Treatment of myelodysplastic syndromes with human granulocytic-macrophage colony stimulating factor (GM-CSF) or GM-CSF combined with low-dose cytosine arabinoside

Economopoulos T, Papageorgiou E, Stathakis N, Asprou N, Karmas P, Dervenoulas J, Bouronikou H, Chalevelakis G, Raptis S. Treatment of myelodysplastic syndromes with human granulocytic-macrophage colony stimulating factor (GM-CSF) or GM-CSF combined with low-dose cytosine arabinoside.
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Abstract: In a phase II study, 21 patients with MDS (RAEB, RAEBt, CMML and RA and RAS with severe cytopenia) were randomized to be treated with 3 courses of GM-CSF (3 μg/kg/day s.c.) alone (11 patients) or in combination with AraC (20 mg/m^2/d s.c.) (10 patients) for 14-d periods, interrupted by 14-d rest periods. Eight patients discontinued the treatment. In the GM-CSF group a marked increase in WBC and neutrophil counts during each course of treatment administration were seen in most patients. Platelet counts decreased in 14 of 24 courses of treatment in the GM-CSF plus AraC group but in none of the GM-CSF group. Although the changes in the circulating blood cells were transient and the counts tended to return to the pretreatment levels during the rest periods, some more durable effects were seen. In 3/6 patients of the GM-CSF group who completed the designed treatment, both WBC and neutrophils remained elevated above the pretreatment levels throughout the 3-month period of treatment, while in one of them thrombocytopenia improved considerably. In the GM-CSF plus AraC group, 4 out of the 7 patients who completed the treatment showed an improvement of neutropenia as well as anaemia. In these 4 patients the BM percentage of blasts was also decreased. In conclusion, the results of this study indicate that GM-CSF given intermittently improves leukopenia in some patients with MDS. In addition, the administration of GM-CSF seems to prevent granulocytopenia of concurrent AraC treatment and may be of benefit in the treatment of these diseases.

T. Economopoulos, E. Papageorgiou, N. Stathakis, N. Asprou, P. Karmas, J. Dervenoulas, H. Bouronikou, G. Chalevelakis and S. Raptis

Second Department of Internal Medicine, Propaedeutic, Athens University, Evangelismos Hospital, Athens, Greece.

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Correspondence: Dr. T. Economopoulos, Second Department of Internal Medicine, Evangelismos Hospital, Athens 106 76, Greece

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Myelodysplastic syndromes (MDS) are a heterogenous group of disorders characterized by refractory cytopenias and qualitative and quantitative abnormalities of bone marrow (BM) affecting one or more cell lines. While the progress into acute nonlymphoblastic leukaemia (ANLL) is high in these disorders, a comparable proportion of patients die of infection or bleeding (1, 2). The only treatment so far that has produced remission of some duration in MDS is low-dose cytosine arabinoside (AraC). However considerable myelotoxicity is observed during this treatment. Colony stimulating factors (CSF) are glycoproteins controlling the proliferation and differentiation of haematopoietic progenitors as well as a series of end cell functions. Since infections, difficult to manage because of neutropenia and/or neutrophil dysfunction, are a leading cause of death in MDS, both granulocyte-macrophage colony stimulating factor (GM-CSF) and granulocyte colony stimulating factor (G-CSF) were studied in the treatment of these disorders (3–6). In addition GM-CSF combined with low-dose AraC has been used (7, 8) in the treatment of MDS. This combination may ameliorate the degree of cytopenias due to cytotoxic effect of AraC or it may induce proliferation in the leukaemic cells, making them

more sensitive to the cytotoxic action of low-dose AraC.

The object of the present randomized study was to investigate the efficacy of the GM-CSF given intermittently in the treatment of MDS alone or in combination with low-dose AraC.

