

# The Hematologic Response to Anti-apoptotic Cytokine Therapy: Results of Pentoxifylline, Ciprofloxacin, and Dexamethasone Treatment for Patients with Myelodysplastic Syndrome

TNF- $\alpha$  mediated apoptosis of the hematopoietic cells has been thought to contribute to the ineffective hematopoiesis observed in myelodysplastic syndrome (MDS). The combination of pentoxifylline (P) and ciprofloxacin (C) has been shown to reduce the serum levels of TNF- $\alpha$ , and an earlier trial of P and C with dexamethasone (D) provided good palliation for patients with MDS. The purpose of this study is to assess the hematologic response to PCD therapy for patients suffering with MDS. 21 of 25 patients who completed at least of 12 weeks of treatment were evaluable for the treatment efficacy. At baseline, the patient's median age was 60 yr (range: 18-75 yr). The diagnoses according to WHO classification included: RA (n=5), RCMD (n=10), RARS (n=1), RCMD/RS (n=1), RAEB (3), and CMML (n=1). 11 patients (52%) had at least single lineage response. 3 patients (11%) showed improvement of triple lineage cytopenia. There were no differences in the response rates between the FAB subtypes. The median time to response was 4 weeks (range: 2-12 weeks), and it is interesting that 9 of 11 patients who had a response remained without relapse for a median of 177 days (range: 78-634 days). These preliminary results indicate that anti-cytokine therapy with PCD is an effective and well tolerated palliative treatment for patients with MDS.

Key Words : Myelodysplastic Syndromes; Tumor Necrosis Factor-alpha; Apoptosis

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## INTRODUCTION

Myelodysplastic syndrome (MDS) refers to a heterogenous group of acquired bone marrow disorders that is characterized by dysplastic growth of the hematopoietic progenitors, a hypercellular bone marrow with peripheral cytopenia and a propensity for these disease to progress onward to acute leukemia (1). The overproduction of the proapoptotic cytokines such as tumor necrosis factor-alpha (TNF- $\alpha$ ), soluble Fas ligand, MIP-1 $\alpha$ , TGF- $\beta$ , IL-1 $\beta$ , IL-6 and interferon-gamma (IFN- $\gamma$ ) has been demonstrated in the bone marrow microenvironment and in the plasma of the patients with MDS, and this may contribute to the excessive apoptotic cell death observed in MDS (2, 3). TNF- $\alpha$  is a pleotropic immunomodulatory cytokine and a potent inhibitor of hematopoiesis; in vitro, TNF- $\alpha$  suppresses colony formation and the proliferation of normal hematopoietic progenitor cells and the malignant hematopoietic cell lines (4-7). Further, neutralization of TNF- $\alpha$  enhances the outgrowth of the hematopoietic progenitor cells in MDS (8). Elevation of the plasma TNF- $\alpha$  level correlates with oxidative DNA injury and depletion of cellular glutathione in CD34+ cells, as well as caspase-3 activity (9, 10). These findings support an effec-

tor or potentiating role for these cytokines in the ineffective hematopoiesis of MDS.

Pentoxifylline is known to interfere with the lipid-signaling pathway used by TNF- $\alpha$ , TGF- $\beta$  and IL-1 $\beta$ , and it reduces the activity of these cytokines. Ciprofloxacin is known to reduce the hepatic metabolism of pentoxifylline and dexametason, and it down-regulates the translation of the mRNA for TNF- $\alpha$  (11, 12).

Pentoxifylline, ciprofloxacin and dexamethasone (PCD) therapy induced positive hematologic responses in 18 of 43 patients with MDS. The mechanism of action was found to be cytokine related by the fact that the responders showed a sustained reduction of their TNF- $\alpha$  levels (12). The purpose of this study was to verify the response rate and the toxicity profile for the PCD therapy that was observed in the first study by Raza (12).

## MATERIALS AND METHODS

### Patients

From April 2002 to December 2003, 17 female patients

and 8 male patients with untreated MDS were enrolled in this study. The diagnosis of MDS was established based on the characteristic morphological abnormalities in the bone marrow and/or by the presence of cytogenetic abnormalities and peripheral cytopenia: all the patients were subclassified according to both the French-American-British (FAB) nomenclature and the WHO classification scheme (13-15). The study protocol was reviewed and approved by the Institutional Review Boards of the Yeungnam University Medical Center and Daegu Catholic University Hospital. All the patients provided us with a written informed consent.

Twenty-one of 25 patients completed at least 12 weeks of treatment, and so 21 patients are finally evaluable for the treatment efficacy.

