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Erythropoietin plus granulocyte colony-stimulating factor in the treatment of myelodysplastic syndromes. Identification of a subgroup of responders

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ABSTRACT

Background and Objectives. **Anemia leading to transfusion is probably the most important problem in patients with myelodysplastic syndromes (MDS). Human recombinant erythropoietin (rHuEpo) and granulocyte colony-stimulating factor (G-CSF) have been used to treat patients with anemia of MDS, but fewer than 50% respond. The aim of this work was to evaluate the benefit of rHuEpo ± G-CSF treatment and to isolate the response predictive variables in a group of selected patients with MDS.**

Design and Methods. **A non-randomized multicenter trial was carried out in 32 patients with MDS. The inclusion criteria were age ≥ 18 years, refractory anemia (RA) or refractory anemia with ringed sideroblasts, Hb ≤ 100 g/L or receiving transfusions and serum erythropoietin ≤ 250 U/L. These patients were treated with subcutaneous rHuEpo (300 U/kg) three times a week for 8 weeks. In the case of partial response (PR) or no response (NR) subcutaneosuly administered G-CSF (1 µg/kg) three times a week was added to the rHuEpo for 8 more weeks. If the patient achieved complete response (CR) or PR in the second phase, he was included in a follow-up phase of 24 weeks in which the dose of growth factors was tapered down. Several variables, including the score published by the Scandinavian-American group, were used as possible predictive variables.**

Results. **An erythroid response was observed in 16 patients (50%); in 12 it was a CR and in 4 it was a PR. During the period of rHuEpo administration, 7 CR and 4 PR (34.4%) were documented. Of the 14 patients in whom G-CSF was added to rHuEpo, 7 (50%) responded (3 CR and 4 PR). No major side-effects associated with growth factors were observed. The multivariate analysis showed that of the different variables evaluated only the Scandinavian-American response score was significant with a relative probability of response of 11.8 (95% confident intervals: 2.5-53) when this score was > +1 (77% of cases responded). In contrast, when this score was ≤ 1 only 15 % of the cases responded.**

Interpretation and Conclusions. **Use of the Scandinavian-American response score is to be recommended in a patient-oriented approach to treating MDS cases with the Epo and G-CSF. Treatment with rHuEpo and G-CSF is safe, its main drawback being its cost. However, a long-term study evaluating the regimen's cost-benefit ratio is warranted.**

Key words: myelodysplastic syndromes, erythropoietin. granulocyte-colony stimulating factor (G-CSF)

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Myelodysplastic syndromes (MDS) are clonal hematopoietic disorders in which incomplete maturation of hemopoietic precursors in one or more lineages leads to cytopenias and qualitative abnormalities. The French-American-British (FAB) classification is used to group the different types of MDS and this classification has been shown to have a prognostic value.[1,2]

However, the range of clinical expression is broad. Patients with refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS) have been considered to form a group with a good prognosis, although, in this group, cytopenias are a major problem. Recently, the International Prognostic Score System (IPSS) provided a patient-oriented system for evaluating the survival of MDS patients.[3]

Approximately two-thirds of MDS patients have anemia at diagnosis, and nearly all develop anemia during the evolution of the disease, and often become transfusion-dependent. In this regard, if anemia is severe and symptomatic, periodic transfusion of red cells is required.[1]

Anemia treatment with recombinant human erythropoietin (rHuEpo) is useful in 20-25% of MDS patients,[4-6] probably because there is an inadequate production of Epo in these patients.[7,8] Some studies have confirmed that the addition of granulocyte colony-stimulating factor (G-CSF) acts synergistic with rHuEpo in MDS patients and this addition increases the percentage of response to 40-50%.[6,8,9]

Recently, a meta-analysis of 205 patients with

MDS from 17 groups, demonstrated a response to rHuEpo in 16% of cases with MDS. However, in cases with the lowest levels of serum Epo (sEpo) and with low or no transfusion requirements, a response was obtained in more than 50% of patients.[9] In these studies different doses were used, but the results were fairly similar. In general, a dose of rHuEpo ≥ 150 U/kg was administered three times a week.[9]

Several factors have been identified and could be used to predict a possible response, e.g. serum levels of Epo, number of transfusions, type of MDS, and platelet counts.[9,11] Some researchers have described a score to select patients with a high likelihood of response to rHuEpo and G-CSF.[12]

There were two aims of this multicenter study: to evaluate the possible benefit of treatment with rHuEpo ± G-CSF and to establish response predictive variables in a group of selected patients with MDS.

