Combined therapy with amifostine plus erythropoietin for the treatment of myelodysplastic syndromes

Twelve patients with myelodysplasia were treated with amifostine plus recombinant human erythropoietin (rHuEpo) for 6 weeks. A complete erythroid response was obtained in 2/12 (16.6%) and a partial response in 4/12 (33.3%). Two of 8 patients with a platelet count ≤100×10⁹/L had a complete response, as did 3/9 with a neutrophil count <1.5×10⁹/L. Compared to rHuEpo or amifostine used as single agents, their combination did not offer substantial advantages.

The treatment of cytopenias accompanying myelodysplastic syndromes (MDS) is often deceptive. Nevertheless recombinant human erythropoietin (rHuEpo) ameliorates anemia in about 20-30% of MDS, and higher rates of response are obtainable in patients with low-risk MDS, low baseline serum Epo levels and low or absent transfusion needs.[1,2,3] The aminothiol prodrug amifostine stimulates normal and myelodysplastic hematopoiesis[4,5] and improves cytopenia, especially neutropenia, in selected groups of MDS patients.[5,6] In a previous work we speculated that in MDS patients rHuEpo stimulates total erythropoiesis, while amifostine reduces ineffective erythropoiesis.[7] In this study we treated 12 patients (6 males, 6 females) with MDS with amifostine (200 mg/m² three times a week, i.v.) in combination with rHuEpo (150 U/kg every other day s.c.) for 6 weeks. According to the international prognostic scoring index (IPSS)[8] patients were classified as follows: 1 Int-1 refractory anemia (RA), according to FAB,[9] 1 Int-2 (RA), 9 High risk (2 RA, 5 RA with excess blasts (RAEB) with blasts < 10% and 2 RAEB with blasts >10%). One patient (RAEB with blasts <10%) was not classified according to the IPSS because the karyotype was not available. Eleven out of 12 were transfusion-dependent and resistant to other therapies; 7/12 had received rHuEpo as a single agent. Neutropenia (<1.5×10⁹/L) was present in 9/12 and thrombocytopenia (<100×10⁹/L) in 8/12. Cytogenetic aberrations were present in 7/11 cases. The characteristics of the patients are detailed in Table 1. Patients were checked weekly and final results were evaluated at day 60. Response to therapy was evaluated as hematologic improvement, as recently proposed by Cheson *et al.*[10]

Transfusion support was abolished (complete response-CR) in 2/12 patients (16.6%), and in 4 more cases (33.3%) a ≥ 50% reduction (partial response-PR) was observed. Three out of 9 (33.3%) with baseline levels <1.5×10⁹/L obtained an absolute increase of at least> 0.5×10⁹/L(CR). A platelet increase of at least 30×10⁹/L (CR) was reached in 2/8 (25%) patients with baseline levels <100×10⁹/L. Side effects were mild and included general malaise (1), fever (2; in 1 case the treatment was stopped), vomiting (1) and skin infection (1). Two out of 6 erythroid responders were still in remission 8 months and 3 years after completion of therapy. Six months after completion of therapy the platelet response had been lost in all cases and only one patient maintained a neutrophil response. Of four patients who died after completion of therapy, 2 developed AML within 6 months and 2 died of infections.

Table. 1. Patients' characteristics.

No. of enrolled patients	12
Male/Female	6/6
Mean age, years (range)	65.6 (48-80)
Median age, years	65.5
Diagnosed more than 6 months before therapy	11/12
Pre-treated patients	11/12
pre-treated with rHuEpo	7/12
Pre-transfused patients	12/12
IPSS classification	
Intermediate-2 risk	2
High risk	9
non classified (karyotype not available)	1
FAB classification	
Refractory anemia	4
Refractory anemia with excess of blasts ≤10%	6
Refractory anemia with excess of blasts >10%	2
Cytogenetic aberrations	
Refractory anemia	+8
Refractory anemia	5q-
Refractory anemia with excess of blasts ≤10%	46,XY/48,XY, der(14) +marker
Refractory anemia with excess of blasts ≤10%	46,XY/45,XY, -7, +marker
Refractory anemia with excess of blasts ≤10%	46,XY/45,XY, -7, +marker
Refractory anemia with excess of blasts ≤10%	del6q
Refractory anemia with excess of blasts >10%	del1

Table 2. Individual response to treatment.

