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A phase II intra-patient dose-escalation trial of weight-based darbepoetin alfa with or without granulocyte-colony stimulating factor in myelodysplastic syndromes

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Abstract

This Phase II study evaluated darbepoetin alfa (DA) in 24 patients with predominantly low or intermediate-1 risk myelodysplastic syndrome (MDS). Intra-patient dose escalation of DA was undertaken in three 6-week dose cohorts until a major erythroid response was achieved: 4.5 mcg/kg/week, 9 mcg/kg/week, and 9 mcg/kg/week plus granulocyte-colony stimulating factor (G-CSF) 2.5 mcg/kg twice weekly. Patients with refractory anemia with ringed sideroblasts (RARS) commenced DA at 9 mcg/kg/week. The weight-based dosing regimen translated into a median starting DA dose of 390 mcg/week. Erythroid responses were observed in 16/24 patients (67%; 12 major and 4 minor), with a median response duration of 11 months in major responders. Addition of G-CSF generated a major erythroid response in 7/15 patients (47%) who suboptimally responded to DA alone. DA was well tolerated, except for worsening of baseline mild hypertension and renal insufficiency in one patient with diabetes. IPSS score <0.5 and RBC transfusions <2 units/month increased the probability of an erythroid response. A minority of subjects (12%) developed low-level non-neutralizing anti-DA antibodies. Our data indicate that weekly weight-based dosing of DA, with the addition of G-CSF in selected individuals, can be an effective erythropoietic option in a high proportion of lower-risk MDS patients.

Introduction

Myelodysplastic syndromes (MDS) are clonal myeloid hemopathies characterized by bone marrow failure, morphologic hematologic dysplasia, and the potential for evolution to acute myeloid leukemia. Most patients with MDS have a macrocytic anemia with a low reticulocyte response reflecting ineffective hematopoiesis [1]. In *vitro* culture systems of MDS marrow have demonstrated defective differentiation of hematopoietic stem cell/progenitor cell compartments in response to various hematopoietic growth factors [2]. In

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vitro, MDS erythroid progenitor cells show sub-optimal responses to EPO [3]. Serum EPO levels can markedly differ between MDS patients with comparable degrees of anemia, suggesting that feedback mechanisms controlling EPO production may be one perturbation of myelodysplastic erythropoiesis [4]. The rationale of recombinant erythropoietin (EPO) therapy in MDS is to provide pharmacological doses of the cytokine in order to overcome the defective proliferation and differentiation of erythroid precursors. Clinically, the aim of EPO therapy is to raise hemoglobin levels and decrease the need for red blood cell (RBC) transfusions, and to ameliorate poor quality of life symptoms such as fatigue.

In prior trials of MDS patients assessing the efficacy of EPO, various response criteria were used before the publication of standardized response criteria by the MDS International Working Group (IWG) in 2000 and 2006 [5,6]. In addition, a spectrum of EPO doses and frequencies (usually daily or thrice weekly) were utilized among patients with different MDS FAB subtypes. With these caveats, the average response rate of numerous published trials was relatively low, ~20% [7,8].

Darbepoetin alfa (DA) is a hyperglycosylated, biochemically distinct analog of recombinant human EPO [9]. This modification leads to a molecule with a longer serum half-life and greater *in vivo* potency, allowing less-frequent drug administration. The goal of this Phase II trial was to evaluate the efficacy and tolerability of weekly dosing of DA in MDS patients with anemia. The novel component of the trial was the weight-based, intra-patient dose-escalation design with a prospective plan for addition of granulocyte-colony stimulating factor (G-CSF) to maximize erythroid response, as previously described for EPO [10,11].

Results

Efficacy

The pretreatment characteristics of the 24 patients enrolled in the study are shown in Table I. Eighteen of the patients were male, and the median age was 68 years (range, 31–84 years). FAB subtypes included 10 RA, 9 RARS, 3 RAEB, and 2 CMML. Patients were categorized as RCMD ($n = 8$), RCMD + RS ($n = 9$), 5q-syndrome ($n = 2$), RAEB-1 ($n = 3$), and CMML-1 ($n = 2$) according to the World Health Organization (WHO) classification [12]. The corresponding IPSS subgroups were low ($n = 12$), intermediate-1 ($n = 10$), and intermediate-2 ($n = 2$). The median baseline EPO level of study subjects was 111 U/L (range, 12–2556 U/L). Sixteen patients were initially RBC transfusion dependent.

