Patients with myelodysplastic syndromes benefit from palliative therapy with amifostine, pentoxifylline, and ciprofloxacin with or without dexamethasone

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Thirty-five patients with myelodysplastic syndrome (MDS) were registered on protocol MDS 96-02 and were receiving continuous therapy with pentoxifylline 800 mg 3 times a day and ciprofloxacin 500 mg twice a day by mouth; dexamethasone was added to the regimen for the partial responders and the nonresponders after 12 weeks at a dose of 4 mg by mouth every morning for 4 weeks. Amifostine was administered intravenously 3 times a week at 3 dose levels (200 mg/M², 300 mg/M², and 400 mg/M²) to cohorts of 10 patients each. Therapy has been continued for 1 year in responders. Twenty-nine have completed at least 12 weeks of therapy and are available for response evaluation. Of the 21 men and 8 women (median age, 67 years), 20 had refractory anemia (RA), 3 had RA with ringed sideroblasts (RARS), 5 had RA with excess blasts (RAEB), and 1 had chronic myelomonocytic leukemia (CMMoL). Five had secondary MDS. No differences were noted in response rates among the 3 dose levels. Seven patients did not respond at all, and 22 showed an improvement in cytopenias (76%). Three had a triple lineage response, 10 had a double lineage response, and 9 had a single lineage response (8 of 9 in absolute neutrophil count [ANC] and 1 had more than a 50% reduction in packed red blood cell transfusions). Fifteen patients responded only after the addition of dexamethasone, whereas 7 responded before. When examined by lineage, 19 of 22 showed improved ANC, 11 of 22 demonstrated more than 50% reduction in blood transfusions, improved Hb levels, or both, and 7 of 22 showed improvement in platelet counts. Interestingly, the responses were frequently slow to appear, and continued improvement in counts was seen up to 12 months of therapy and beyond. This study supports the feasibility of treating patients with MDS with the unique approach of cytoprotection and anticytokine therapies as well as the principle that prolonged commitment to treatment is desirable when noncytotoxic agents are administered. (Blood. 2000;95: 1580-1587)

Introduction

No single therapeutic approach appears to have made a significant impact on survival of patients with myelodysplastic syndromes (MDS).[1,2] Allogeneic bone marrow (BM) transplantation,[3,4] a choice available to few patients given that the median age at diagnosis is approximately 70 years, is the only exception. Options range from supportive care to the use of stem cell transplantation. Based on the assumption that the cytopenias may reflect a primary bone marrow failure, colony-stimulating growth factors with overlapping activities designed to stimulate proliferation of hematopoietic progenitors have been extensively investigated.[5-7] The problem is that administered as single agents, granulocyte-macrophage colony-stimulating factor (GM-CSF) or G-CSF rarely improves the anemia and the thrombocytopenia so commonly the pathognomonic features of MDS. Erythropoietin alone produces an improvement in the anemias of approximately 20% of patients, which increases to almost 50% when combined with G-CSF.[8,9] However, only a proportion of patients respond, the response is usually temporary, and there is some concern related to an incidence of accelerated transformation.[10]

Acute leukemia-like intensive induction therapies have been attempted in patients with high-risk MDS (those with excess blasts or chronic myelomonocytic leukemia), with as many as half the patients achieving complete remission.[11,12] Short duration of remission marked by a relentless return of MDS cells in most patients, treatment-related complications or mortality, frequent encounters with drug-resistant clones, and the morbidity caused by the appearance of unexpected and unusual opportunistic infections reflecting the enormously compromised state of the immune system in these patients make the intensive chemotherapy option less desirable. In summary, save for allogeneic transplantation, MDS is a universally fatal illness, and no single approach has either altered the natural history of the disease or improved survival.

Given the biologic complexity and the unpredictable course of the disease ranging from chronic, insidious, and slowly progressive cytopenia to a rapidly evolving, lethal transformation to acute leukemia, it is not surprising that therapeutic options range widely between supportive care to intensive induction-type chemotherapy. Clearly, a better understanding of the basis for cytopenias in MDS is critical to design therapies tailored for individual needs. Recent biologic studies have demonstrated that cytokine-mediated excessive

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Submitted June 16, 1999; accepted November 3, 1999.

