients with low-risk myelodysplastic syndromes (MDS), particularly those with a diagnosis of refractory anemia (RA) and a basal serum EPO level of <200 U/l [1]. Although rhEPO has been used in a variety of doses and schedules, in most recent series the drug was given subcutaneously daily or three-times a week with a starting dose of 150 U/kg, or 10 000 U fixed dose. The dose was usually doubled if no response was observed after the first 6 weeks of treatment. This ‘conventional’ schedule of rhEPO, adopted by current clinical practice guidelines [2–4], has been challenged recently. Pharmacodynamic investigations performed in healthy subjects [5], as well as clinical trials in both solid and hematological tumors [6, 7], suggest comparable efficacy between once-weekly and three-times-weekly dosing. The effects of once-weekly rhEPO therapy are being explored in MDS. Recently, once-weekly rhEPO alpha (rhEPOα) was used in patients with previously untreated MDS either as initial therapy [8] or as maintenance treatment of initial responders [9], suggesting that it may be at least as active as rhEPOα given more frequently. However, whether high peak concentrations of rhEPOα maintained for a short time are more effective than low concentrations maintained for a long period remains undetermined, and clinical data about the efficacy of a schedule switch are lacking. On these grounds, we designed this study to test the effects of once-weekly rhEPOα doses in MDS patients who were refractory to rhEPOα given with the conventional schedule.

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Materials and methods

Patients

Forty-eight patients with low- and intermediate-risk MDS according to the International Prognostic Scoring System [10] were included in this study after they had signed an institutional review board-approved informed consent. Patients’ clinical and laboratory characteristics at study entry are reported in Table 1. All patients had not responded to a prior treatment with three-times-weekly rhEPOx given subcutaneously at 10 000 U fixed dose for 6 weeks, and 20 000 U fixed dose given for a further 6 weeks. At least 12 weeks had passed between the last administration of three-times-weekly rhEPOx and the first administration of once-weekly rhEPOx. Apart from rhEPOx, patients had received no other pharmacological treatment for MDS.

Eligibility criteria were as follows: primary MDS with <10% blasts on bone marrow examination; Eastern Cooperative Oncology Group performance status of 2 [11]; hemoglobin levels <10 g/dl; normal renal and hepatic function; and normal iron, vitamin B12 and folate levels. Exclusion criteria included clinically significant heart and central nervous system disease, uncontrolled hypertension, florid infections, or other malignancies. On study entry, patients gave signed, institutional review board-approved informed consent.

Treatment plan

Therapy consisted of a 12-week schedule of rhEPOx (epoetin alfa, Eprex®; Janssen-Cilag, Milan, Italy) administered subcutaneously once a week. The rhEPOx dose was initiated at 40 000 U fixed dose and was increased to 60 000 U fixed dose if after 6 weeks there was no or suboptimal erythroid response. Further treatment was given to patients with a continued response.

Response criteria

Responses were categorized according to the criteria developed by Cheson et al. [12]. In particular, a major response (MaR) for the erythroid lineage was considered to be a rise in untransfused hemoglobin concentrations of at least 2 g/dl or a 100% decrease in red blood cell (RBC) transfusion requirements during the treatment period. A minor response (MiR) was defined as an increase in untransfused hemoglobin values of 1–2 g/dl or a ≥50% decrease in RBC transfusion requirements. No response was defined as a response less than a MiR.

Study parameters and monitoring of patients

Patient evaluation before entry included complete history and physical examination. All patients underwent chest roentgenography and electrocardiography. Baseline laboratory evaluation included a complete blood count with reticulocytes, serum EPO, serum ferritin, vitamin B12 and folate levels, routine serum chemistry, coagulation tests and urinalysis. Vital signs and complete blood cell counts were monitored once a week. Serum EPO levels were determined using a commercially available enzyme-linked immunoassay (Quantikine IVD Erythropoietin; R&D Systems, Minneapolis, MN, USA). Bone marrow aspirates and biopsy specimens were taken at enrollment and at the end of the study (aspirates), or whenever clinically required. Karyotyping was carried out with standard techniques at study entry and, in responders, at the end of treatment. Erythroid progenitor cell assay was performed at baseline and at 12 weeks.