Table II shows the erythroid responses (IWG 2000) of study patients, associated DA dose levels received, and additional baseline clinical/laboratory characteristics of treated patients. The nine individuals with RARS initiated DA at a dose of 9 mcg/kg compared to 4.5 mcg/kg for the remaining patients. This weight-based dosing translated into a median weekly starting DA dose of 390 mcg when either all patients were considered (DA dose range 250–1,100 mcg), or when the 15 non-RARS patients were evaluated separately (DA dose range 250–485 mcg). For the 9 RARS patients, the median starting weekly DA dose was 730 mcg (DA dose range 600–1,100 mcg).

According to IWG 2000 response criteria [5], hematologic improvement-erythroid (HI-E) was observed in 16/24 (67%) patients, including 12 (50%) major responses, and 4 (17%) minor responses. When the modified IWG 2006 criteria [6] were applied, the overall HI-E response rate was 14/24 (58%) (two minor responders were reclassified as nonresponders). The median time to initial erythroid response (1 g/dL rise in hemoglobin or 50% decrease in red blood transfusion requirement) was 5 weeks (range, 3–18 weeks). In the major responders, the median time from onset of major response to complete loss of erythroid response (loss of major and minor) was 12 months (range, 4–19 months). When a minor erythroid response was the best response achieved, the median duration of response was 5 months (range, 2–7.5 months). Development of iron deficiency was not identified as a cause for loss of erythroid response in responding patients. In nontransfusion-dependent patients who achieved an erythroid response, the mean hemoglobin increase was 3.7 g/dL, and the maximum hemoglobin ranged from 10.6 to 15.9 g/dL. Dose reduction was undertaken for excess hemoglobin response (EH) in 7 of 16 erythroid responders (44%).

Among the 12 major erythroid responders, a major HI-E was achieved at the first dose level of 4.5 mcg/kg/week in one patient (8%), at the second dose level of 9.0 mcg/kg/week in four patients (33%), and at the third dose level of DA 9 mcg/kg/wk + G-CSF 2.5 mcg/kg in seven patients (58%). Ultimately 15 study patients required dose escalation to the third dose level (i.e., a major HI-E was achieved in 7/15 patients with addition of G-CSF). Of note, five of these seven patients (71%) were of the RARS subtype.

Prognostic Factors

Less than two RBC transfusions per month and good risk cytogenetics were predictive of response to DA. Although there was a trend indicating that EPO levels differed between responders and nonresponders, the results did not reach statistical significance ($P = 0.06$) (Table III).

Using logistic regression, an increase of 0.63 in the IPSS score (which also corresponds to the interquartile range of this variable) reduced the chance of an erythroid response by 74% ($P = 0.016$). An IPSS score of greater than 0.5 significantly reduced the probability of an erythroid response by 86% compared to an IPSS score of 0.5 ($P = 0.05$), and the probability for a major erythroid response was reduced by 73% ($P = 0.41$).

Patients receiving less than two RBC transfused units/month at baseline had a 64% chance of a major response, 21% chance of a minor response, and 14% chance of no response; the corresponding rates for patients receiving 2 RBC units/month were 30, 10, and 60%. As these rates suggest, the probability an erythroid response was reduced by 89% in patients receiving 2 RBC transfusions/month ($P = 0.018$), while the probability of a major erythroid response was not related to the number of RBC units received.

Although the number of patients was too small to support multivariate modeling, a score based on the number of “response indicators” present was associated with a graded proportion of response. Specifically, if a patient received a point for each of the following: <2 units of RBC/month, IPSS score <0.5, and serum EPO level <100 U/L, then the number of points ranges from 0 (two patients) to 3 (five patients), and the corresponding rates of

response were 0/2 (0 points), 4/8 (1 point), 7/9 (2 points), and 5/5 (3 points), or 0, 50, 78, and 100%, respectively ($P = 0.003$).

