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Darbepoetin alpha for the treatment of anaemia in low-intermediate risk myelodysplastic syndromes

Pellegrino Musto,[1,*] Francesco Lanza,[2,*] Enrico Balleari,[3] Alberto Grossi,[4] Antonietta Falcone,[1] Grazia Sanpaolo,[1] Carlo Bodenizza,[1] Potito Rosario Scalzulli,[1] Antonio La Sala,[1] Diana Campioni,[2] Riccardo Ghio,[3] Nicola Cascavilla[1] and Angelo Michele Carella[5]

[1]Hematology and Stem Cell Transplantation Unit, IRCCS 'Casa Sollievo della Sofferenza' Hospital, S. Giovanni Rotondo, Italy, [2]Hematology Institute, University of Ferrara, Ferrara, Italy, [3]Department of Internal Medicine, Hematology–Oncology Section, University of Genova, Genova, Italy, [4]'Leonardo da Vinci' Institute, Firenze, Italy, and [5]Hematology, Unit, 'S. Martino' Hospital, Genova, Italy

**These authors contributed equally to this study.*

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Correspondence: Dr Pellegrino Musto, Hematology and Stem Cell Transplantation Unit, IRCCS 'Casa Sollievo della Sofferenza' Hospital, S. Giovanni Rotondo, Italy.
E-mail: p.musto@tin.it

Summary

Thirty-seven anaemic subjects with low-to-intermediate risk myelodysplastic syndrome (MDS) received the highly glycosylated, long-acting erythropoiesis-stimulating molecule darbepoetin-alpha (DPO) at the single, weekly dose of 150 μg s.c. for at least 12 weeks. Fifteen patients (40·5%) achieved an erythroid response (13 major and two minor improvements, respectively, according to International Working Group criteria). Such results are currently maintained after 7–22 months in 13 of the responders, one of whom required iron substitutive therapy during the treatment. One patient relapsed after 4 months. Another responder died after 5 months because of causes unrelated to the treatment. No relevant side-effects were recorded. At multivariate analysis, significant predictive factors of response were baseline serum levels of endogenous erythropoietin <100 IU/l, absent or limited transfusional needs, no excess of blasts and hypoplastic bone marrow. This study suggests that DPO, at the dose and schedule used, can be safely given in low-intermediate risk MDS and may be effective in a significant proportion of these patients.

Keywords: darbepoetin, erythropoietin, myelodysplastic syndromes, anaemia, transfusion.

Darbepoetin-alpha (DPO) is a novel erythropoiesis stimulating protein (NESP), which, compared with human alpha or beta recombinant erythropoietin (r-EPO), has augmented sialylated carbohydrated content producing a prolonged serum half-life and a possible increased *in vivo* biologic activity (Smith, 2002; Egrie *et al*, 2003). Recent data from clinical trials have indicated that DPO is effective in alleviating anaemia and improving the quality of life in neoplastic patients undergoing chemotherapy, with longer intervals between administration (Glaspy *et al*, 2003; Hedenus *et al*, 2003; Kotasek *et al*, 2003). Such dosing schedules may clearly ameliorate patients' convenience and compliance with respect to more frequent administrations usually required for r-EPO.

Many studies have evaluated the role of r-EPO in the treatment of anaemia in myelodysplastic syndromes (MDS) (reviewed by Hellstrom-Lindberg, 1995; Stein, 2003; Musto, 2004). However, no data are currently available regarding the efficacy of DPO as a single agent in this specific setting. Thus, we performed a pilot study to investigate the safety and the efficacy of DPO in low-intermediate risk MDS patients.

Patients and methods

Thirty-seven anaemic patients (23 of whom were transfusion-dependent) with low-to-intermediate risk MDS, according to the International Prognostic Scoring System (IPSS) (Greenberg *et al*, 1997), were entered into this study. Twenty-five patients were males and 12 were females. The average age was 63·1 years (range 39–84 years). Other main clinical and laboratory characteristics are reported in Table I. According to the World Health Organization (WHO) classification (Harris *et al*, 1999), there were 12 refractory cytopenias with trilineage dysplasia (RCMD), 11 refractory anaemias (RA), five RA with ringed sideroblasts (RARS), two of which also had multilineage dysplasia (RCMD-RS), seven RA with excess of

Table I. Clinical and laboratory characteristics of patients with myelodysplastic syndrome (MDS) treated with darbepoetin. Patients 1–15 were responders.