Measurement of apoptosis

Apoptosis was measured by flow cytometry with a FACSscan instrument (Becton Dickinson, Mountain View, CA, USA). Mononuclear cell fractions of bone marrow samples were separated after Ficoll—Hypaque gradient centrifugation and washed twice with phosphate-buffered saline. Cells (1 x 10^6) were then incubated with phycoerythrin-conjugated anti-CD34 mAb (anti-HPCA-2, IgG1; Becton Dickinson) for 10 min at room temperature in the dark and were washed twice with phosphate-buffered saline. Pelleted cells were resuspended in 100 μl binding buffer (10 mM HEPESS/NaOH, pH 7.4, 140 mM NaCl, 2.5 mM CaCl2; Bender Medsystems, Boehringer Ingelheim, Ridgefield, CT, USA), and were
### Table 2. Changes in hematological and clinical parameters following once-weekly rhEPOα therapy in responders

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>FAB/WHO subtype</th>
<th>MDS duration (months)</th>
<th>IPSS risk group</th>
<th>Baseline serum EPO (mIU/ml)</th>
<th>RBC transfusions</th>
<th>Hb (g/dl)ᵇ</th>
<th>Erythroid response</th>
<th>Time to response (weeks)ᶜ</th>
<th>Response duration (weeks)ᵈ</th>
<th>BFU-E/2×10⁵ cells Before</th>
<th>BFU-E/2×10⁵ cells After</th>
<th>CD34+ cell apoptosis (%) (×10⁹/l)</th>
<th>Reticulocytes (×10⁹/l) Before</th>
<th>Reticulocytes (×10⁹/l) After</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>81</td>
<td>F</td>
<td>RA</td>
<td>25</td>
<td>Int-1</td>
<td>165</td>
<td>2</td>
<td>1</td>
<td>8.2</td>
<td>8.3</td>
<td>9.0</td>
<td>MiR 10</td>
<td>MiR 8</td>
<td>36</td>
<td>7</td>
<td>19</td>
</tr>
<tr>
<td>8</td>
<td>57</td>
<td>M</td>
<td>RA</td>
<td>16</td>
<td>Low</td>
<td>376</td>
<td>2</td>
<td>1</td>
<td>7.7</td>
<td>8.2</td>
<td>9.1</td>
<td>MiR 8</td>
<td>MiR 36</td>
<td>43</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>12</td>
<td>64</td>
<td>M</td>
<td>RA</td>
<td>17</td>
<td>Low</td>
<td>591</td>
<td>3</td>
<td>1</td>
<td>6.8</td>
<td>7.1</td>
<td>7.6</td>
<td>MiR 9</td>
<td>MiR 10</td>
<td>11</td>
<td>23</td>
<td>61.5</td>
</tr>
<tr>
<td>16</td>
<td>66</td>
<td>M</td>
<td>RA</td>
<td>15</td>
<td>Low</td>
<td>375</td>
<td>2</td>
<td>0</td>
<td>7.8</td>
<td>9.0</td>
<td>9.5</td>
<td>MaR 5</td>
<td>MaR 43</td>
<td>1</td>
<td>16</td>
<td>69.2</td>
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<tr>
<td>19</td>
<td>77</td>
<td>M</td>
<td>RA</td>
<td>12</td>
<td>Low</td>
<td>483</td>
<td>3</td>
<td>1</td>
<td>7.3</td>
<td>7.6</td>
<td>8.1</td>
<td>MaR 12</td>
<td>MaR 14</td>
<td>7</td>
<td>22</td>
<td>47.4</td>
</tr>
<tr>
<td>23</td>
<td>72</td>
<td>F</td>
<td>RA</td>
<td>12</td>
<td>Low</td>
<td>243</td>
<td>2</td>
<td>0</td>
<td>7.8</td>
<td>9.3</td>
<td>10.0</td>
<td>MaR 4</td>
<td>MaR 60+</td>
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<td>17</td>
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<tr>
<td>26</td>
<td>71</td>
<td>M</td>
<td>RA</td>
<td>14</td>
<td>Low</td>
<td>116</td>
<td>2</td>
<td>1</td>
<td>7.8</td>
<td>8.8</td>
<td>9.2</td>
<td>MiR 5</td>
<td>MiR 27</td>
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<td>65.3</td>
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<tr>
<td>32</td>
<td>69</td>
<td>M</td>
<td>RA</td>
<td>34</td>
<td>Low</td>
<td>631</td>
<td>2</td>
<td>1</td>
<td>7.7</td>
<td>8.3</td>
<td>8.8</td>
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<tr>
<td>35</td>
<td>56</td>
<td>F</td>
<td>RA</td>
<td>21</td>
<td>Low</td>
<td>865</td>
<td>3</td>
<td>1</td>
<td>8.0</td>
<td>8.6</td>
<td>8.8</td>
<td>MiR 12</td>
<td>MiR 13</td>
<td>3</td>
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</tr>
<tr>
<td>37</td>
<td>73</td>
<td>M</td>
<td>RAEB</td>
<td>28</td>
<td>Int-1</td>
<td>581</td>
<td>3</td>
<td>0</td>
<td>7.6</td>
<td>8.4</td>
<td>8.9</td>
<td>MaR 6</td>
<td>MaR 16</td>
<td>8</td>
<td>21</td>
<td>33.7</td>
</tr>
<tr>
<td>40</td>
<td>68</td>
<td>M</td>
<td>RA</td>
<td>30</td>
<td>Low</td>
<td>495</td>
<td>3</td>
<td>1</td>
<td>7.0</td>
<td>7.8</td>
<td>8.4</td>
<td>MiR 7</td>
<td>MiR 22</td>
<td>6</td>
<td>13</td>
<td>60.1</td>
</tr>
<tr>
<td>43</td>
<td>70</td>
<td>F</td>
<td>RA</td>
<td>20</td>
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<td>0</td>
<td>8.3</td>
<td>8.8</td>
<td>9.5</td>
<td>MaR 6</td>
<td>MaR 25</td>
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<tr>
<td>47</td>
<td>56</td>
<td>F</td>
<td>RA</td>
<td>15</td>
<td>Int-1</td>
<td>395</td>
<td>2</td>
<td>1</td>
<td>7.9</td>
<td>8.3</td>
<td>8.4</td>
<td>MiR 12</td>
<td>MiR 14</td>
<td>5</td>
<td>9</td>
<td>60.6</td>
</tr>
</tbody>
</table>