Material and methods

Patients

In the study, patients with refractory anaemia with excess of blasts (RAEB), refractory anaemia with excess of blasts in transformation (RAEBt) and chronic myelomonocytic leukaemia (CMML) were enrolled. Patients with refractory anaemia (RA) or refractory anaemia with ring sideroblasts (RAS) were enrolled only in the case of increased transfusion needs or severe cytopenia. All patients were classified according to FAB criteria for MDS (9).

Patients were excluded if they had a serum creatinine greater than 180 μmol/l, Karnofsky score $<50\%$, or hepatocellular enzyme levels $>2.5\times$ of normal (3). In addition, patients were excluded if they had received chemotherapy within the previous 6 weeks. Patients with secondary MDS were included in the trial.

The patients had not been treated before the entry into the study (apart from blood transfusion) with the exception of 1 patient who had been given low-dose AraC 6 months before the start of the trial.

Written informed consent was required from all patients before the start of therapy. The study was submitted and approved by the local ethics committee.

Study design

The study was that of a randomized phase II trial: In arm 1 GM-CSF (Shering-Plough, Sandoz) 3 μg/kg/d was given subcutaneously (s.c.) for 14 d. In arm 2 GM-CSF was administered as above plus low-dose AraC (20 mg/m^2/d s.c.) for 14 d. A 14-d rest period was followed in both arms. The protocol was designed to give 3 courses in each arm.

Patients monitoring

Patients were monitored daily and all constitutional symptoms were recorded. Complete blood counts, including differential and reticulocyte counts were performed before treatment and then every 48 h. During the rest period, full blood counts and differential counts were performed every 4 d. Serum chemistry and leukocyte alkaline phosphatase score (LAP) were performed before and every 4 d during the treatment period. BM aspiration and biopsy were undertaken before the start of treatment and were repeated regularly before each course of treatment.

Results

From November 1990 to December 1991, 21 cases were randomised (11 in the GM-CSF group and 10 in the GM-CSF plus AraC group). The characteristics of the patients in each group are presented in Table 1. There were 20 patients with primary and 1 with secondary MDS. The latter was a case of RAEBt developed after treatment for Hodgkin's disease and was randomised to the GM-CSF group.

Treatment with GM-CSF

Six of the 11 patients entered completed 3 courses of treatment, 4 patients completed at least 1 course while 1 patient discontinued the treatment on the 7th d of the 1st course, because of generalized rash. The last patient was considered as ineligible on evaluation. The reasons for GM-CSF withdrawal are shown in Table 2.

During the first cycle of treatment, 9 out of 10 patients responded with significant 1.7-fold to 6.5-fold) increases in WBC counts. Neutrophil counts were also increased (2.4-fold to 12.6-fold) in 8 out of 10 patients. Both WBC and neutrophils were increased after 48 h from the start of treatment and remained elevated throughout the 14-d period of GM-CSF administration.

Among the 6 patients who completed the designed 3 courses of therapy, 1 did not respond at all, 2 responded in each cycle but the counts returned to pretreatment levels during the rest intervals, and in the remaining 3 patients the counts of both WBC and neutrophils remained elevated above the baseline pretreatment levels throughout the 3 months period of treatment (Figs. 1,2).

In addition to neutrophils, significant (>2-fold) increases were seen in the absolute monocyte count (12/22 courses), eosinophils (16/22 courses) and peripheral blood blasts (9/22 courses). However, during the rest periods the above increased counts returned to pretreatment levels. Only in 1 case did marked eosinophilia (7.5×10^9/l) remain during the rest period and thereafter. In 1 case the increase of peripheral blood blasts persisted and BM aspiration showed progression to ANLL.