Patient	Age	Sex [male/female (M/F)]	WHO	Time from diagnosis (months)	EPO (IU/l)	IPSS	Transfusion/ month (pre/post)	Hb (g/dl) (pre/post)
1	69	M	5q- syndr.	1	91	Low	0/0	9·2/10·5^{m}
2	58	M	RA	4	27	Int-1	2/0	7·9/10·9^{M}
3	56	M	RA	4	44	Low	0/0	8·9/12·1^{M}
4	83	M	RA	6	76	Int-1	0/0	8·9/12·2^{M}
5	84	M	RA	72	N.A.	Int-1	1/0	8·7/13·1^{M}
6	63	F	RA*	13	34	Low	2/0	8·5/11·2^{M}
7	72	M	RA	26	65	Int-1	2/0	8·9/9·9^{M}
8	83	M	RARS	4	188	Low	0/0	9·4/12·7^{M}
9	70	M	RCMD-RS†	240	19	Low	7/0	8·8/11·3^{M}
10	77	F	RCMD†, ‡	76	282	Int-1	3/0	8·6/10,7^{M}
11	39	F	RCMD*, §	24	45	Int-1	0/0	9·6/13·7^{M}
12	75	F	RCMD*, ‡	40	27	Low	0/0	10·7/12·8^{M}
13	78	M	RCMD‡	48	N.A.	Int-1	4/1	8·0/9·6^{m}
14	71	M	RCMD*, ‡	20	50	Int-1	0/0	9·2/11·5^{M}
15	53	M	RAEB-1	2	90	Int-2	0/0	8·4/10·5^{M}
16	73	M	RA†	14	320	Low	4/4	6·9/7·1
17	79	F	RA§	2	66	Int-1	0/0	8·4/8·8
18	68	M	RA†	10	1320	Int-1	2/2	7·4/7·6
19	82	M	RA	20	95	Int-1	0/0	8·9/9·8
20	78	M	RA†	31	571	Low	4/4	6·7/6·7
21	66	F	RARS	2	98	Low	2/2	7·7/7·8
22	70	F	RARS†	21	82	Low	2/2	7·5/8·2
23	80	M	RCMD-RS	14	>200	Int-1	2/2	6·6/7·7
24	69	F	RCMD	6	1150	Low	0/0	8·9/7·9
25	79	F	RCMD	1	785	Low	0/0	9·4/10·1
26	84	M	RCMD	2	45	Low	4/4	6·2/7·0
27	42	M	RCMD‡	1	650	Int-1	4/4	6·8/6·4
28	41	M	RCMD‡	31	60	Low	1/1	8·2/7·8
29	76	M	RCMD	120	N.A.	Low	0/0	10·4/11·3
30	60	F	RCMD	43	185	Int-1	0/0	9·0/10·0
31	71	M	RAEB-1	2	>2000	Int-1	6/8	6·8/5·9
32	69	F	RAEB-1§	23	280	Low	4/4	8·0/7·9
33	60	M	RAEB-1†	34	>700	Int-1	8/8	6·4/6·1
34	78	M	RAEB-1†	50	140	Int-2	6/5	5·5/5·6
35	67	M	RAEB-1	51	210	Int-2	1/1	8·6/8·4
36	64	F	RAEB-1	42	120	Int-1	4/3	8·2/8·4
37	65	M	RAEB-2	23	190	Int-2	4/3	8·4/8·6

*DPO maintenance with dose reduction to 150 μg every 2–4 weeks.

†Previously treated with recombinant-erythropoietin.

‡Hypoplastic bone marrow.

§Abnormal creatinine.

^{m}Minor/^{M}major erythroid haematological improvement.