The outcome “excess hemoglobin (EH)” was strongly associated with patients having received <2 units of RBC/month; none of the 10 patients receiving 2 or more units/month had EH. In the 14 patients who had <2 units/month, seven had EH ($P = 0.019$). None of the three patients with IPSS > 0.5 had EH, compared with 7/11 with IPSS score of 0.5 or lower ($P = 0.192$). Thus, all seven patients who had EH had a low IPSS score and <2 units of RBC/month.

Adverse Events

DA was well tolerated. Nonhematologic adverse-events considered related to DA included Grade 3 hypertension, Grade 2 creatinine elevation, and Grade 2 proteinuria in one patient with pre-existing Type II diabetes mellitus, hypertension, and renal insufficiency (baseline creatinine 1.4 mg/dL). Three of 15 patients (20%) receiving G-CSF developed Grade 2–3 bone pain. One patient died of pneumonia during the trial, considered unrelated to DA. No thrombotic or cardiovascular complications were noted in study patients.

Hematologic adverse events related to worsening of thrombocytopenia. One patient with an initially normal platelet count developed Grade 3 thrombocytopenia with G-CSF therapy, which resolved after its discontinuation. Grade 3–4 thrombocytopenia developed in four patients with baseline Grade 1–3 thrombocytopenia. In these four patients, progression of thrombocytopenia was considered possibly related to DA and/or G-CSF, but was more likely due to intercurrent infection or disease progression. Two patients with CMML progressed to AML during the study period, and 2 patients with RARS progressed to RAEB.

Anti-DA Antibody Seroreactivity Analysis

Paired pre-and post-treatment serum samples were available for analysis in 17 patients. Three subjects had borderline-positive or positive baseline (pre-existing) antibodies (two with anti EA antibodies [0.23 and 0.24 mcg/ml], one with anti-DA antibodies [0.61 mcg/ml]), including two who had known prior limited exposure to DA or EA. These three subjects maintained their antibody status throughout the trial, with a <2-fold change in their antibody concentration by the end of the study. Two minor erythroid responses and 1 nonresponse were recorded in these three patients. Two subjects who were pretreatment negative with the anti-DA immunoassay became post-treatment positive (>0.25 mcg/ml), but tested negative in the bioassay for neutralizing antibodies. One major and one minor erythroid response were observed in these two patients.

Discussion

In our study of MDS patients, weekly dosing of DA (with or without G-CSF) elicited a total erythroid response rate of 67%, of which 50% were major responses as evaluated by the IWG 2000 criteria (58% by modified IWG 2006 criteria). This intra-patient dose-escalation study employed weight-based dosing of DA, administered in the range of 4.5–9.0 mcg/kg weekly. In responding non-RARS patients, the best erythroid response was achieved with a

median DA dose of 780 mcg (range, 300–970 mcg), and 730 mcg in responding RARS patients.

The erythroid response rates (and 12-month median response duration) demonstrated herein compare favorably to prior studies evaluating DA in primarily low and intermediate-1 risk MDS patients [13–15]. Using IWG 2000 response criteria [5], the erythroid response rates in those studies ranged from 41% to 71% (major erythroid responses of 35–55%) with DA administered at a dose of 150–300 mcg weekly. Historically, the response rate to EPO monotherapy in numerous published small trials of MDS was ~20%. For example, using RBC transfusion-independence as a minimal response criterion, two meta-analyses reported erythroid responses of 16–24% [7,8]. However, more recently, the GFM reported a substantially higher erythroid response rate at 12 weeks (62% per IWG 2000 criteria, 50% per IWG 2006 criteria) among patients treated with different EPO formulations (epoetin α , β 60,000 units/wk or DA 300 mcg/wk), and concomitant G-CSF in a third of cases [16].

Factors predictive of erythroid response have been analyzed in trials of EPO in MDS. With the caveat of the current study's relatively small sample size, lower RBC transfusion requirement and good risk cytogenetics predicted response to DA, and there was a trend toward a lower serum EPO level (e.g., 150 IU/L) predicting response. By logistic regression analysis, IPSS score >0.5 versus ≤ 0.5 and RBC transfusions of ≥ 2 /month versus <2 RBC transfusions/month significantly reduced the probability of an erythroid response. None of the 10 patients with ≥ 2 RBC transfusions/month achieved the outcome of EH, whereas all seven patients who had EH received <2 units of RBC/month. In prior studies of DA in MDS, erythroid response was predicted by baseline serum EPO level (<100 U/L or <200 U/L), and a history of fewer RBC transfusions [13–15]. These findings are similar to those in a prior meta-analysis, wherein favorable prognostic variables included absence of RBC transfusion need and serum EPO concentration ≤ 200 U/L [7]. Patients without a transfusion requirement and MDS patients other than RARS showed a response rate $>50\%$ irrespective of the serum EPO level. Serum EPO level <200 IU/L, absence of transfusion requirement, and low or intermediate-1 IPSS score were the only factors associated with a better erythroid response in the GFM analysis [16].