Design and Methods

From September 1995 to October 1997, a non-randomized multicenter phase IV trial in MDS patients was conducted by the *Spanish Erythropathology Group*. The protocol was approved by the ethical committee of each participating hospital and by the Spanish Ministry of Health.

Inclusion criteria

All patients had RA or RARS, were receiving red blood cell transfusions or had a Hb ≤ 100 g/L, and serum erythropoietin ≤ 250 U/L. All patients were told of the aims and characteristics of the protocol (Table 1) and gave their informed consent to it. A committee made up of the three main investigators (RA, AB, VA) confirmed that each candidate met the established criteria. Thirty-three patients entered the study. However, one patient withdrew his consent before the treatment was started and was not included in the evaluations. Thus, 32 cases were evaluated. The characteristics of the patients are reported in Table 2, which shows that 66% of them were receiving transfusions.

Design of the study

The study was divided into three phases (Table 3).

The pre-treatment phase lasted 3 months; in this period the transfusion requirements were recorded and the patients received vitamin B6 (300 mg/d) and folic acid (5 mg/d). The Hb level to be used as the pre-treatment control was that recorded the week before the treatment was started.

The treatment phase consisted of two parts: rHuEpo (Erantin, Roche), was administered subcutaneously at a dose of 300 U/kg three times a week for 8 weeks. If the patient obtained a complete response (CR), he was included in a follow-up phase of 24 weeks in which the rHuEpo was tapered off. Hematologic tests were carried out every week; biochemical monitoring was performed every two weeks and iron metabolism was evaluated every four weeks. If transferrin saturation decreased below 20%, the patient was given 100 mg/d of oral iron sulphate. In the case of partial response (PR) or no response (NR) subcutaneously administered G-CSF (Filgastrim, Roche) 1 µg/kg 3 times a week was added to the rHuEpo for 8 more weeks.

The follow-up phase was only carried out in patients who achieved a CR or PR and lasted until week 24 (Table 3). This phase was conducted with two aims: 1) to taper down the dose in those patients who had achieved a CR. The dose of both growth factors was tapered down beginning with G-CSF every two weeks after a hematologic test; 2) to obtain a CR in those patients who had only reached a PR. In this situation, the same dose was continued until CR was achieved.

A post-treatment check-up was carried out three months after the conclusion of the follow-up study.

Table 1. Inclusion and response criteria.

Inclusion criteria
- age ≥ 18 years
- diagnosis: RA or RARS
- Hb ≤ 100 g/L or transfusions
- sEpo ≤ 250 U/L

Response criteria
- complete response (CR):
  - *no more transfusions*
  - *increase in Hb ≥ 20 g/L*
- partial response (PR):
  - *decrease in transfusions ≥ 50%*
  - *increase in Hb 10-20 g/L*
- no response (NR)

RA: simple refractory anemia; RARS: refractory anemia with ringed sideroblasts.

Table 2. Characteristics of patients included in the study.

Number of patients	32
Male/female	22/10
Mean age, yrs. (range)	68 (41-89)
Type of MDS	
RA	9
RARS	23
Time of evolution in years, mean (interval)	4.1 (1-14)
Neutrophils ($\times 10^9$/L)	2.8±1.5
Neutropenia (<1.8$\times 10^9$/L)	8 (25%)
Platelets ($\times 10^9$/L)	300±224
Thrombocytopenia (<150$\times 10^9$/L)	5 (16%)
Hb (g/L)	83±10
Transfusions (units/month)	1.7±1.6
Patients receiving transfusions (%)	21 (66%)

Results expressed as mean ± standard deviation unless otherwise stated.

Table 3. Phases of the study.

Phase	*Period/treatment*
Pre-treatment	3 months → transfusions
Treatment	0-8 w → rHuEpo 300 u.i./kg/3 /sc 9-16 w* → rHuEpo + G-CSF 1 mg/kg/3/sc
Follow-up	8-24 w (CR) taper rHuEpo±G-CSF 16-24 w (PR) maintain doses

**NR or PR patients. CR, complete response, PR, partial response. NR no response.*

Response criteria

CR was considered to have occurred when Hb rose ≥ 20 g/L or transfusions were no longer needed. PR was considered to be present when Hb rose by 10 to 20 g/L or when transfusion requirements were reduced by 50% or more.