IPSS, international prognostic scoring system (low or intermediate-1/2); EPO, serum endogenous erythropoietin level at baseline; WHO, World Health Organization classification; N.A., not available; RA, refractory anaemia; RARS, RA with ringed sideroblasts; RAEB-1/2, RA with excess of blasts, type 1/2; RCMD, refractory cytopenia with multilineage dysplasia; RCMD-RS, RCMD with ringed sideroblasts.

blasts type 1 (RAEB-1), one RAEB-2 and one 5q- syndrome. Three patients had a moderate degree of renal failure (serum creatinine ranging from 141·4 to 203·3 μmol/l) and two had therapy-related MDS because of prior chemotherapy for non-haematologic tumours. Eight patients had previously received r-EPO at doses ranging from 30·000 up to 90·000 units/week, in single or multiple administrations, for not <12 weeks, without significant improvement of haemoglobin (Hb) levels or transfusional need (seven patients) or with loss of efficacy after an initial, prolonged response (one patient).

All patients received DPO (NESPO, Dompe'-Biotec or ARANESP; Amgen, Milan, Italy) at the dose of 150 μg s.c. once

a week (q.w.), for at least 12 weeks, without additional therapies. Such a dose corresponded approximately to a mean of 30·000 U of recombinant alpha or beta r-EPO per week (i.e. 150 U/kg t.i.w., considering that the median weight of our patients was 64·8 kg, range 54–85 kg), which is the currently recommended initial r-EPO dose for MDS patients (Rizzo *et al*, 2002). In most cases, the drug was kindly provided free of any charge by both Companies, on a compassionate-based therapeutic programme. The local Ethics Committee approved the study and all patients gave written informed consent.

Clinical examination, haematological parameters and other routine laboratory tests of liver, renal and coagulative function were monitored every 2 weeks. Bone marrow examination, including trephine biopsy, was performed at baseline and after 12 weeks of treatment. The possible development of iron deficiency under DPO therapy was evaluated by monitoring serum ferritin levels, saturation of circulating transferrin and automated count of hypochromic erythrocytes, as previously reported (Musto *et al*, 1994). International Working Group (IWG) criteria were applied to define response (Cheson *et al*, 2000). In particular, erythroid haematological improvements (HI-E) were classified as major (increase in haemoglobin levels >2 g/dl and/or termination of transfusions) or minor (increase in haemoglobin levels of 1–2 g/dl and/or reduction of transfusional support >50%).

Fisher's exact test was used to detect differences between responders and non-responders in terms of possible predictive factors. Modifications in Hb values before and after DPO treatment in different groups were analysed using non-parametric statistics (Wilcoxon's test). $P < 0{\cdot}05$ were considered significant. A multivariate Cox proportional hazard analysis was used to determine which baseline clinical and laboratory parameters were the best predictors for erythroid haematological response.

Results

All patients completed at minimum of 12 weeks of therapy. No significant changes in platelet and peripheral white blood cell counts were observed during treatment. Moreover, no relevant adverse events or significant side-effects were recorded throughout the study period. In particular, no case of pure red cell aplasia (PRCA), thrombosis, leukaemic evolution or uncontrolled hypertension was observed.

Twenty-two patients did not show any improvement in Hb levels or transfusional support and they withdrew from the study (Table I). No evidence of iron deficiency was demonstrated in these patients, according to monitoring parameters applied (serum ferritin, saturation of transferrin and hypochromicerythrocytes).

Fifteen patients (40·5%, 95% confidence intervals 24·7–57·9%) responded to DPO (13 major and two minor HI-E, see Table I). Two of them had previously received r-EPO (30 000/90 000 U/week, without any benefit (after 4 months of treatment, patient 10) or with loss of efficacy of the drug after a response that lasted 7 years (patient 9) respectively. One responder (patient 11) had a moderate degree of renal failure (serum creatinine 203·3 μmol/l). In this case, the diagnosis of MDS was based on trilineage marrow dysplasia, peripheral pancytopenia and abnormal karyotype (trisomy 8).

Thirteen responders maintained stable haemoglobin levels >9·5 g/dl after 7–22 months of treatment (nine without modifications of the initial DPO dose, four currently receiving DPO at the dose of 150 μg every 2–4 weeks) (Table I). One responder (patient 4) showed a drop in Hb levels after 8 weeks of DPO therapy because of the development of iron deficiency and required substitutive therapy to achieve a new response. One patient (patient 1) relapsed after 16 weeks. Another responder (patient 8) died after 5 months because of causes unrelated to DPO treatment. Median time to response was 9 weeks (range 2–11 weeks). The modifications in Hb levels after DPO treatment and the median Hb increase in different groups of MDS patients are reported in Fig 1, together with the detailed results of the statistical analysis.