Supported by the National Cancer Institute (grant PO1CA 75606), The Markey Charitable Trust, and the Dr Roy Ringo Grant for basic research in myelodysplastic syndrome.

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intramedullary apoptosis of hematopoietic cells may form this basis in most patients with MDS.[13-16] This insight offers a novel therapeutic window of opportunity because it naturally follows that suppression of the proapoptotic cytokines should lead to an improvement in cytopenias. The proinflammatory/proapoptotic cytokines that have so far been demonstrated to be candidates for this role are tumor necrosis factor α (TNF-α), transforming growth factor β (TGF-β), and interleukin 1b (IL-1b).[17-20] Because the pathologic course most likely results from the activity of a cascade of cytokines, suppression of any single cytokine by specific antibodies would not be the most desirable therapy. Rather, agents that interfere with the activity of several cytokines would be preferred. We chose to use pentoxifylline (PTX), a xanthine derivative known to interfere with the lipid-signaling pathway used by TNF-α, TGF-β and IL-1b[21] and thus reduces the activity of these cytokines.[22-24] Ciprofloxacin (Cipro) was concomitantly administered because it reduces the hepatic degradation of PTX,[25] and dexamethasone (Decadron) was added to down-regulate the translation of mRNA for TNF-α.[26] This pentoxifylline–ciprofloxacin–dexamethasone (PCD) therapy resulted in encouraging hematopoietic responses in 18 of 43 patients with MDS,[27] and the mechanism of action was found to be cytokine related because responders showed the most sustained reductions in TNF-α levels.[28]

More recently, the cytoprotective agent amifostine has been found to have substantial activity in improving cytopenias of patients with MDS.[29] In the current study, therefore, the anticytokine and cytoprotective approaches were combined to determine whether the gains in improving ineffective hematopoiesis of MDS could be further enhanced. This article reports on the first trial that combined all 4 agents namely, pentoxifylline, ciprofloxacin, amifostine, and dexamethasone.

Patients and methods

All patients were entered on the protocol MDS 96-02. The protocol was reviewed and approved by the Institutional Review Board (IRB) of the Rush–Presbyterian–St. Luke's Medical Center and by the IRBs of other participating institutions. All patients considered potential candidates for treatment on MDS 96-02 had the protocol explained to them by the Principal Investigator, and if they agreed to participate in the study, they signed an informed consent form before therapy began. All patients underwent a bone marrow examination before the start and after approximately 12 weeks of therapy. Weekly complete blood counts with differentials were obtained on all the patients; only adults older than 18 years of age were eligible for the study. All pretherapy and posttherapy bone marrow examination results were reviewed at Rush University by a hematopathologist.

Clinical studies

Thirty-five patients with MDS were formally registered on the protocol MDS 96-02 after a bone marrow examination confirmed the diagnosis. Twenty-nine have completed at least 12 weeks of therapy and are available for a response evaluation. All patients began by taking pentoxifylline 400 mg by mouth 3 times a week for 1 week. This was increased to 800 mg by mouth 3 times a week from the second week until the termination of the protocol. Ciprofloxacin (Cipro) was started at a dose of 500 mg by mouth twice a week from the 3rd week. Amifostine was administered 3 times per week (Monday, Wednesday, Friday) at 3 dose levels to cohorts of 10 patients each. The first cohort received 200 mg/M^2, the second cohort received 300 mg/M^2, and the third cohort received 400 mg/M^2 intravenously 3 times/week. After 12 weeks of therapy with pentoxifylline, Cipro, and amifostine, responses were evaluated according to the criteria described below. Partial responders, nonresponders, or both were then given dexamethasone at 4 mg by mouth every morning in addition to the other drugs for a period of 4 weeks. After this 4-week course, dexamethasone was tapered and stopped, and then a maintenance dose of 4 mg by mouth was given for 5 days every month after 6 weeks.