Statistical analysis

To assess the response predictive factors, a univariate survival analysis was carried out (Kaplan-Meier analysis using the Log-Rank test). Next, the most significant variables (p<0.1) were included in a multivariate survival analysis (Cox's proportional risk analysis, using a forward procedure).

Sex, type of MDS, time from diagnosis, number of transfusions per month, level of sEpo, and counts of leukocytes, neutrophils and platelets were used as possible predictive variables.

During this study Hellström-Lindberg *et al*.[12] published a score based on sEpo and number of transfusions. This Scandinavian-American response score was included in our work. In brief, the score is as follows: sEpo < 100 U/L = +2, sEpo 100-500= +1, sEpo >500= –3. Transfusions, <2 units/month= +2, ≥ 2 units/months = –2. The scores are used to predict response. Patients with a score < -1 have a 7% rate of response, those with a score –1 to +1 have a 23% rate and those with a score > +1 have a 74%% rate.[7] All the patients in our study had a score higher than –1.

Results

An erythroid response was observed in 16 cases (50%); the response was complete in 12 and partial in 4. Median time of response was 8 weeks (95% confidence intervals (CI): 6-10 weeks) (Table 4).

Role of rHuEpo

During the first 8-week period, 7 CR and 4 PR (34.4%) were recorded. Of these 11 patients, 2 patients withdrew (1 in CR because of pneumonia and 1 in PR because of withdrawal of consent).

The second phase of treatment was not started in 6 non-responders because consent was withdrawn. Recombinant human Epo was continued alone for the second phase (8 more weeks) in two non-responders. Both these patients continued to have no response (Table 4).

Table 4. Response to the treatment and follow-up phase.

	8 w rHuEpo alone		*Follow-up study (16-24 w)*
CR	7 cases		2 not completed (withdrawal 16 w) 5 completed 2 in CR week 24. 3 loss of response (14,16 and 21 w)
	8 w rHuEpo alone	*8-16 w rHuEpo+ G-CSF*	*Follow-up study (16-24 w)*
PR	4 cases	2 CR 1 loss of response 1 not completed	2 not completed (withdrawal 16 w).
NR	21 cases	6 not completed 1 CR 4 PR 10 no response	1 in CR loss response in 16 w. 4 in PR, 2 CR (20 and 24 w). 2 not completed (withdrawal 16, 19 w).

CR: complete response; PR: partial response; NR: no response.

Role of G-CSF

G-CSF was added to rHuEpo in 14 cases (3 PR and 11 NR). An erythroid response was demonstrated in 7 cases (50%). An increase in leukocytes and neutrophils was observed in 13 out of 14 cases (92.8%). Only in one case did blast cells appear in peripheral blood during treatment.

Complete response was achieved in 2 out of 3 PR cases, the third case lost the PR after 5 weeks of G-CSF treatment during pneumonia.

A response was observed in 5 (1 CR and 4 PR) of 11 previous non-responders (Table 4).

Side-effects

No major side-effects related to growth factors were observed. One case showed a pseudogripal syndrome which was controlled by paracetamol.

One patient with RA and NR to rHuEpo and G- CSF evolved into acute leukemia two weeks after discontinuing the treatment. Another patient with RA who did not respond to treatment with both growth factors did respond to corticoid treatment.

Compliance to treatment

Thirty-two out of 33 cases participated in the first 8-week period of treatment (rHuEpo). However, during the second phase (rHuEpo+ G-CSF) and the follow-up period some patients, especially those without response, withdrew their consent (Table 4).

Predictive variables

Table 5 shows the most significant variables. The Scandinavian-American response score,[7] leukocyte counts and transfusion requirements were significant (p<0.05). However, in the multivariate analysis only