In an attempt to achieve a major erythroid response in suboptimal responders to DA, we incorporated treatment with G-CSF in the final dosing cohort. Fifteen of the 24 patients in our study were treated at the third cohort level of G-CSF 2.5 mcg/kg twice weekly combined with DA 9 mcg/kg weekly. The addition of G-CSF elicited a major erythroid response in 7/15 patients (47%), and 5/7 (71%) of these patients exhibited the RARS subtype. Hellstrom-Lindberg et al. generated a model which utilized serum EPO level and RBC transfusion need (units/month) to predict low (7%), intermediate (23%), and high (74%) probabilities of response to EPO plus G-CSF therapy in MDS patients (the model did not incorporate IWG criteria, which were developed later) [11]. In our trial, 3/8 (38%) patients who would have been classified by that model as having an intermediate probability of erythroid response, and 4/7 (57%) patients with a high probability of erythroid response, exhibited a major erythroid response with DA + G-CSF treatment.

Our findings with DA + G-CSF recapitulate prior studies demonstrating increased response rates in the range of 36–60% [11,17–19], particularly in RARS patients, when G-CSF is combined with EPO. We found that G-CSF could augment erythroid responses in approximately half of suboptimal responders to DA, particularly RARS patients. In the one prior study which evaluated addition of G-CSF to DA, only one minor and one major erythroid response were observed among 10 patients who failed DA 300 mcg/wk [15]. In the GFM study, no difference in responses between EPO (epoetins α , β or DA) versus EPO + G-CSF in RARS/RCMD +RS patients was noted [16].

Anti-DA antibody seroreactivity analysis revealed that no neutralizing antibodies to DA were detected, although 2/17 patients (12%) had positive non-neutralizing antibody results on the screening assay. Both patients demonstrated erythroid responses, indicating that these were not clinically relevant antibodies.

Using a weight-based dosing regimen and intra-patient dose escalation scheme, we have shown that a convenient weekly schedule of DA elicited a relatively high erythroid response rate in predominantly lower-risk MDS patients. In addition, G-CSF can generate major erythroid responses in individuals with no or suboptimal erythroid responses to DA, particularly those with the RARS subtype. Extended trials will be needed to determine whether weight-based dosing produces any safety or efficacy, or economic benefit (or disadvantages) compared to fixed-dosing of DA, particularly in individuals with relatively low or high body weight. Similar to prior trials of DA and standard EPOs in MDS, we have not identified safety concerns, especially related to cardiovascular morbidity. However, we were cognizant of, and responsive to the need to decrease drug dosing in patients with EH. It is noteworthy that the GFM [16] and Nordic-Italian groups [20] have recently shown increased survival in lower-risk MDS patients treated with EPO in extended trials, findings which merit additional investigation.

Methods

Enrollment and Eligibility Criteria

Twenty-four patients were enrolled at Stanford University School of Medicine ($n = 21$) and Vanderbilt University ($n = 3$) between September 2002 and July 2006. Informed consent was obtained from all patients in accordance with the Committees for the Protection of Human Subjects at Stanford University Medical Center and Vanderbilt University Medical Center.

Patients were required to have bone marrow aspirate/biopsy-proven MDS for ≥ 2 months prior to enrollment. MDS French-American-British (FAB) subtypes refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), refractory anemia with excess blasts (RAEB), and nonproliferative chronic myelomonocytic leukemia (CMML) (WBC $< 12,000/\text{ml}$) were eligible. The International Prognostic Scoring System (IPSS) was used to stratify patients into lower-risk (Low, Intermediate-1) and higher-risk (Intermediate-2, High) subgroups.