No consistent changes in lymphocyte and reticulocyte counts and no variations in the LAP score were noted. A gradual increase in the platelet count, during the 3-month period of treatment, was seen in 1 out of 6 patients who completed the study (from 30×10^9/l to 120×10^9/l). BM aspirations showed that the cellularity and the M:E ratio were increased in all cases. Dysplastic features of the marrow cells

Table 1. Patient characteristics before treatment

Patient No	Sex/ Age	FAB Subtype	Peripheral blood PCV (%)	WBC ($\times 10^9$/l)	Neutrophils ($\times 10^9$/l)	Platelets ($\times 10^9$/l)	Bone Marrow Blasts (%)	Time from diagnosis (months)
Patients treated with GM-CSF								
1	M/60	RAEBt	24	3.2	1.10	25	22	6
2	M/67	RA	21	8.1	5.80	260	0	15
3	F/73	RAEB	23	6.5	4.80	8	12	7
4	M/65	RA	20	6.5	3.64	80	3	12
5	F/75	RA	33	1.0	0.26	140	2	18
6	F/62	RAEB	26	2.0	0.14	30	15	3
7	M/64	CMML	20	3.5	1.40	19	7	10
8	M/72	RAEB	20	1.1	0.30	80	10	5
9	F/74	RAEB	33	2.5	0.22	25	11	12
10	M/80	RAEB	28	1.1	0.12	12	10	11
11	M/61	RAEB	26	3.1	1.40	30	7	5
Patients treated with GM-CSF+AraC								
1	F/63	RA	22	4.1	0.40	10	2	9
2	M/69	RAEB	19	3.5	0.63	110	10	2
3	F/72	CMML	27	6.5	1.70	150	15	18
4	M/70	RAEBt	25	3.6	1.40	105	23	3
5	F/73	RAEB	28	14.0	9.50	45	15	24
6	F/74	RAEB	25	6.5	3.90	210	18	4
7	M/60	CMML	19	20.5	14.40	400	20	8
8	F/75	RAEBt	23	7.0	3.60	65	28	4
9	M/65	RAEB	18	4.9	1.60	40	14	12
10	F/71	RAEB	20	5.0	1.65	55	15	9

Table 2. Causes of withdrawal and final response to GM-CSF or GM-CSF+AraC treatment

Patient No	Cause of withdrawal	Persistent response throughout the study	Alive at the end of the trial
GM-CSF Group			
* 1	ANLL	–	No
2	–	No	Yes
* 3	Bleeding	–	No
4	–	No	Yes
5	–	No	Yes
6	–	Yes	Yes
* 7	Persistent eosinophilia ($>4.5\times10^9$/l)	–	No
8	–	Yes	Yes
** 9	Generalised rash	–	Yes
* 10	Intracranial bleeding	–	No
11	–	Yes	Yes
GM-CSF+AraC Group			
* 1	Bleeding	–	No
2	–	Yes	Yes
3	–	Yes	Yes
4	–	No	Yes
* 5	Refuse	–	Yes
6	–	Yes	Yes
7	–	No	Yes
8	–	Yes	Yes
* 9	Septicæmia	–	No
10	–	No	Yes

* Patients completed only one course. ** Patient discontinued treatment on the 7th day.