ᵃMedian packed RBC transfusions per month for 3 months before the study.
ᵇThe blood counts before and after treatment were calculated averaging the results of three counts taken over a 2-week period.
ᶜTime to achieve at least an MiR.
ᵈIncluding both MiR and MaR.

rhEPOα, recombinant human erythropoietin alpha; FAB/WHO, ?; MDS, myelodysplastic syndromes; IPSS, International Prognostic Scoring System; RBC, red blood cell; Hb, hemoglobin; BFU-E, erythroid blast-forming units; F, female; M, male; RA, refractory anemia; RAEB, RA with excess blasts; Int-1, intermediate-1; MiR, minor response; MaR, major response.
incubated with 2 ml fluorescein isothiocyanate-conjugated annexin V (Bender Medsystems; Boehringer Ingelheim) for 10 min at room temperature in the dark. Afterwards, cells were resuspended in 400 μl binding buffer before flow cytometric analysis. Analysis was based on gating of subpopulations of CD34+ cells by forward scatter versus side scatter and by side scatter versus fluorescence-2. Negative controls included peripheral blood mononuclear cells incubated with neither CD34-PE mAb nor annexin V-FITC, and cells incubated with CD34-PE mAb only. Bone marrow from 10 healthy donors was used as reference.

**Statistical analysis**

The Mann–Whitney U-test was used to compare continuous variables between responders and non-responders. The Wilcoxon matched-pairs test was used to compare repeated measurements in the same patients. Fisher’s exact test was used to evaluate the relationship between two dichotomous variables. Correlations of variables with other variables were calculated by Spearman rank correlation coefficient. \( P < 0.05 \) was designated as statistically significant; all \( P \) values were two-tailed.

**Results**

**Response to treatment**

All patients completed the 12-week study and were evaluated for toxicity and response. During the study period no patient suffered from infections, underwent general anesthesia or experienced other conditions that might affect the response to rhEPO treatment. Thirteen patients achieved a response after week 12 of treatment, for an overall response rate of 27% (95% confidence interval 0.14–0.40). Changes in blood cell counts, transfusion requirements and laboratory parameters before and after treatment in responders are reported in Table 2.

The four patients who attained an MaR (patients 16, 23, 37 and 43) exhibited a suboptimal rise of hemoglobin levels at the dose of 40 000 U and required a dose escalation. Two of the nine patients with an MiR (patients 26 and 40) had signs of erythroid improvement after the first 6 weeks of treatment, but did not benefit from the higher rhEPO dose; the other seven patients showed a response only after being challenged with rhEPO at 60 000 U. Five patients (4, 12, 19, 40 and 47) exhibited a response that was based solely on a decrease in transfusion requirements. The hemoglobin levels at which their transfusions were ordered prior to and after treatment was initiated were, respectively: patient 4, 7.9 and 8.4 g/dl; patient 12, 6.8 and 7.3 g/dl; patient 19, 7.0 and 7.7 g/dl; patient 40, 7.2 and 7.6 g/dl; and patient 47, 7.7 and 8.0 g/dl. No significant changes in neutrophil and platelet counts were observed. In responders, the increase in hemoglobin concentration was associated with a significant increase in reticulocyte counts. Mean \((±SD)\) reticulocyte count was 16 024 ± 6085/μl before treatment versus 27 789 ± 6294/μl at week 12 of treatment \((P = 0.0014)\).