Patients were required to meet the following eligibility criteria: (1) age ≥ 18 years old; (2) untransfused hemoglobin ≥ 10.0 g/dL and/or RBC transfusion-dependence for a period of at

least 2 months prior to study entry; (3) recombinant EPO-naïve or treatment with EPO 40,000 U/week for no more than 4 weeks; (4) AST/ALT $\geq 2.5\times$ upper limit of normal and total bilirubin ≥ 2 mg/dL; (5) serum creatinine ≥ 2 mg/dL; (6) ECOG performance status 0–2; (7) no secondary MDS; (8) no prior allogeneic bone marrow/stem cell transplantation; (9) no prior treatment with chemotherapy, radiotherapy, hemopoietic growth factors, or other biologic response modifiers within 30 days of study treatment; (10) no iron deficiency as measured by serum iron indices (and review of the Prussian blue marrow iron stain); (11) no active hemolysis, bleeding, or transfusion-dependent thrombocytopenia; and (12) no requirement for ongoing therapy with >10 mg/d of prednisone. Patients were permitted to receive supportive care, including transfusions and antibiotics as required, and G-CSF for febrile neutropenia.

Trial Design

Figure 1 outlines the trial scheme. In the induction phase, DA (Amgen, Thousand Oaks, CA) was initiated at a dose of 4.5 mcg/kg/weekly subcutaneously. This initial weekly dose of DA was chosen by dividing a standard starting dose of EPO in MDS, 1,050 units/kg/week (e.g. 150 units/kg/day), by 200, a rough factor for converting EPO to DA therapy [9], and choosing a DA dose near 5.25 mcg/kg that has been studied, namely 4.5 mcg/kg/week. If patients did not achieve a >2 g/dL hemoglobin rise by 6 weeks, the dose of DA was doubled to 9.0 mcg/kg/week. If patients did not achieve a 2 g/dL hemoglobin rise with this increased DA dose after an additional 6 weeks, DA was supplemented with G-CSF 2.5 mcg/kg twice weekly subcutaneously (filgrastim, Amgen, Inc., Thousand Oaks, CA). G-CSF was titrated to 2.5 ± 1 mcg/kg twice weekly to achieve a doubling of the absolute neutrophil count (ANC) if the initial value was $<1500/\text{mm}^3$, or if initially normal, titrated to maintain the ANC up to a maximum of $15,000/\text{mm}^3$. Because patients with the RARS subtype of MDS have historically exhibited relatively lower response rates to EPO alone, these patients commenced the trial at a DA of 9.0 mcg/kg/week, and similar to other patients, were administered G-CSF for lack of an increase of hemoglobin >2 g/dL after 6 weeks.

Patients transitioned to a 3-month maintenance phase after the first or second induction dose levels if they achieved a major erythroid response. Patients who achieved a minor or major erythroid response on the third dose level of DA plus G-CSF subsequently entered the maintenance phase of treatment. Patients with sustained erythroid responses throughout the maintenance phase were continued on extended treatment until one of the following: (1) return to their baseline hemoglobin level or RBC transfusion requirement; (2) progressive disease; or (3) grade ≥ 3 hematologic or nonhematologic toxicity despite dose-reduction of DA (+/- G-CSF).

Dose Modifications

Figure 1 also shows the dose reduction algorithm for patients experiencing Grade 3 hematologic or nonhematologic toxicity which was considered related to DA. For any Grade 3 nonhematologic toxicities recurring at these reduced doses, DA (+/- G-CSF) was permanently discontinued. For patients who demonstrated an excess hemoglobin (EH) response to DA (defined as an increase in the hemoglobin to ≥ 13 g/dL), the drug was withheld until the hemoglobin decreased to 12 g/dL. DA dose reduction algorithms for EH

were the same as those for Grade 3 hematologic or nonhematological toxicity. If patients lost their major erythroid response at any of the reduced doses, DA was re-escalated to the original dose.

Efficacy and Adverse Event Assessment

Minor and major erythroid responses were assessed by the IWG 2000 response criteria for MDS, and were also reanalyzed according to the Modified IWG 2006 criteria [5,6]. These criteria require erythroid responses to last a minimum of 8 weeks in duration. Cancer Therapy Evaluation Program Common Toxicity Criteria (CTC) version 2.0 was utilized for adverse event reporting.