The protocol was written to continue all drugs for a period of 6 months and then to reduce the amifostine frequency to twice a week and continue all drug administration for a total of 1 year. These drug durations and schedules were chosen for a variety of reasons. PTX and Cipro have been safely administered to patients with MDS for up to 3 years in our previous study[27] and therefore were continued for 1 year at full dose. Because the administration of dexamethasone at 4 mg by mouth every morning for 12 weeks was associated with many of the expected side effects,[27] in the current protocol this was changed to a 5-day per month intermittent schedule after continuous daily administration for 4 weeks. After 6 months of thrice weekly amifostine, the dose was reduced to twice weekly mainly for the convenience of the patients.

Response criteria

Responses were defined according to criteria previously reported.[29,30] Restoration of normal hematopoiesis with normal peripheral blood counts was defined as complete remission. Partial remission was defined as improvement in 1 of the following parameters: (1) a decrease in monthly packed red blood cell (PRBC) transfusions by at least 50% was defined as a partial response; (2) an increase in hemoglobin by 2 g/dL over pretreatment value was considered a good response, whereas an increase by 1 g/dL was considered a partial response and anything less as no response; (3) an increase in platelet count by more than 30 000/μL above pretreatment value if the pretreatment count was less than 150 000/μL was considered a good response, and an increase by 10 000/μL was a partial response; (4) an increase in granulocyte count by 500/pL over pretreatment value or a 50% increase over pretreatment value; (5) disappearance of 1 or more cytogenetic abnormalities.

Cytogenetic studies

Standard karyotypic analysis using GTG banding was performed on every case before therapy was started and each time a marrow was performed thereafter.

Statistical analysis

Mann-Whitney *U* tests were used for 2 sample comparisons of continuous variables. Contingency tables with χ^2 statistics or the Fisher exact test were used for analysis.

Results

Thirty-five patients with a confirmed diagnosis of MDS were registered on protocol 96-02, and 29 patients could be evaluated because they completed the minimum specified period of 12 weeks on the study. Of the 29 patients who are the subject of this report, there were 21 men and 8 women, 27 were white, 1 was Hispanic, and 1 was African American. The median age was 67 years (range, 46-81 years), and 5 patients had a history of toxic exposure (secondary MDS). Of the 5 patients with secondary MDS, patient 2 had a history of myelofibrosis but did not receive any cytotoxic therapy (Table 1), patient 17 underwent autologous stem cell transplantation for non-Hodgkin's lymphoma, patient 19 underwent autologous bone marrow transplantation for AML 10 years before the diagnosis of MDS, patient 23 had breast cancer and underwent 6 cycles of chemotherapy 1 year before the diagnosis, and patient 29 underwent multiple cytotoxic therapies for chronic lymphocytic leukemia. Twenty patients had refractory anemia (RA) according to the French-American-British (FAB) classification, 3 had RA with ringed sideroblasts (RARS), 5 had RA