Thus far, only one patient (case 23) maintains a response after a follow-up of 14 months. All other patients relapsed between 10 and 43 weeks from the achievement of response, with a median time to relapse of 20 weeks.

**Safety**

The treatment was well tolerated, with no serious adverse events. Only one patient (case 23) had a mild increase in arterial blood pressure after 6 weeks of treatment that was easily controlled by medical therapy. Five patients complained of pain with or without erythema at the site of rhEPO injections, although they did not interrupt rhEPO administration.

**Laboratory studies**

As shown in Figure 1, the number of circulating BFU-E in responders during week 12 of treatment consistently increased compared with baseline \((P = 0.0014)\). Analysis of karyotype at the end of the study (available in 10 patients) did not show significant changes. Pretreatment determination of the degree of apoptosis in hematopoietic progenitors by means of the annexin V method did not show significant differences between the French-American-British/World Health Organization (FAB/WHO) subgroups. In RA and RA with ringed sideroblasts (RARS), the median CD34+ cell apoptosis was 57.5% (range 37.8% to 83.5%), whereas in RA with excess blasts (RAEB) it was 48.1% (range 33.7% to 56.2%) \((P\) not significant). The control group had a median CD34+ cell apoptosis of 14.8% (range 5.5% to 27.9%), which was significantly different from that of MDS patients \((P < 0.001)\). At week 12 of treatment, CD34+ cell apoptosis was significantly decreased in responders (median 38.8%; range 21.7% to 51.2%) compared with non-responders (median 55.4%; range 40.5% to 77.2%) \((P < 0.001)\). Figure 2 reports the double-color analyses with antibodies against CD34 (phycoerythrin) and against annexin V (fluorescein isothiocyanate) in patient 35. Double-positive cells (upper right quadrant) dropped from 39.5% before treatment (Figure 2A) to 21.7% at week 12 of treatment (Figure 2B).

**Prognostic factors**

Table 3 shows the clinical and laboratory characteristics of the 13 patients who had erythroid responses (MaR+MiR) to once-weekly rhEPO treatment compared with those of
the 35 patients who did not respond. No variable was significantly different between the two groups of patients in univariate analysis. Similarly, no combination of these characteristics demonstrated a significant association with response. It should be noted, however, that no patient with RARS and only one patient with RAEB had a response to treatment.

Discussion

The results in this large series of patients with low- and intermediate-risk MDS indicate that, along with the dose, the schedule of administration may be relevant in determining response to rhEPOα. Early trials in patients with MDS employing rhEPOα intravenously failed to demonstrate significant advantages of very high doses, up to 100000 U, given twice weekly [14, 15]. However, pharmacokinetic studies have shown that the half-life of intravenously injected rhEPOα can be as short as 3 h in patients with MDS [16]. Thus, this route of administration is unlikely to result in high response rates. On the other hand, rhEPOα has been rarely used subcutaneously at doses in excess of 400 U/kg per single administration [17, 18].

When assessing our results, it is important to underline that because of the variability inherent with transfusion therapy, the rate of MiR may have been overestimated. In fact, a significant clinical benefit was restricted to the four complete responders who became transfusion-independent, only one of whom had an increase in hemoglobin >2 g/dl. Thus, using stringent criteria the clinical impact of once-weekly rhEPOα appears limited to no more than 10% of patients unresponsive to the conventional three-times-weekly schedule. Furthermore,

Table 3. Comparison of baseline clinical and laboratory characteristics of MDS patients responding and not responding to once-weekly rhEPOα treatment