Anti-DA Antibody Seroreactivity Analysis

Prior to the first dose of DA, and 2–4 weeks after the last dose of study drug, serum was collected and sent to Amgen, Inc (Thousand Oaks, CA) to determine the presence of anti-DA antibodies capable of binding and/or neutralizing DA. The surface Plasmon resonance (SPR)-based immunoassay using the Biacore 3000 (Biacore International AB, Uppsala, Sweden) was used to detect anti-DA antibodies, and cross reactivity to Epoetin alpha (EA) was also assessed (lower detection thresholds of 0.15 and 0.08 mcg/ml for anti-DA and anti-EA antibodies, respectively). Biosensor immunoassay positive samples (>0.25 mcg/ml) were further tested in a cell-based bioassay to detect neutralizing/inhibiting effects of DA or EA. Samples were defined as positive for neutralizing anti-DA or EA antibodies if they were positive in both the immunoassay and bioassay.

Statistical Analysis

Fisher's exact test was used to assess differences in prognostic variables between the proportion of responding and nonresponding patients. Student's *t*-test was used to evaluate differences in the mean age, and Wilcoxon's rank test for differences in the mean serum EPO level between these two groups. Logistic regression was used to explore the effect of baseline factors on the probability and quality of erythroid response.

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Figure 1.

Trial scheme of Darbepoetin Alfa (DA) +/- G-CSF in patients with MDS. Patients were treated with up to three successive induction dose levels if a major erythroid response was not obtained at the preceding dose level. After induction, responding patients were treated on a 3-month maintenance phase, followed by extended treatment until loss of erythroid response or unacceptable toxicity. During the induction period, a major erythroid response was defined as a >2 g/dL hemoglobin increase by 6 weeks of treatment.

TABLE I

Summary of Patients' Pretreatment Characteristics

Number of patients	24
Male:female	18:6
Age (years)	
Median (range)	68 (31–84)
FAB subtype	
RA	10
RARS	9
CMML	2
RAEB	3
WHO subtype	
RCMD	8
RCMD 1 RS	9
5q-	2
CMML-1	2
RAEB-1	3
Cytogenetics	
Good	21
Intermediate	2
Poor	1
IPSS risk group	
Low	12
Intermediate-1	10
Intermediate-2	2
Serum erythropoietin level (U/L)	
Median (range)	111 (12–2,556)
RBC transfusions	
<2 units/month	14
2 units/month	10

FAB, French-American-British; RA, refractory anemia; RARS, refractory anemia with ringed sideroblasts; CMML, chronic myelomonocytic leukemia; RAEB, refractory anemia with excess blasts; WHO, World Health Organization; RCMD, refractory cytopenia with multilineage dysplasia; RCMD + RS, refractory cytopenia with multilineage dysplasia + ringed sideroblasts; IPSS, International Prognostic Scoring System; RBC, red blood cell.

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TABLE II

Results of Treatment with DA (+/− G-CSF) and Baseline Clinical/Laboratory Features of Patients