### Treatment

The patients were treated with 1,200 mg of pentoxifylline (P) that was divided into three doses per day, 500 mg of ciprofloxacin (C) that was divided into two doses per day, and 4 mg of dexamethasone (D) that was divided into two daily doses, and this combined treatment was given for 4 weeks. After this 4-week course, P 800 mg and C 500 mg were given 3 times a week with 4 mg of D being given for 5 days every month for 2 months. The therapy was stopped for the nonresponding patients at this time and they were taken off the study. The protocol called for continuing all the drugs for 1 yr for the responders if the side effects were tolerable and the responses were persistently observed.

### Response evaluation and its criteria

The complete blood counts with differentials were obtained every week for all the patients. The hematologic response was evaluated using the International Working Group criteria (16).

The erythroid response (HI-E) was classified as follows: a major response was defined for those patients with a pretreatment hemoglobin level less than 11 g/dL as greater than a 2 g/dL increase in their hemoglobin level; for the RBC transfusion-dependent patients, a major response was independence from RBC transfusions. A minor response was defined for those patients with a pretreatment hemoglobin level less than 11 g/dL as a 1 to 2 g/dL increase in their hemoglobin level; for the RBC transfusion-dependent patients, a major response was a 50% decrease in the transfusion requirement.

The platelet response (HI-P) was identified as follows: a major response for patients with a pretreatment platelet count of less than 100,000/ $\mu$ L was defined as an absolute increase of 30,000/ $\mu$ L or more; for the platelet transfusion-dependent patients, a major response was defined as stabilization of the platelet counts and independence from platelet transfusion. A minor response was defined for patients with a pretreatment platelet count of less than 100,000/ $\mu$ L as a 50% or more increase in the platelet count with a net increase greater

than 10,000/ $\mu$ L, but less than 30,000/ $\mu$ L.

The neutrophil response (HI-N) was classified as follows: a major response was defined for the patients with an absolute neutrophil count (ANC) less than 1,500/ $\mu$ L before therapy as at least a 100% increase or an absolute increase of more than 500/ $\mu$ L. A minor response was defined for patients with an ANC less than 1,500/ $\mu$ L before therapy as an ANC increase of at least 100%, but an absolute increase less than 500/ $\mu$ L.

To be considered as a major or minor improvement, the hematologic improvements must have lasted for at least 2 months in the absence of ongoing cytotoxic therapy.

### Cytogenetic studies

Karyotypic analysis using GTG banding was initially performed for every patient by using unstimulated 24 hr cultures and/or methotrexate-thymidine synchronized cultures.

### Statistical analysis

Paired t-tests were used for 2 sample comparisons of the continuous variables. The comparisons of the categorical vari-

**Table 1.** The patients' demographics and baseline characteristics (n=21)

Median age, yr (range)	60 (18-75)
Gender, n (%)	
Male	7 (33%)
Female	14 (67%)
FAB/WHO classification	
RA	5 (24%)
RCMD	10 (48%)
RARS	1 (5%)
RCMD/RS	1 (5%)
RAEB	1/2 (14%)
CMML	1 (5%)
MDS/MPD	
IPSS	
Low	1 (5%)
Intermediate-1	16 (76%)
Intermediate-2	2 (10%)
High	2 (10%)
Karyotype*	
Good	12 (57%)
Intermediate	8 (38%)
Poor	1 (5%)
Disease duration (months)	17.9 $\pm$ 38.2
ANC counts ( $\times 10^9/L$ )	1.22 $\pm$ 0.65
Hemoglobin levels (g/dL)	7.5 $\pm$ 1.6
Platelet counts ( $\times 10^9/L$ )	79.3 $\pm$ 88.7

\*Good, normal, -Y, del(5q), del(20q); Poor, complex ( $\geq 3$  abnormalities) or chromosome 7 abnormalities; Intermediate, other abnormalities.

RA, refractory anemia; RCMD, refractory cytopenia with multilineage dysplasia; RARS, refractory anemia with ringed sideroblasts; RCMD-RS, refractory cytopenia with multilineage dysplasia with ringed sideroblasts; CMML, chronic myelomonocytic leukemia; MDS/MPD, myelodysplastic/myeloproliferative disease; IPSS, international prognostic scoring system; ANC, absolute neutrophil count.

ables were performed by using  $\chi^2$ -tests or Fisher's exact tests as appropriate. All the tests were two-sided and the *p*-values less than 5% were considered statistically significant. The analyses were performed using SPSS for Windows version 12.0 (SPSS Inc., Chicago, IL, U.S.A.).