Id.	*Sex*	*Age (years)*	*Diagnosis FAB*	*IPSS*	*Hemoglobin (g/dL) day 0*	*day 60*	*Neutrophils (×10⁹/L) day 0*	*day 60*	*Platelets (×10⁹/L) day 0*	*day 60*	*Red cells units (per month) before*	*after*
1	F	79	RA	H	7	8.2	0.76	5.04	113	154	4	3
2	M	73	RA	Int[1]	9.1	8.4	4.30	3.76	370	434	2	<1
3	F	52	RAEB ≤10%	H	7.8	6.8	0.47	0.06	3	8	3	0
4	M	62	RA	H	9	10.4	0.35	1.42	211	474	6	6
5	M	60	RAEB >10%	H	7.8	8.6	0.31	0.01	9	10	4	0
6	F	69	RAEB >10%	H	7.9	7.2	0.81	0.71	28	40	7	8
7	M	70	RAEB ≤10%	H	9.1	7.5	4.57	3.68	13	8	0	0
8	F	80	RAEB ≤10%	–	8.3	8.5	0.76	0.80	243	203	2	<1
9	M	61	RAEB ≤10%	H	7.5	8	0.21	0.72	8	53	4	4
10	M	57	RAEB ≤10%	H	7	7	0.56	0.88	15	50	4	2
11	F	48	RA	Int[2]	9	9	2.32	2.40	15	20	3	2
12	F	76	RAEB ≤10%	H	7.4	8	0.51	0.24	34	14	2	1

MDS are a group of disorders whose heterogeneity is reflected by the variety of bone marrow cytologic alterations, cytogenetic aberrations and clinical outcome. The response rate to treatment is generally low and predicting factors very difficult to establish, but about 50% of patients presenting with a diagnosis of RA, transfusion independence and a low baseline serum Epo may have a complete or partial response to rHuEpo.[1] The studies published so far are difficult to compare because of the different sizes of patient populations and the heterogeneous response criteria adopted. In the present study we evaluated the efficacy of the combination of rHuEpo-amifostine according to the response criteria proposed by Cheson *et al.*,[10] who recently approached the issue of standardization of such criteria. The results indicate that this combination does not offer a substantial advantage compared to each drug used as a single agent.[5,6] Adopting the same response criteria as those in our previous study on amifostine alone in MDS,[6] the number of erythroid and neutrophil responses was comparable, while platelet response was worse, possibly because of the specific erythroid stimulus of erythropoietin. Our data are in agreement with those reported by Tefferi *et al.*[7] who also concluded that the combination of amifostine plus rHuEpo does not offer substantial advantages in the treatment of MDS.

The response rate is influenced by the criteria selected, and we suggest that these must be stringently defined in the evaluation of results of clinical trials in MDS. Two major points might have negatively affected the results in our study: a) alternate day instead of daily rHuEpo administration used in a previous work;[1] b) selection of a group of patients with negative predictive factors, as indicated by their need of transfusion support prior to therapy, the resistance to previous treatments and their inclusion in IPSS high risk (Int-2 and High) classes, despite the fact that 10/12 were FAB low risk. In this respect it seems that a multifactorial classification of patients (IPSS) predicts the outcome of therapy in MDS better.

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Hemoglobin F synthesis is not restricted to fetal erythropoietic organs during extramedullary hematopoiesis

We investigated whether the anatomic distribution of hematopoietic cells determines the type of hemoglobin produced in patients with extramedullary hematopoiesis (EMH). Fetal hemoglobin (HbF) production is not restricted to fetal erythropoietic organs during EMH. A shift of erythropoiesis to fetal hematopoietic organs in EMH does not necessarily induce HbF synthesis in adulthood.

In normal adults, fetal hemoglobin (HbF) production is minimal and HbF is restricted to a specific population referred to as F-cells.[1,2] Extramedullary hematopoiesis (EMH) is characterized by the appearance of hematopoietic elements at sites in addition to bone marrow, particularly sites of hematopoiesis in fetal life such as liver and spleen.[3] Shifts in sites of erythropoiesis during development coincide with changes in the hemoglobin composition of red cells.[4] We investigated whether HbF production during EMH is restricted to the erythropoietic organs that were active in fetal life, and whether erythroid cells in organs corresponding to fetal hematopoietic environments necessarily express HbF.

From autopsy cases, 31 patients were selected as having splenic (n = 20) or intrahepatic (n = 11) EMH. Formalin-fixed paraffin blocks (n = 31) from bone marrow clot specimens, 20 from spleen, and 11 from liver were investigated in these patients; diagnoses included acute leukemia (n = 8), carcinoma (n = 12) or lymphoma (n = 6) involving bone marrow, and hemolytic anemia (n = 5). As controls, we examined 12 spleens, 10 livers, and 15 bone marrows obtained at autopsy from individuals who had not had hematologic diseases. Erythropoiesis was immunohistochemically assessed using anti-glycophorin C (GPC) antibody (Dako, Glostrup, Denmark), anti-hemoglobin A (HbA) antibody (Calbiochem, La Jolla, CA, USA), and anti-HbF