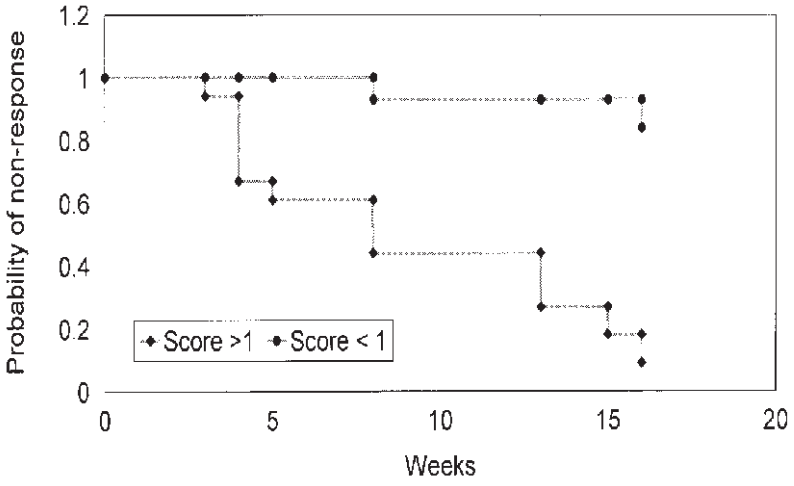

Figure 1. Probability of response of MDS to rHuEpo ± G-CSF.

the Scandinavian-American response score was significant. When the score was > +1, a relative risk of response of 11.8 (CI: 2.5-53) was calculated (14 of 18 cases responded, 77%), but if the score was ≤ 1 only 15 % responded (Figure 1). Platelets and the type of MDS were not significant.

Follow-up study (Tables 5, 6 and 7)

Cases achieving CR

After rHuEpo treatment. One patient withdrew his consent in week 16 in CR and the follow-up phase could not be completed. Only 2 out of 6 cases in CR with rHuEpo alone were in CR at the end of the follow-up period (75 U/kg once per week and 100 U/kg once per week; in this case oral iron was added). Three patients lost the response in weeks 14, 16 and 21 of the follow-up study (in one case during pneumonia).

Cases with rHuEpo plus G-CSF treatment. The 2 patients in partial remission with rHuEpo and CR upon addition of G-CSF withdrew in week 16. One case with no response to Epo alone achieved CR after G-CSF was added. This patient dropped out of the protocol in week 16.

Cases achieving PR

Of the 4 cases with a partial remission with rHuEpo + G-CSF, 2 achieved CR in weeks 20 and 24. The other 2 patients dropped out of the study in weeks 15 and 19 while in partial remission.

A hematologic test performed 3 months after the follow-up study showed that all cases had returned to their clinical status before the protocol. The treatment was restarted outside the protocol with good effect in several patients who responded to growth factors.

The characteristics of responders and non-responders are given in Tables 6 and 7.

Discussion

In 1995 the Spanish Erythropathology Group initiated a study in a group of MDS patients selected in accordance with criteria that seemed to be characteristic of potential responders at the time.

The aim of this work was to establish more accurately the predictive criteria for identifying the responders. Secondary objectives were to evaluate the qual-

Table 5. Response to rHuEpo ± G-CSF depending on the possible predictive variables.

	Value	*Response patients (%)*	*Univariate (p value)*	*Multivariate (p value)*
Score	> 1	14/18 (78%)	0.0001	0.0016.
	≤ 1	2/14 (15%)		RR: 11.6 (I.C.2.5-53)
TRF/m	≤ 1	12/16 (75%)	0.0008	N.S
	>1	4/16 (25%)		
Leuk x10^9/L	>3.5	14/23 (61%)	0.03	N.S.
	≤3.5	2/9 (22%)		
Plt x10^9/L	>150	14/25 (56%)	0.2	N.S.
	≤150	2/7 (29%)		
MDS	RA	6/9 (76%)	0.2	N.S.
	RARS	10/23 (44%)		
Evol.	≤ 3	14/23 (61%)	0.1	N.S.
	> 3 y	2/9 (22%)		
Sex	Male	10/22 (46%)	0.1	N.S.
	Female	6/10 (60%)		

Score: the Scandinavian-American response score. TFR/m: transfusions per month. RR: response risk. N.S. not significant. Evol. Years of evolution. Leuk: leukocytes. Plt: Platelets.

Table 6. Characteristics of patients with MDS who responded to treatment.