## RESULTS

### Patient and disease characteristics

Of the 25 patients enrolled in this study, 1 patient died of sepsis immediately after registration to this study, and 1 other patient was registered, but that patient could not keep taking the medication due to a concomitant herniated cervical disc that required an operation. Of the 23 patients who were evaluable for toxicity, 2 patients prematurely stopped their therapy because of intolerable nausea and epigastric sores, respectively.

Twenty-one patients completed at least a 12-week course of therapy and so they were evaluable for a response to treatment. The patients' demographics and baseline disease characteristics are summarized in Table 1.

Table 2. Hematologic improvement (HI) to the PCD treatment

Response	No. of patients (%)
Any response	11 (52%)
No response	10 (48%)
Erythroid response	7 (33%)
Major	4 (19%)
Minor	3 (14%)
No response	14 (67%)
Platelet response	5 (24%)
Major	3 (14%)
Minor	2 (10%)
No response	16 (76%)
Neutrophil response	6 (29%)
Major	6 (29%)
Minor	0 (0%)
No response	15 (71%)

### Hematologic improvement

The hematologic improvement (HI) is summarized in Table 2 and the individual patient data and their baseline characteristics are listed in Table 3. The median time to response varied depending upon the nature of the response: the median time to response was 4 weeks for HI-E (range; 2-8 weeks), 6 weeks for HI-P (range; 2-8 weeks), and 3 weeks for HI-N (range; 2-16 weeks). Fig. 1, 2, and 3 depicts the serial hemoglobin levels, the RBC requirements, the platelet counts and the neutrophil counts for the responding patients. With the exception of the patient 8, whose disease progressed on to acute myelogenous leukemia at 8.2 months after PCD therapy, the other 10 responding patients were still responding at the time of analysis. Therefore the median duration of response was not reached with a range of 3.6-20.9 months.

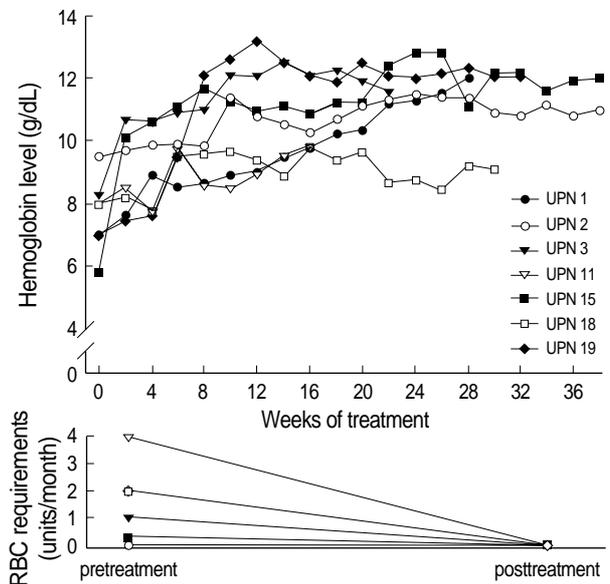


Fig. 1. Graphic presentation of the hemoglobin levels and RBC requirements for the patients with a RBC response after PCD treatment.

Table 3. The clinical and laboratory characteristics and the hematologic response in the responding patients (n=11)

Patient	Age (yr)	Sex	FAB/WHO	IPSS	Baseline			Hematologic improvement
					ANC ( $\times 10^9/L$ )	Hb (g/dL)	Plt ( $\times 10^9/L$ )	
1	64	M	CMML	INT-1	1.66	7.0	415	HI-E,major
2	19	F	RA/RCMD	INT-1	1.40	9.5	33	HI-E,minor; HI-P,minor; HI-N,major
3	33	F	RA/RCMD	INT-1	1.24	8.3	55	HI-E,major; HI-P,major; HI-N,major
6	73	F	RARS/RCMDRS	INT-1	1.30	8.2	102	HI-N,major
9	75	F	RA/RCMD	INT-1	0.65	5.3	21	HI-N,major
11	62	M	RA/RA	LOW	1.22	5.8	114	HI-E,major; HI-N,major
12	60	M	RA/RA	INT-1	0.89	11.4	14	HI-P,major
13	55	F	RAEB/RAEB-II	HIGH	0.38	9.5	88	HI-P,major
15	72	F	RARS/RARS	INT-1	2.25	8.0	152	HI-E,minor
18	62	F	RA/RA	INT-1	0.86	8.0	86	HI-E,minor; HI-P,minor; HI-N,major
19	58	F	RA/RCMD	INT-1	0.70	7.0	20	HI-E,major