Responders tended to have lower baseline serum levels of endogenous EPO, lower transfusion requirement and lower blast count in bone marrow than non-responders (Table II). Hypoplastic bone marrow (cellularity below 30%) also was more frequent among responders, but the difference was not statistically significant (Table II).

The multivariate analysis confirmed that predictive factors of major erythroid response were baseline serum levels of endogenous EPO < 100 IU/l ($P < 0{\cdot}001$), no excess of blast in bone marrow ($P < 0{\cdot}005$), no or low (≤2 red cell transfusions/month) transfusional requirement ($P < 0{\cdot}02$) and hypoplastic bone marrow ($P < 0{\cdot}007$). Age, sex, serum creatinine levels, iron status, MDS subtype according to the WHO classification, time from diagnosis and disease category according to IPSS had no significant impact in multivariate analysis (data not shown).

Discussion

Overall, approximately 20–25% of patients with MDS show improved haemoglobin levels when receiving r-EPO (Hellstrom-Lindberg, 1995; Stein, 2003; Musto, 2004). Usually, subjects with no or low transfusion need and reduced levels of endogenous EPO have the best probability of responding to this drug (Italian Cooperative Study Group for r-Hu-Epo in Myelodysplastic Syndromes, 1998; Hellstrom-Lindberg, 2003). Higher response rates to alpha or beta r-EPO (36–45%) have been reported in some studies optimizing the schedule of treatment, i.e. by administering the drug daily (Italian Cooperative Study Group for r-Hu-Epo in Myelodysplastic Syndromes, 1998) or for a prolonged time (Terpos *et al*, 2002), or by combining r-EPO with granulocyte colony-stimulating factor (Hellstrom-Lindberg *et al*, 2003). Our group has recently demonstrated that a r-EPO dose of 40·000 U given once a week is equally effective in MDS patients (Musto *et al*, 2003).

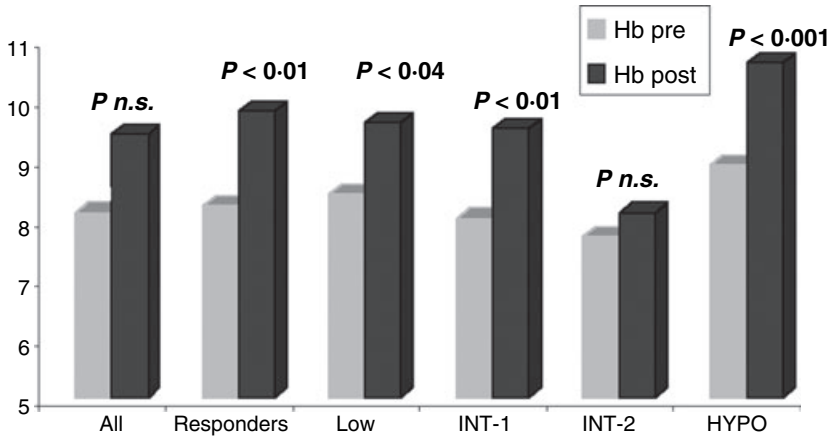

Fig 1. Median haemoglobin levels (Hb, g/dl), before and after therapy with darbepoetin, (DPO) in all myelodysplastic syndrome (MDS) treated patients (all patients), in all responders (responders), in different international prognostic scoring system (IPSS) groups; low, intermediate-1 (Int-1) and intermediate-2 (Int-2), and in patients with hypoplastic (hypo) bone marrow. NS, not significant.

Table II. Incidence of possible predictive factors of response to darbepoetin-alpha (DPO) in myelodysplastic syndrome (MDS).

	Responders	Non-responders	*P*-value
Serum EPO levels <100 IU/l	11/13 (84·6%)	6/21 (28·5%)	<0·003
Red blood cell transfusions ≤2/month	13/15 (86·6%)	11/22 (50%)	<0·03
Marrow blasts <5%	14/15 (93·3%)	7/22 (31·8%)	<0·0002
Hypoplastic bone marrow	4/15 (26·6%)	2/22 (9%)	NS

EPO, erythropoietin; NS, not significant.