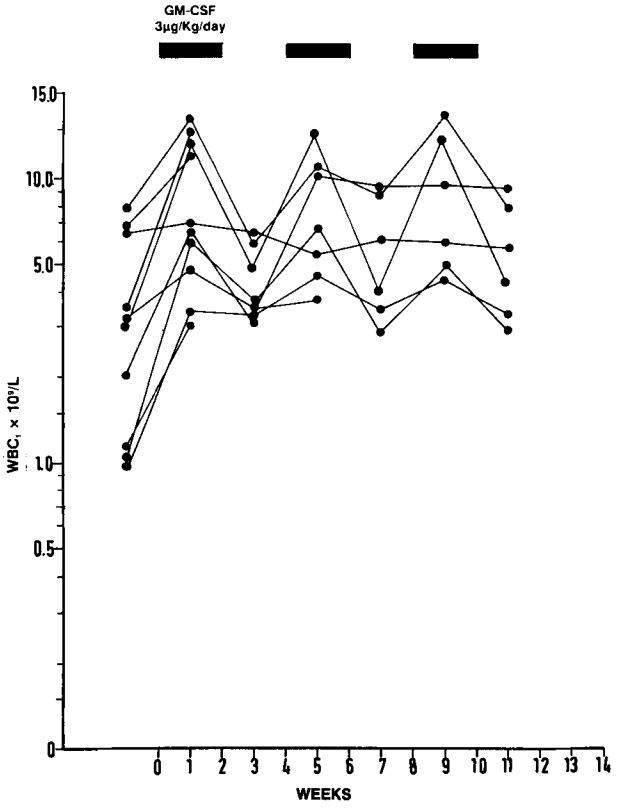

Fig. 1. Median WBC counts during the three 14-d courses of GM-CSF administration and 14-d rest intervals.

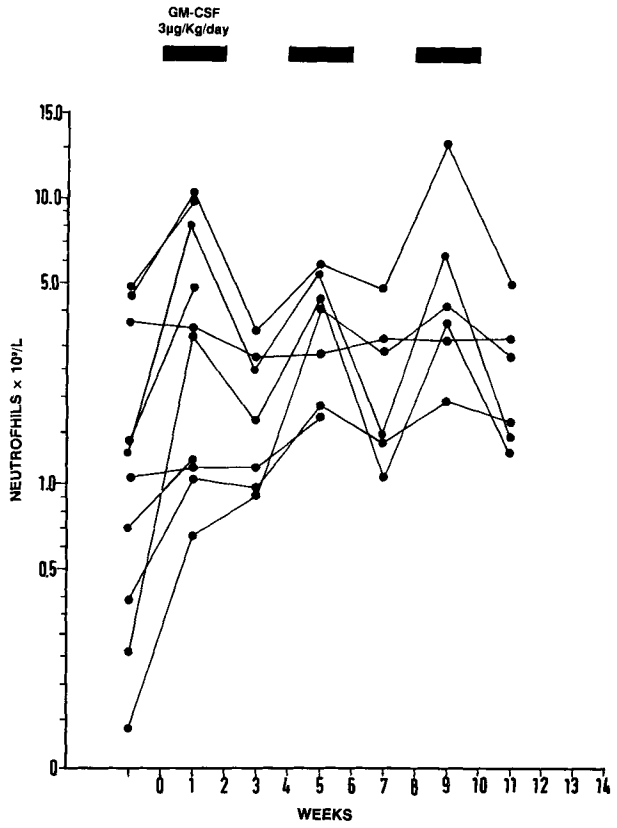

Fig. 2. Median neutrophil counts during the three 14-d courses of GM-CSF administration and the 14-d rest periods.

remained essentially unchanged. No substantial changes in the blast percentage of the BM were noted, apart from the 1 patient who progressed to ANLL.

Treatment with GM-CSF plus AraC

Three out of 10 patients who entered the study did not complete the designed 3 courses of treatment (Table 2). Four out of the 7 patients who received the 3 courses had a partial, short-lived (3–4 months) response. In these patients the percentage of BM blasts became lower with an improvement of the anaemia (3/4 patients) and neutropenia (4/4 patients).

In none of the patients did the WBC and neutrophils decrease during the administration of the combined treatment. On the contrary, considerable increases (>2-fold) of both were noted in 15/24 courses of treatment. Increase in monocytes (11/24 courses), eosinophils (12/24 courses) and peripheral blasts (12/24 courses) were seen too. These changes in WBC neutrophils, monocytes and eosinophil counts were transient and returned to lower levers during the 14-d rest period, although remaining higher than baseline pretreated levels in the responding patients. The peripheral blast counts also returned to pretreatment levels during the rest periods, while in the 4 responding patients they gradually disappeared. The platelet counts decreased significantly during the drug administration in 14 out of the 24 courses of treatment, but they were gradually restored to pretreatment levels during the rest periods.