Table 1. Clinical and laboratory characteristics of MDS patients on protocol

				Baseline				Week 12/Before Dexamethasone				Week 24/After Dexamethasone				
S. No	Age (y)	Sex	FAB	ANC	Hb (g/dL)	RBC Trans. (units)	Plt	ANC	Hb (g/dL)	RBC Trans. (units)	Plt	ANC	Hb (g/dL)	RBC Trans. (units)	Plt	Responses
1	72	F	RA	0.43	9.8	—	54	NA	8.90	—	27	1.33	7.20	—	21	ANC + D
2	63	M	RA	0.26	10	—	99	0.36	9.00	—	106			OFF STUDY		NR
3	49	M	RA	1.50	7.5	2q1wk	44	NA	7.70	2q1wk	35	3.116	7.60	2q1wk	21	ANC + D
4	67	M	RA	1.86	8.8	3q3wk	115	2.32	6.50	2q2wk	112			OFF STUDY		ANC
5	58	M	RA	0.18	9.6	—	54	1.12	9.00	3q8wk	148	1.99	10.60	1q6wk	123	Trilineage
6	82	M	RARS	0.26	7.3	2q1wk	44	0.19	6.70	2q1wk	49	0.30	7.30	1q6wk	43	pRBC >50% + D
7	52	M	RA	1.50	7.7	2q1wk	14	0.88	8.00	2q1wk	12	3.11	10.50	1q1wk	28	Trilineage + D
8	73	M	RAEB	9.20	9.2	2q2wk	89	6.96	8.00	1q2wk	136	6.28	8.00	2q4wk	160	Bilineage (plts + trans.)
9	78	F	RARS	1.12	9.1	1q2wk	434	2.9	10.40	1q2wk	426	3.75	9.30	1q3wk (8wk gap)	447	Bilineage (ANC + trans.)
10	61	F	RA	0.36	6.8	1q3wk	151	0.42	8.50	1q8wk	150			OFF STUDY		Bilineage (ANC + trans.)
11	59	M	RARS	2.19	6.8	2q1wk	242	1.24	9.90	2q1wk	93	5.02	9.60	2q6wk (after 24 wks)	179	Bilineage (trans. (Hb) + ANC + D)
12	71	M	RAEB	1.45	7.2	2q2wk	48	0.65	8.00	2q4wk	27	3.28	10.30	nil	65 → 84	Trilineage (transfusion without D; ANC + plt were with D)
13	74	M	CMMoL	2.39	11.4	—	33	NA	8.50	—	34	4.08	9.10	—	45	ANC + D; blasts 30% to <5%
14	81	M	RA	2.41	7.3	2q1wk	110	2.01	10.00	2q1wk	138	2.54	13.40	—	133	Bilineage (trans. Hb + ANC)
15	52	F	RA	1.60	6.9	2q2wk	229	1.94	7.90	2q2wk	161	5.58	8.70	2q2wk	242	Bilineage ANC + plt + D
16	73	M	RAEB	0.29	6.7	3q1wk	21	0.16	8.50	3q1wk	21	NA	10.10	3q3wk	115 → 242	Bilineage pRBC >50% + plt + D
17	56	M	RA	0.55	7.9	1q4wk	159	0.32	7.60	2q2wk	81	0.64	9.50	2q2wk	49	NR
18	69	M	RAEB	0.91	7.6	2q1wk	6	0.93	7.70	2q1wk	20	1.56	8.00	2q2wk	18	Bilineage + D (ANC + trans.)
19	47	M	RA	3.48	9.4	nil	27	1.98	8.10	nil	19	5.77	9.30	nil	26	ANC + D
20	69	M	RA	1.04	9.3	3q4wk	41	0.68	7.80	3q4wk	28	4.2	7.00	3q4wk	36	ANC + D
21	68	M	RA	0.31	9.2	NA	63	0.176	6.40	2q4wk	66	1.18	8.80	2q4wk	105	Bilineage ANC + plt + D
22	75	M	RA	1.43	9.8	nil	84	1.36	8.50	nil	65	1.3	10.20	nil	57	NR
23	52	F	RA	0.67	9	3q2wk	16	2.32	7.60	3q2wk	17	3.02	8.10	3q2wk	18	NR
24	66	M	RAEB	1.97	13.2	NA	42	NA	11.00	NA	38					NR
25	66	F	RA	1.31	9	1q1wk	201	0.75	8.20	1q2wk	89	4.27	9.10	1q2wk	45	NR
26	67	M	RA	2.17	7.4	2q2wk	66	2.05	7.50	2q2wk	47	10.1	8.20	2q2wk	80	ANC + D
27	78	F	RA	2.32	7.1	2q3wk	358	2.16	6.40	2q3wk	280	4.04	6.60	2q3wk	297	ANC + D
28	66	M	RA	1.91	8.5	2q1wk	172	2.55	8.60	3q3wk	51	0.86	8.20	3q3wk	29	NR
29	66	F	RA	0.42	9.3	2q2wk	16	0.48	8.70	1q3wk → none	47			OFF STUDY		Bilineage trans. + plt

M, male; F, female; FAB, French-American-British classification; RA, refractory anemia; RARS, RA with ringed sideroblasts; RAEB, RA with excess blasts; ANC, absolute neutrophil count/mL; Hb, hemoglobin in g/dL; RBC Trans, number of units of packed red blood cells transfused; q, every; wk, weeks; Plt, platelets in thousands per microliter; NA, not available for that date; +D, with dexamethasone; Responses: ANC, response in neutrophils; Plt, response in platelet counts; Hb, response in hemoglobin levels; pRBC >- 50%, decrease in packed red blood cell transfusion requirements by 50%; NR, no response.

with excess blasts (RAEB), and 1 had chronic myelomonocytic leukemia (CMMoL). These data are shown in Table 1.