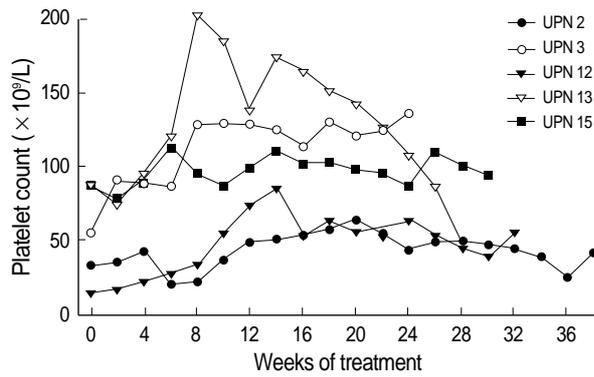


Fig. 2. Graphic presentation of the platelet levels for the patients with a platelet response after PCD treatment.

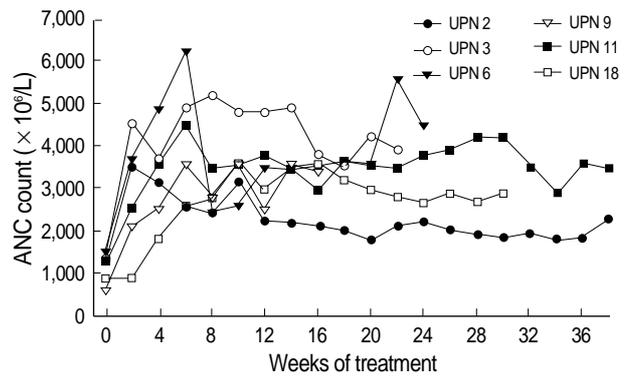


Fig. 3. Graphic presentation of the neutrophil levels for the patients with a neutrophil response after PCD treatment.

Table 4. Adverse effects of PCD therapy

Symptoms	NCI-CTC Grade: No. (%) of patients (n=23)	
	Grade 1	Grade 2
Nausea	0	3 (13)
Anorexia	0	1 (4)
Hypertension	0	0
Cushingoid appearance	NA	3 (13)
Hyperglycemia	3 (13)	0
Mood alteration	0	0
Epigastric sore	1 (4)	1 (4)

**Drug tolerance and toxicities**

Of the 23 patients who could be evaluated for drug toxicities, 39% of the patients experienced some type of toxicities, and 2 patients discontinued their therapy prematurely because of their intolerable epigastric sores and nausea, respectively. However there was no grade 3 or worse severe toxicities, and the treatment was relatively well tolerated (Table 4). Although we were concerned about infectious complications due to the long term steroid therapy, there was no significant incidence of infection.

**Comparison of the clinical characteristics of the responders and non-responders**

The platelet responders had a shorter disease duration ( $p=0.03$ ) and they had a tendency for higher pretreatment neutrophil, hemoglobin and platelet counts ( $p=0.19, 0.06$  and  $0.19$  respectively). The RBC responders had a trend of a better karyotype risk ( $p=0.17$ ), and the neutrophil responders had a tendency for a lower international prognostic scoring system (IPSS) ( $p=0.25$ ) (Table 5).

**DISCUSSION**

Since TNF- $\alpha$  may be the proximal inhibitor of a variety of

proinflammatory cytokines, those treatment strategies that have employed a number of therapeutic agents with anti-TNF properties such as amifostine, pentoxifylline-ciprofloxacin-dexamethasone, thalidomide, soluble tumor necrosis factor- $\alpha$  receptor and monoclonal anti-TNF antibody have been conducted with varying degree of success (17-24). Based on these previous results, we evaluated an experimental regimen that consisted of modified doses of pentoxifylline (P), ciprofloxacin (C) and dexamethasone (D) in an attempt to improve the toxicity profile and to maintain the treatment efficacy for myelodysplastic syndrome. The results of this trial are summarized as follows: Of the 21 evaluable patients, eleven patients (52%) showed an improvement of their cytopenia. 3 patients had a triple lineage response, 1 patient had a dual lineage response, and 7 patients had a single lineage response. No differences were noted for the response rates among the 3 lineages. There were no differences in the response rates between the FAB subtypes, but the responders had a shorter disease duration and a tendency for higher pretreatment neutrophil, hemoglobin and platelet counts, a better karyotype risk and a lower IPSS. These findings are similar to the results of the other anti-cytokine therapies (17, 23).