Table 3. Side effects

1. Related to treatment	
Generalised skin eruption	1
Injection skin reaction	6
Mild fever	4
Bone pains	6
Persistent eosinophilia	1
2. Probably not related to treatment	
Progression to ANLL	1
Major bleeding	3

The persistent response throughout the study and the outcome at the end of the trial of both groups, are presented in Table 2.

Adverse effects

In general the treatment with GM-CSF in the dose of 3 µg/kg/d s.c. was well tolerated by the elderly patients with MDS. The side effects are shown in Table 3. Injection skin reactions, mild bone pains and mild fever were the usual adverse clinical effects. In 1 case only, generalised skin eruption developed on the 7th d of the 1st cycle and the treatment was discontinued for that reason. As already mentioned, 1 patient in the GM-CSF group progressed to ANLL and 3 patients (2 in the GM-CSF and 1 in the GM-CSF + AraC group) developed major bleeding. The relation of these events to treatment is uncertain.

Discussion

Most patients with MDS are elderly with other medical problems which complicate their management. In a vast majority of them supportive treatment with red blood cells and platelet transfusions, as well as the treatment of infections, have been the mainstay of therapy. Many other therapeutic modalities have been reported, such as pyridoxine, androgens, Vit D3, retinoid acid and danazol without substantial effect on survival (10–12). Low dose AraC, given s.c., has proved to be one of the most effective modalities in the treatment of MDS, with a response rate from 10–60% (13). Recently, haemopoietic growth factors, especially GM-CSF and G-CSF, have been used in the treatment of MDS (3–6). The results of these studies showed that the treatment is tolerated reasonably well and is effective in improving neutropenia, transfusion-dependent anaemia and

marrow myeloid differentiation. Following the GM-CSF treatment in some patients an increase of BM blasts was observed which returned to the baseline levels if the treatment was discontinued.

The results of Hoelzer et al. (7) with the combination of GM-CSF and low-dose AraC for 14 d showed that this approach is feasible and appears to control the leukaemic population better than GM-CSF alone. In the large EORTC leukaemia group study (8) GM-CSF and low-dose AraC was given to the high-risk MDS patients (RAEB with blasts $> 10\%$ and RAEBt). The results of this trial showed a high response rate which is relatively durable as compared to other treatments of this disease.

In the present randomized study GM-CSF was given alone or in combination with low-dose AraC. The two modalities of treatment performed in an unselected population of MDS stressed the difficulties of treating such patients, since many entered patients did not complete the designed courses of treatment mainly for reasons unrelated to the therapeutic agents. However, in the GM-CSF arm, a definite improvement of neutropenia, which in some patients was durable, was found. The increase of monocytes, eosinophils and blasts soon returned to pretreatment levels. In only 1 case was frankly leukaemic progression observed. Although this event may represent the natural history of the disease, it is difficult to ignore that the fact that the patient had been treated with GM-CSF. In another patient, persistent eosinophilia was observed. In a recent report (6) it was suggested that patients with MDS and profound eosinophilia after GM-CSF administration may constitute a distinct subset with unique prognostic features. Indeed our patient with this finding deteriorated soon and died of infection.

After the administration of the first course of GM-CSF, 2 patients developed major bleeding events leading to death in 1 of them. Although a thrombocytopenic effect of GM-CSF has been suggested (6), this relation in our patients is rather improbable. Both patients were extremely thrombocytopenic from the start of the treatment. In addition, the degree of thrombocytopenia had not deteriorated during or shortly after the end of the 1st cycle.

In the group of GM-CSF plus AraC the treatment was well tolerated and no neutropenia was seen during the treatment. However, the majority of patients developed thrombocytopenia. The overall efficacy of this combination is not clear yet. In the present study some patients showed a short-lived improvement in terms of neutropenia, transfusion needs and BM blasts.

From the results of the present study it is concluded that the treatment with GM-CSF in MDS clearly improves neutropenia. The combination of GM-CSF and AraC is also effective. However, the ideal use of this combination remains to be clarified.

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