Protocol compliance and toxicity

Of the 35 patients registered on MDS 96-02, 3 died before 12 weeks of therapy could be completed, 1 discontinued therapy because of intolerable nausea, 1 had a myocardial infarction and discontinued therapy within 4 weeks, and 1 was registered but never started treatment. Of the 29 patients who could be evaluated for response because they completed at least 12 weeks of therapy, 9 were treated on the 200 mg/M^2 dose of amifostine, 8 on the 300 mg/M^2 dose, and 12 on the 400 mg/M^2. Twelve patients received the highest dose of amifostine because 3 patients in the lower dose groups could not be evaluated. No differences were noted in response rates among these groups. Responses were seen in 22 of 29 (76%) patients, 7 of 9 (78%) received the lowest dose of amifostine, 6 of 8 (75%) received the intermediate dose, and 9 of 12 (76%) received the highest dose of amifostine ($P = .98$). Although 29 patients completed 12 weeks of therapy, only 8 patients completed 6 months, 5 completed 9 months, and 3 completed the full year of treatment specified in the protocol. Sixteen patients stopped treatment because there was no further improvement in their cytopenias, 5 stopped because of intolerable side effects, 5 showed progression of disease, and 3 completed the full year of

Table 2. Adverse effects of amifostine by dose groups

Symptom	Group	Grade (% Patients) Grade 1	Grade 2
Nausea	1	3.6	0
	2	14	3.6
	3	11	3.6
Vomiting	1	3.6	0
	2	7	7
	3	3.6	7
Decreased appetite	1	0	0
	2	0	3.6
	3	3.6	0
Hypotension	1	0	0
	2	0	7
	3	0	7
Rash	1	0	0
	2	3.6	3.6
	3	0	3.6
Fever	1	0	0
	2	0	7.1
	3	0	0
Depression	1	0	0
	2	0	0
	3	0	0
Anxiety	1	0	0
	2	0	0
	3	0	3.6

Group 1, amifostine 200 mg/M² intravenously 3 times a week; group 2, amifostine 300 mg/M² intravenously 3 times a week; group 3, amifostine 400 mg/M² intravenously 3 times a week.

therapy. Approximately half the treated patients experienced some side effects from the drugs (Table 2). Briefly, 57% patients experienced nausea and 10% vomiting. Among the patients who experienced nausea, vomiting, or both there was a difference in those who received the higher doses of amifostine compared with those who received the lowest dose. For example, in the 200 mg/M² amifostine dose group, the incidence for nausea was 11% compared with 25% and 26% at the higher doses. Similarly, though 7% of patients at the lowest dose of amifostine experienced vomiting, 14% had vomiting at both the higher doses. From 17% to 20% of patients experienced decreased appetite, hypotension, rash, and fever, whereas depression (13%) and anxiety (3%) were rarer. Once again, all these side effects were experienced primarily in the 2 higher dose groups rather than the lowest dose amifostine group (Table 2).

Hematologic responses

Of the 29 evaluable patients, 7 had no response after at least 12 weeks of therapy whereas 22 of 29 (76%) showed partial response in that there was improvement in their cytopenias. There were no complete responders. Seven patients showed some improvement before the addition of dexamethasone, and 15 only responded after PCD + amifostine. The median time to response varied depending on the lineage and on whether the patient received dexamethasone. Nineteen patients showed an improvement in ANC, 11 in hemoglobin or transfusion requirements, and 7 in platelet count. Overall, there were 3 triple lineage responders, 10 double lineage responders, and 9 single lineage responders (8 of 9 in ANC only; 1 showed more than 50% reduction in PRBC transfusions). The details of these responses and the precise blood counts are shown in Table 1. In summary, two-thirds of the responding patients had improved ANC, half showed improvement in the erythroid lineage, and one-third showed improvement in their platelet counts. Improvements in these cytopenias were noted more rapidly after the addition of dexamethasone, whereas a more gradual improvement occurred in the patients who did not receive the additional steroid therapy.