The mechanism of the treatment response is thought to involve the suppression of the proinflammatory cytokines such as TNF- $\alpha$ , with the consequent suppression of apoptosis in the hematopoietic cells, and there is a resultant regression of the MDS clones and stimulation of hematopoiesis in the normal cells (21). Yet in some studies that have used soluble TNF- $\alpha$ , the clinical response rate was low and there was no correlation between the level of TNF- $\alpha$  production and any of the clinical parameters or features of MDS (22). This result may suggest that the apoptotic pathways in MDS are redundant and they are mediated by many cytokines with overlapping specificities, or that the dosage, duration of therapy and frequency of administration may not have been optimal. More recently, one study has reported a 20-38% response rate when using an anti-TNF monoclonal antibody, Remicade (24).

Meanwhile, in addition to the standard chemotherapeutic

Table 5. Categorical and continuous variables in the responding and non-responding patients (n=21)

	RBC response			Platelet response			Neutrophil response			Any response		
	Yes	No	p	Yes	No	p	Yes	No	p	Yes	No	p
Gender												
Male	2	5	0.74	1	6	0.62	1	6	0.61	3	4	0.65
Female	5	9		4	10		5	9		8	6	
FAB												
RA	5	10	0.29	4	11	0.76	5	10	0.53	7	8	0.34
RARS	1	1		0	2		1	1		2	0	
RAEB	0	3		1	2		0	3		1	2	
CMML	1	0		0	1		0	1		1	0	
Karyotype												
Good	6	6	0.17 <sup>†</sup>	4	8	0.48	5	7	0.30	8	4	0.25 <sup>†</sup>
Intermediate	1	7		1	7		1	7		3	5	
Poor	0	1		0	1		0	1		0	1	
Bone marrow blast (%)												
<5%	6	10	0.57	4	12	0.43	6	10	0.27	9	7	0.77
5-9%	1	2		0	3		0	3		1	2	
10-19%	0	2		1	1		0	2		1	1	
Cytopenia lineage												
0-1	3	2	0.28	0	5	0.28	1	4	1.0	3	2	1.0
1-2	4	12		5	11		5	11		8	8	
IPSS												
Low	1	0	0.25 <sup>†</sup>	0	1	0.64	1	0	0.25 <sup>†</sup>	1	0	0.36
Intermediate-I	6	10		4	12		5	11		9	7	
Intermediate-II	0	2		0	2		0	2		0	2	
High	0	2		1	1		0	2		1	1	
ANC (× 10 <sup>9</sup> /L)	1.5±0.6	1.1±0.7	0.19	0.9±0.4	1.3±0.7	0.30	1.1±0.6	1.2±0.7	0.88	1.2±0.6	1.2±7.1	0.94
Hemoglobin (g/dL)	7.7±1.2	7.5±1.8	0.65	9.3±1.3	6.9±1.2	0.06	7.5±1.6	7.5±1.7	0.79	8.0±1.7	7.0±1.4	0.17
Platelet (× 10 <sup>9</sup> /L)	125±35	56±44	0.19	55±32	87±99	0.65	68±37	83±103	0.79	100±113	57±45	0.46
Ds. Duration (months)	15±36	20±41	0.21	0.9±1.3	23.5±42.5	0.03*	26±56	15±31	1.0	23±48	12±26	0.53

\*, Statistically significant; †, Marginally significant; DS, disease.

drugs, a variety of novel agents like decitabine, Mylotarg, farnesyl transferase inhibitors and arsenic have been employed in attempt to eliminate the MDS clones. While each strategy has produced important clinical responses for some of the patient subset, none of these strategies is of universal benefit for all MDS patients (25-27). The nucleoside analogues 5-azacytidine have activity both as a DNA methyltransferase inhibitor and as a cytotoxic agent, and the patients treated with this drug have shown a 60% response rate and a survival benefit over the best supportive care for patients with MDS (28).

There are several limitations to our study. First of all, the use of multiple agents precluded a precise dissection of the mechanism of response, and another limitation was that the TNF- $\alpha$  concentrations were not measured. Thus, whether the hematologic improvements we observed were a direct result of the anti-TNF effect of the PCD therapy remains uncertain. Still another limitation was that the clinical benefit and the improvement of the quality of life after treatment were not assessed.

Since the therapy was well tolerated, it is worthwhile to consider a combination therapy with an agent that directly affects the MDS cell clones such as topotecan, arsenic trioxide,

farnesyl-transferase inhibitor, 5-azacytidine or decitabine.

In conclusion, these preliminary results indicate that anti-cytokine therapy with PCD is well tolerated for patients with MDS. Although this approach may not prove to be wholly curative in the long run, it provides substantial palliative support for at least some of the MDS patients.

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