Case	*Age/sex/diagnosis*	*TF*	*Hb pre g/L*	*Response*	*Follow-up*	*POSTT*
1	71/F/RARS	Y	74	CR 8w (NTF)	LR 16w 150U/w pneumonia	TF
3	69/M/RA	Y	77	CR 8w (NTF)	PR 14s. 150 U/s	TF
9	70/M/RA	N	100	CR 5w (121*)	CR. 75 U/w	NTF (100)
10	58/M/RA	N	90	PR 13w (103)	WI 15 w.	TF
12	68/M/RARS	Y	86	PR 16 w (NTF 8w).	CR 20w (NTF,108)	TF
17	63/M/RARS	N	82	PR 13w (99)	WI 19w	TF
19	78/M/RARS	Y	98	PR 16 w (NTF 8w)	CR NTF (Hb 84-94)	TF
20	76/M/RARS	N	85	PR 4 w (98)	WI 8w	NTF (87)
25	77/M/RA	Y	89	CR 15 w (NTF,109)	WI 16w	TF
26	70/F/RA	N	80	PR 3w (91) CR 15w (102)	WI 16w	TF
27	69/M/RA	N	81	PR 4 w (95)	LR 14 w pneumonia	TF
30	75/F/RARS	N	97	PR 4 w (108).	LR 16 w	NTF (93)
31	67/F/RARS	Y	86	CR 4 w (NTF, 108)	WI 21s (150 U/w)	NTF (86)
32	72/H/ARSB	Y	75	CR 8 w (NTF)	16 w (105, NTF) WI 20 w (150 U/w)	TF
33	69/M/RARS	Y	75	CR 8 w (NTF)	CR 24 w (150 U/w) (Hb 105)	Not reported
34	67/F/RARS	N	96	CR 4 w (125)	WI 8 w. pneumonia	NTF (98)

*Hb pre, Hb pretreatment. TF: transfusions. NTF: no transfusions. *8 w (121). Hb level in week 8, etc., CR, PR, NR complete, partial and no response. LR: loss of response. WI, withdrawal POSTT: control 3 months after the treatment; in brackets Hb (g/L).*

Table 7. Characteristics of patients with MDS who did not respond to treatment.

Case	*Age/sex/diagnosis*	*TF*	*Hb pre g/L*	*Response*	*POSTT*
2	73/F. RARS	Y	77	NR 19 w	3 months later with prednisone Hb 157 g/L
4	69/M. RARS	Y	83	NR 21 w	TF
5	73/M. RARS	Y	61	NR 16 w	TF
6	78/M. RARS	Y	88	NR 16 w	TF
7	66/M. RARS	Y	90	NR 16 w Epo alone	Not reported
8	71/M. RARS	Y	75	NR 16 w Epo alone	Died 2 w after Epo was stopped. Evolution to acute leukemia
13	70/M. RARS	Y	101	WI 8 w	TF
14	78/M. RARS	NO	87	WI 8 w	TF
15	49/M. RA	Y	75	WI 12 w	TF
16	64/M. RARS	Y	89	WI 8 w	TF
18	84/F. RARS	NO	74	WI 8 w Increase in Hb 10 g/l	TF
21	71/M. RARS	SI	104	NR 21 w	TF
22	76/M. RA	Y	87	NR 16 w	TF
23	88/F. RARS	Y	94	NR 16 w	TF
28	60/M. RARS	Y	68	NR 16 w.	TF
29	84/M. RARS	NO	100	WI 8 w	Not reported

*Hb pre, Hb pretreatment. TF: transfusions. NTF: no transfusions. *8 w (121). Hb level in week 8, etc., CR, PR, NR: complete, partial and no response. LR: loss of response. WI, withdrawal POSTT: control 3 month after the treatment.*

ity of the response in a follow-up study, the side-effects and the capacity of patients to complete the treatment. It is worth remembering that most MDS patients are old and that following a protocol consisting of three or six subcutaneous injections a week is not easy.

During the course of our study an American-Scandinavian group[12] published some interesting research including a score that identified a group of good responders. Our study evaluated this Scandinavian-American response score *a posteriori* and other probable predictors. However, our group did not include patients with refractory anemia with excess blasts (RAEB) given that a possible role of G-CSF in this group had not been clarified at the start of the study and given the unavailability of the International Prognostic Scoring System (IPSS).[3] This patient-oriented system provides a tool for evaluating prognosis in individual MDS patients.

As for the treatment, we preferred to start with a high dose rather than escalate the dose to achieve a rapid response. This dose was tapered down during the follow-up study. As far as regards the therapeutic scheme, rHuEpo was given first and then, in the absence of response or if only a partial response occurred, G-CSF was added. If a response to rHu-Epo alone is obtained, the addition of G-CSF is unnecessary and the cost of this therapy is accordingly reduced. Should this treatment be considered for a subgroup of good responders, our methods

would probably be the easiest and cheapest way of administering the growth factors.