The data of the present study are in line with these results. The DPO dose employed (150 μg/week) corresponded approximately to the weekly global dose of r-EPO (30·000 U, usually fractionated in 10·000 U t.i.w.) most widely utilized and currently recommended in MDS (Rizzo *et al*, 2002). Given an equal efficacy, such dosing scheme could clearly optimize patients' convenience compared with more frequent administrations of r-EPO, with the possibility to improve patients' compliance and, possibly, their quality of life (Cella *et al*, 2003). Whether higher doses may further ameliorate the response rate needs to be investigated. Our preliminary data, however, obtained from five cases, do not seem to support the efficacy of DPO at the dose of 300 μg q.w. in MDS patients who failed to respond in the present study (P. Musto, unpublished observations).

The characteristics of our responders (low levels of endogenous EPO, no or low transfusion need and absence of marrow blasts) were not different from those of MDS patients who usually benefit from r-EPO treatment (Italian Cooperative Study Group for r-Hu-Epo in Myelodysplastic Syndromes, 1998; Hellstrom-Lindberg, 2003). In addition, we observed that the majority of patients with hypoplastic bone marrow responded to the drug. This is an observation which needs to be specifically addressed in future studies.

As previously reported (Musto *et al*, 1994), one of our patients responsive to DPO developed iron deficiency during treatment and required substitutive therapy to maintain his response. This finding confirms that this event, although unusual in the specific setting of MDS treated with r-EPO (that often has an iron overload, rather than a deficiency), should be considered a possible cause of treatment failure also in these conditions, especially in untransfused subjects or in patients with a short history of disease.

In our series DPO did not induce severe side-effects. Recently, Steurer *et al* (2003) described a high percentage of thomboembolic events in a group of MDS patients treated with a combination of DPO and thalidomide. The thrombogenic activity of thalidomide is well known in patients treated for multiple myeloma (Zangari *et al*, 2003). Therefore, it could be expected to be increased by combining this drug with DPO. However, we did not observe any relevant case of thrombosis in a recent series of MDS patients treated with a combination of r-EPO and thalidomide (P. Musto, unpublished observations). Likewise, no case of PRCA caused by anti-EPO antibodies (Casadevall *et al*, 2002) occurred in the present study, although this finding has been recently reported in two MDS patients treated with alpha or beta r-EPO (Quint *et al*, 2004).

As is the case for r-EPO, the exact mechanism(s) of action of DPO in MDS is not clear. Among the various possibilities, the reduction of apoptosis, a process of programmed cell death that is clearly increased in stem cells and in more mature erythroid progenitors of low-risk MDS patients (Raza *et al*, 1995; Greenberg, 1998), is probably the most important effect. In addition, at least in some patients, the persistence of a normal, residual non-clonal erythropoiesis could have relevance in providing a still functional substrate for DPO (Rigolin *et al*, 2002). It is also unknown whether, besides the differences in their pharmacokinetic and pharmacodynamic properties, DPO and r-EPO may exert specific different biological activities in MDS patients. It is intriguing, in this setting, that in our study two patients with a long history of disease that were previously unresponsive or lacked any response to r-EPO, responded to DPO.

In conclusion, our results suggest that weekly administration of DPO is safe and may be effective in a proportion of MDS

patients, and is at least comparable with that obtained in recent studies employing alpha or beta r-EPO. Some responders may be 'maintained' receiving even less frequent administrations of DPO (once in every 2–4 weeks) and this could also represent a further significant advantage of DPO over 'conventional' r-EPO.

Larger clinical trials are required to confirm these data. In addition, as responders are mostly those patients who require no or few red blood cell transfusions, future studies should include careful quality of life and cost-effectiveness measures, in order to further delineate the role of DPO in the treatment of MDS patients and to justify its possible integration into practice guidelines (Alessandrino *et al*, 2002; Rizzo *et al*, 2002; Bowen *et al*, 2003), currently based on t.i.w. administration of r-EPO.

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