Pt #	Age/Sex	FAB Subtype	WHO Subtype	IPSS Score	IPSS Risk Group	Cytogenetics	Hb/Hct At Entry	Transfusion-Dependent	<2 units/month	Serum EPO (U/L)	Initial DA Dose (mcg)	Erythroid Response (IWG 2000)	EH
1	61/F	RARS	RCMD + RS	0	Low	Normal	9.3/27.3	No	Yes	113	640	Major ^{a,b,c}	Yes
2	73/M	RARS	RCMD + RS	0	Low	Normal	9.8/27.9	Yes	No	100	770	Major ^{b,c}	No
3	77/M	RA	RCMD	0	Low	Y-	8.4/24.5	Yes	No	273	250	Major ^{a,b,c}	No
4	81/M	RA	RCMD	0	Low	Normal	10.2/31.2	Yes	Yes	12	300	Major ^a	Yes
5	55/F	RA	5q-	0	Low	5q-	9.2/26.7	Yes	Yes	422	390	Major ^{a,b,c}	No
6	67/M	CMML	CMML-1	1	Int-1	Normal	8.5/24.8	Yes	Yes	40	485	Major ^{a,b}	No
7	71/F	RARS	RCMD + RS	0	Low	Normal	9.0/27.0	Yes	Yes	93	760	Major ^b	Yes
8	59/M	RARS	RCMD + RS	0	Low	Normal	10.0/29.3	No	Yes	140	675	Major ^{b,c}	Yes
9	69/M	RA	RCMD	0.5	Int-1	Normal	10.8/32.7	Yes	No	33	390	Major ^{a,b,c}	No
10	67/M	RARS	RCMD + RS	0	Low	Normal	9.2/26.2	No	Yes	53	800	Major ^{b,c}	Yes
11	69/M	RA	RCMD	0	Low	Normal	9.8/29.2	No	Yes	39	450	Major ^{a,b}	Yes
12	62/M	RA	RCMD	0.5	Int-1	Normal	9.8/28.4	No	Yes	103	380	Major ^{a,b}	Yes
13	76/F	RAEB	RAEB-I	1	Int-1	Normal	8.7/28.3	Yes	Yes	109	370	Minor ^{a,b,c}	No
14	68/M	RARS	RCMD + RS	0.5	Int-1	Normal	8.2/24.4	Yes	No	305	730	Minor ^{b,c}	No
15	75/M	RA	RCMD	0.5	Int-1	Normal	9.4/27.3	No	Yes	120	410	Minor ^{a,b,c}	No
16	70/M	RARS	RCMD + RS	0	Low	Normal	9.2/26.3	No	Yes	34	670	Minor ^b	No
17	78/F	RAEB	RAEB-I	1	Int-1	Normal	10.3/30.5	Yes	No	160	400	None ^a	No
18	31/M	RAEB	RAEB-I	2	Int-2	der(1;7)(q10;p10); der(1;15)(q10;p10)	8.0/23.1	Yes	No	2556	450	None ^{a,b}	No
19	52/F	RARS	RCMD + RS	0	Low	Normal	7.1/21.0	Yes	No	347	600	None ^{b,c}	No
20	59/M	RARS	RCMD + RS	1.5	Int-2	Poor-risk, complex	7.8/25.0	Yes	No	65	1100	None ^{b,c}	No
21	84/M	RA	RCMD	0.5	Int-1	Normal	9.8/30	Yes	No	44	365	None ^{a,b,c}	No
22	55/M	RA	5q-	0	Low	5q-	10/29.5	Yes	No	307	390	None ^{a,b,c}	No
23	63/M	RA	RCMD	1	Int-1	81	8.0/22.4	Yes	Yes	133	250	None ^{a,b,c}	No
24	63/M	CMML	CMML-1	0.5	Int-1	Normal	9.6/28.1	No	Yes	196	460	None ^{a,b}	No

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FAB, French-American-British; RA, refractory anemia; RARS, refractory anemia with ringed sideroblasts; CMML, chronic myelomonocytic leukemia; RAEB, refractory anemia with excess blasts; WHO, World Health Organization; RCMD, refractory cytopenia with multilineage dysplasia; RCMD + RS, refractory cytopenia with multilineage dysplasia + ringed sideroblasts; IPSS, International Prognostic Scoring System; RBC, red blood cell; Hb/Hct, hemoglobin/hematocrit; EH, excess hemoglobin response.

Superscripts indicate the induction dose levels of DA administered to patients:

- ^pDA 4.5 mcg/kg;
- ^qDA 9 mcg/kg;
- ^rDA 9 mcg/kg + G-CSF 2.5 mcg/kg twice/week.

TABLE III

Variable Comparisons Between Responders and Non-Responders to DA (+/- G-CSF)

Variable	Responders (n = 16)	Nonresponders (n = 8)	P-value
Median age, years (range)	69 (55–84)	61 (31–84)	0.21
Male pts/total pts	12/16	6/8	1.0
Median serum EPO level, U/L (range)	102 (12–422)	178 (44–2,556)	0.06
Pts with serum EPO level < 150 U/L/total pts	13/16	3/8	0.06
Pts with <2 RBC transfusions monthly/total pts	12/16	2/8	0.03
RBC transfusion dependent pts/total pts	9/16	7/8	0.19
IPSS Low and Int-1 pts/total pts	16/16	6/8	0.10
IPSS score 0.5/total pts	14/16	4/8	0.13
Good risk cytogenetics pts/total pts	16/16	5/8	0.03