Although serum Epo is increased in most MDS, some individuals (approximately one third) show inappropriately low serum Epo levels.[7,8] These inadequately low levels are the basis of a response to exogenous rHuEpo treatment.[7] Several factors, such as inflammatory cytokines, and hyperviscosity,[13] have been considered to play roles in the reduction of the serum Epo concentration. Other studies have demonstrated that the cell receptor for Epo is intact in MDS, although a functional abnormality in the receptor or its metabolical pathway has not been ruled out.[14] G-CSF has been shown to have an effect on erythroid cells. This effect was demonstrated *in vitro* by cultures of bone marrow[15] and *in vivo* during progenitor harvesting with G-CSF alone.[16]

As expected, 50% of our cases responded to treatment and G-CSF demonstrated a synergistic effect with rHuEpo. Interestingly, minimal side-effects were recorded despite the high dose of rHuEpo used. These results are in accordance with the minimal side-effects found in other studies.[8,17]

In this protocol the main objective was to look at possible predictive criteria of response and to taper down the dose of growth factors. Surprisingly, when the Scandinavian-American response score[12] was applied to our patients, the results were reproduced despite differences in the treatment protocol and inclusion criteria. Our patients were in intermediate (score –1 to +1) and good (score > +1) prognostic subgroups according to the Scandinavian-American response score classification despite the patients in the Scandinavian-American trial having received Epo and G-CSF daily. In a multivariate analysis only this score remained significant.

These results are worth noting given that a group of experts emphasized the advantage of recognizing potential responders to growth factors in a patient-oriented approach to treatment.[18] It should, however, be pointed out that in our study no attempt was made to improve the response by increasing the number of doses, as suggested by an Italian multicenter study.[17]

Bearing in mind our results and those of the American-Scandinavian group,[12] the Scandinavian-American response score should be recommended for selecting candidates for growth factor treatment.

Patients with RAEB and good prognostic features[3] should be included among the candidates, despite a poor response in one study.[17] The conclusions and recommendations of the Italian multicenter group resemble those of this study. The Italian group added that an increase in serum transferrin receptor >50% at week 4 predicted a response, whereas a < 18% increase plus a serum erythropoietin level >200 U/L predicted a non-response.[17]

The follow-up study showed a number of interesting features. The main feature was that in many cases the response was lost during the tapering down of the growth factor dose and some patients dropped out of the study after the first or the second phase of treatment. One important reason for abandoning the study was that old patients found this treatment too difficult to follow.

Indeed, in the open phase of the Italian multicenter group double-blind study,[17] the rate of response dropped to 16%. This group suggested that the rate of administration (daily in the blind phase vs thrice weekly in the open phase) played a role. However, considering our study, and the results of the Scandinavian MDS group[19] and those of an American group,[20] the loss of response could lend support to the concept of some changes in cell biology.

A post-translational defect in the erythropoietin response pathway in MDS has recently been reported[21] and *in vitro* abnormalities in erythroid progenitors have been demonstrated, e.g., BFU-E needs higher concentrations of Epo to respond[22] and normal progenitors coexist with abnormal ones in MDS.[23]

Another interesting aspect of the follow-up study that in certain cases it was possible to complete the titration of the dose. Those that achieved and maintained complete response responded to rHuEpo when it was restarted as a compassionate treatment in their institutions.

The third most important finding in the follow-up study was that some patients with a partial response then went on to achieve a complete response, which indicates that a longer period of treatment was necessary. Other studies have reported similar findings.[17,19]

In conclusion, use of the American-Scandinavian group's scoring system[12] is to be recommended in a patient-oriented approach treatment of MDS since it can be predict a subgroup of patients with a greater than 70% of probability of response. Moreover, this score is based only on plasma/serum Epo concentrations and transfusion requirements. Treatment with rHuEpo and G-CSF is safe, but costly, which is its main drawback. These data warrant further studies to evaluate long-term response, quality of life and the economic and social implications of the treatment.

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AFR, BA and AV designed the study and co-ordinated the group. AFR and RM collected the clinical data and made the analysis. AFR and RM wrote the manuscript, which was reviewed by BA and AV. The recombinant human Epo and G-CSF were generous gifts from Roche.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

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