Significant statistical improvement was seen in ANC after 16 weeks ($P = .01$) and 24 weeks ($P = .02$) of therapy. The erythroid and platelet count responses were not statistically significant ($P = .52$ and $P = .72$, respectively, at 24 weeks). Figure 1 graphically depicts the serial ANC counts in all 29 patients. Figure 2 graphically demonstrates the hematologic responses in 4 responding patients. These 4 patients were chosen for more detailed description because they represent a variety of responses after therapy with PCD + amifostine:

Patient 14

This 81-year-old white man was diagnosed with RA on 11/1/96 (Table 1, Figure 2a). He had a hypercellular BM and normal cytogenetics. At the time of diagnosis, his white blood cell count was 4200/μL, Hb level was 5.7 g/dL, and platelet count was

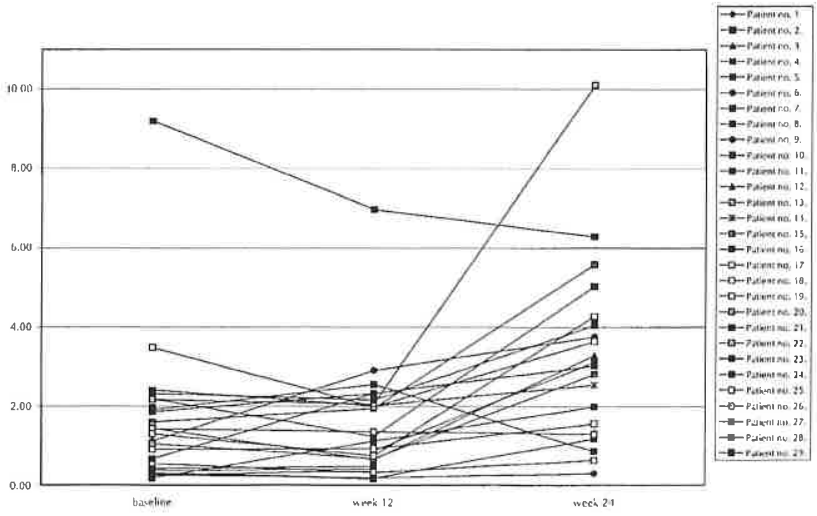

Figure 1. Graphic presentation of absolute neutrophil counts in patients with MDS during therapy.