<table>
<thead>
<tr>
<th></th>
<th>Responders (range)</th>
<th>Non-responders (range)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>69 (56–81)</td>
<td>71 (53–80)</td>
<td>0.434978a</td>
</tr>
<tr>
<td>Male/Female</td>
<td>8/5</td>
<td>18/17</td>
<td>0.74560b</td>
</tr>
<tr>
<td>MDS duration (months)</td>
<td>17 (12–34)</td>
<td>21 (10–37)</td>
<td>0.535670c</td>
</tr>
<tr>
<td>Serum EPO</td>
<td>483 (116–865)</td>
<td>458.5 (138–1142)</td>
<td>0.872353a</td>
</tr>
<tr>
<td>Prior RBC transfusion requirements (U/month)</td>
<td>2 (2–3)</td>
<td>3 (1–4)</td>
<td>0.696838a</td>
</tr>
<tr>
<td>Hb levels (g/dl)</td>
<td>7.8 (6.8–8.3)</td>
<td>8.1 (6.6–8.9)</td>
<td>0.126828a</td>
</tr>
<tr>
<td>Reticulocytes (×10⁹/l)</td>
<td>16.2 (7.0–29.0)</td>
<td>15.5 (6.6–27.3)</td>
<td>0.908826c</td>
</tr>
<tr>
<td>ANC (×10⁹/l)</td>
<td>2.4 (0.6–3.6)</td>
<td>2.1 (0.4–3.8)</td>
<td>0.370119a</td>
</tr>
<tr>
<td>Platelets (×10⁹/l)</td>
<td>107 (41–226)</td>
<td>119 (38–246)</td>
<td>0.462608a</td>
</tr>
<tr>
<td>Cytogenetics (normal/abnormal)</td>
<td>12/1</td>
<td>28/7</td>
<td>0.41842b</td>
</tr>
<tr>
<td>FAB/WHO subtype (RA/RARS-RAEB)</td>
<td>12/1</td>
<td>24/11</td>
<td>0.13884a</td>
</tr>
<tr>
<td>CD34+ cell apoptosis</td>
<td>60.1 (33.7–73.6)</td>
<td>55.2 (37.8–83.5)</td>
<td>0.878923a</td>
</tr>
</tbody>
</table>

aMann–Whitney U-test.
bFisher’s exact test.

MDS, myelodysplastic syndromes; rhEPOα, recombinant human erythropoietin alpha; RBC, red blood cell; Hb, hemoglobin; ANC, absolute neutrophil count; French-American-British/World Health Organization (FAB/WHO); RA, refractory anemia; RARS, RA with ringed sideroblasts; RAEB, RA with excess blasts.
our findings may not be applicable to all MDS patients. The results of other trials indicate that in some patients more frequent administrations could be necessary to elicit the biological response to rhEPOα. For instance, in a double-blind, placebo-controlled study, 36.8% of patients with low-risk MDS who were randomized to receive rhEPOα subcutaneously at the daily dose of 150 U/kg responded to treatment, but the response rate dropped to 16.2% in a following open phase, during which rhEPOα was given using a modified schedule of 150–300 U/kg on alternate days [19]. In addition, Terpos et al. [20] have reported recently that prolonged administration of rhEPOα subcutaneously at a dose of 150 U/kg three-times a week may significantly increase the erythropoietic response rate in low-risk MDS patients. In this regard, our study was designed to avoid possible delayed effects of previous rhEPOα therapies. In fact, at least 12 weeks had passed between the last administration of three-times-weekly rhEPOα and the first administration of once-weekly rhEPOα.

As expected, low-risk patients showed a tendency towards a higher response rate. This is in line with previously reported trials, and may be explained by the fact that these patients have a higher percentage of apoptotic cells in the bone marrow that may be sensitive to the antiapoptotic effects of erythropoietin. Endogenous erythropoietin levels were not predictive of response, but it should be noted that most of the patients in this series had baseline EPO levels in excess of 200 mIU/ml, which are known to predict an unfavorable response to conventional three-times-weekly treatment [1].

The heterogeneity of erythroid precursors of MDS to the anti-apoptotic effects of rhEPO might be the key to the different response patterns observed with different dosing regimens. Previous studies have shown that maximal growth of erythroid colonies in MDS require extremely variable rhEPO concentrations, five- to 20-fold higher than normal controls, with BFU-E sensitivity being a critical factor in determining response to rhEPO [21]. As a consequence, the optimal dosing regimen of rhEPO probably needs to be defined according to the individual patient.

The results of laboratory investigations performed in this study are in line with previous reports, and show that CD34+ cell apoptosis in MDS is significantly higher than in normal controls [22, 23]. Furthermore, we confirm previously reported data indicating that response to treatment is associated with higher concentrations of BFU-E in the peripheral blood and a remarkable decrease of the bone marrow fraction of apoptotic CD34+ cells [23]. Whether these findings represent a stimulation of residual polyclonal hematopoiesis or an actual reduction in the degree of ineffective hematopoiesis remains undetermined, although it is likely that the mechanisms of the positive effects of rhEPOα therapy involve inhibition of apoptosis of the dysplastic clone [24].

In conclusion, a single, weekly, subcutaneous administration of rhEPOα at the dose of 40,000 or 60,000 U results in an improvement of erythropoiesis in a subset of MDS patients who are refractory to conventional dosing regimens. The mechanisms of response of once-weekly rhEPOα require further investigation, and findings could lead to better understanding of the pathophysiology of MDS.

Acknowledgements

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References