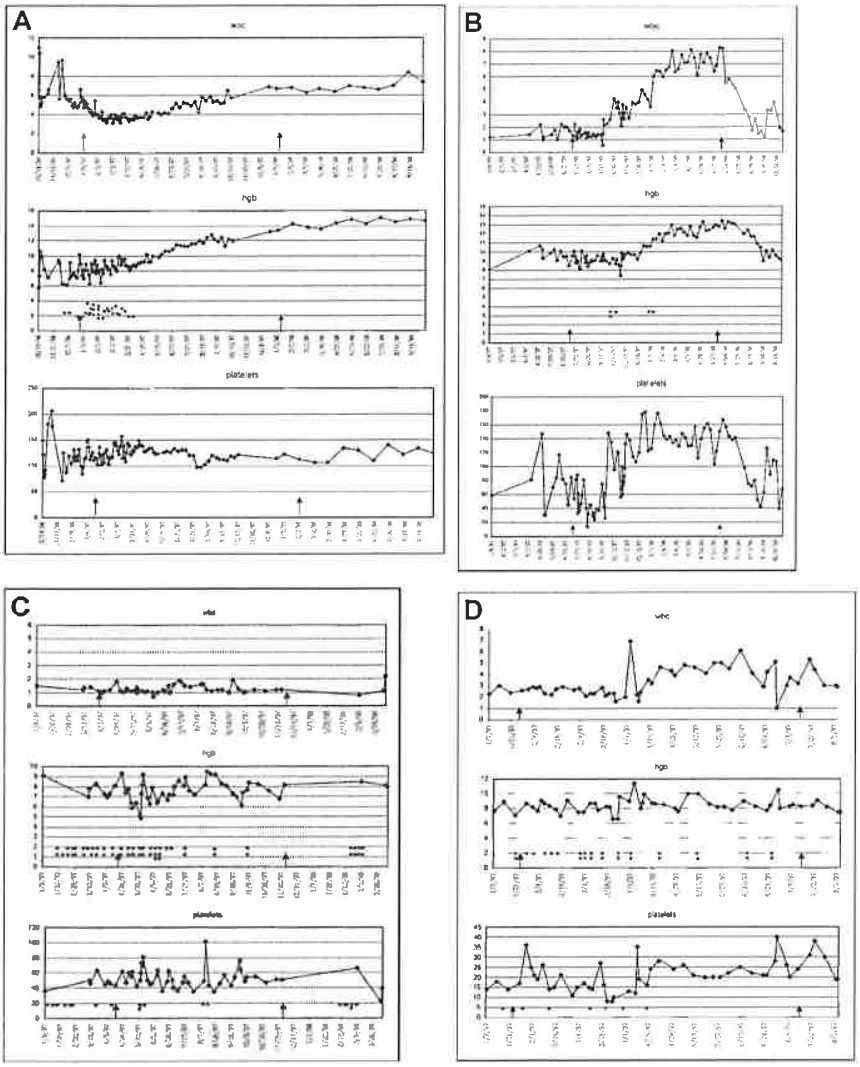

Figure 2. Graphic presentation of peripheral blood indices in 4 (A-D) patients treated with PCD and amifostine. *2 U PRBC transfusion.

149 000/μL. He received 5 U PRBC, which brought his Hb level to 10 g/dL. Patient started treatment approximately 6 weeks after diagnosis (12/16/96) and continued to require 2 to 3 U PRBC each week until March 1997. Of note, however, was the gradual increase in his hemoglobin values between transfusions. Once the transfusion requirements stopped, the hemoglobin continued to increase until the end of therapy at 1 year, as shown in the graph. The patient has been off therapy since 01/06/98, and his latest values on 9/10/98 were Hb, 14.9 g/dL; WBC, 8 400/μL; and platelet count, 134 000/μL. He feels well.

Patient 12

This 58-year-old white man was diagnosed with RA in June 1997 when he sought treatment for profound pancytopenia and severe fatigue (Table 1, Figure 2b). He had a hypercellular BM and cytogenetic abnormality 46, XY, del20(qll .2ql3.3)/46 × Y). After several PRBC transfusions, his Hb level increased to 9.6 g/dL, WBC was 1500/μL, and platelet count 54 000/μL when he started on the protocol. As seen in Figure 2B, he did require PRBCs twice in the next 3 months, but then his Hb level continued to improve, reaching a maximum of 13.9 g/dL. His WBC and platelet counts also improved (8200 μL and 180 000 μL, respectively). After approximately 11 months of treatment, the patient experienced a severe hypotensive episode after a routine amifostine injection. All study drugs were stopped at this point (6/12/98), and the patient began to experience a slow decline in all his counts within 6 weeks of halting therapy. By October, he was placed on PCD therapy because his Hb fell to 8.5 g/dL and his platelet count decreased to the 70 000/μL range. He has been showing response to this therapy.

Patient 6

This 82-year-old white man was diagnosed with RARS on 9/9/96 (Table 1, Figure 2C). He was started on MDS 96-02 on 3/31/97, at which time his WBC count was 1100/μL, Hb level was 7.3 g/dL, and platelet count was 44 000/dL. He had normal cytogenetics and hypercellular BM with 3% blasts. He required 2 U PRBC almost every 7 to 10 days and platelets every 2 to 3 weeks. After treatment with amifostine + PC, the patient continued to require the same level of transfusions until dexamethasone was added. At that point, he showed a dramatic response by becoming transfusion independent for 5 months. After approximately 8 months of therapy, the patient was taken off all medications because no further improvement

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