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Thalidomide abolishes transfusion-dependence in selected patients with myelodysplastic syndromes

Among 25 transfusion-dependent patients with myelodysplastic syndromes (MDS) receiving up to 300 mg/d thalidomide p.o., 5 became transfusion-free within 4-9 weeks and for 6 to +24 months. Responders had a recent diagnosis, normal karyotype, no excess of marrow blasts and were younger than non-responders. Thalidomide may be effective for treating anemia in selected MDS patients.

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The potential efficacy of thalidomide in myelodysplastic syndromes (MDS), although recently reported,[1-5] has not been extensively investigated so far. We conducted a pilot study by administering thalidomide to 25 patients with MDS (14 males, 11 females, mean age 65 years, range 48-85), previously unresponsive to treatments including recombinant erythropoietin, alone or in association with other growth factors or amifostine.[6-8] All patients were heavily transfusion-dependent (Hb < 8 g/dL), requiring 4-8 units of packed red-cell transfusions every month. According to the WHO classification, there were 12 cases of refractory anemia (9 with trilineage myelodysplasia), 8 of refractory anemia with blast excess (4 < 10%, 4 > 10%), and 5 cases of refractory anemia with ring sideroblasts (1 with trilineage myelodysplasia). The International Prognostic System Score was low in 9 patients, intermediate 1-2 in 13 and high in 3 patients. Thalidomide was given at the dose of 100 mg/d *per os*, at bedtime, for 1 week (to test tolerance) and then the dose was progressively increased every 4 weeks. No patient tolerated more than 300 mg/d.

Table 1. Characteristics of transfusion-dependent MDS patients who responded to thalidomide.

	1	*2*	*3*	*4*	*5*
Age	62	69	48	64	51
Sex	M	M	F	M	F
IPSS	int-low	low	int-low	low	low
WHO	RA	RARS	RA	RA with fibrosis	RA
Time from diagnosis (months)	9	11	3	8	11
Karyotype	46XY	46XY	46XX	46XY	46XX
Marrow blasts (%)	< 5	< 5	< 5	< 5	< 5
Transfusions/Month	3	4	6	4	4
EPO (miu/L) pre/post	673/105	286/424	257/3900	155/667	303/612
WBC (×10⁹/L) pre/post	1.9/2.3	9.3/4.2	2.9/2.1	6.7/8.3	3.5/3.2
PLT (×10⁹/L) pre/post	39/26	236/108	42/32	319/632	107/122
Hb (g/dL) pre/post	7.8/11.3	7.3/9.3	7.5/10	6.6/9.3	7.1/11.4
Hb F (%) pre/post	1.1/n.d.	1/ 4.1	*13/48.3	0/0.5	1/5.1
Dose of thalidomide (mg)	200	200	250	200	300
Duration of response (months)	+24	6	12	+5	+19

**Concomitant thalassemic syndrome caused by a β°39 point mutation.*

Ten patients (eight more than 75 years old), stopped thalidomide early because of relevant side effects (fatigue, somnolence, constipation, numbess and tingling in fingers and/or toes, fluid retention, renal failure, skin rash). Ten additional patients stopped the treatment after 2 months because of inefficacy. The remaining 5 patients became completely transfusion-free within 4-9 weeks (Table 1). Due to a slight worsening of peripheral white blood cell and platelet counts, thalidomide was stopped in two of the responders. Since the hemoglobin value rapidly dropped to less than 8 g/dL, the drug was re-started and both patients returned to being transfusion-free (Figure 1). No further significant cytopenias were recorded in non-responders. Erythroid responses are currently maintained in 3 patients (Table 1). Two of them are still receiving thalidomide therapy, with adjusted doses of 50 to 100 mg/d. The patient who maintains his erythroid response after 2 years received the drug for only 12 months because of the subsequent occurrence of gastric carcinoma.

Few studies have investigated the therapeutic role of thalidomide in MDS so far, and all of them agree that thalidomide may significantly increase Hb levels in about one third of treated patients.[1-5] In one study thalidomide also improved neutropenia and thrombocytopenia in some patients.[5] Our findings confirm that thalidomide, at a relatively low dose, may be a very effective therapy for treating anemia in a selected group of

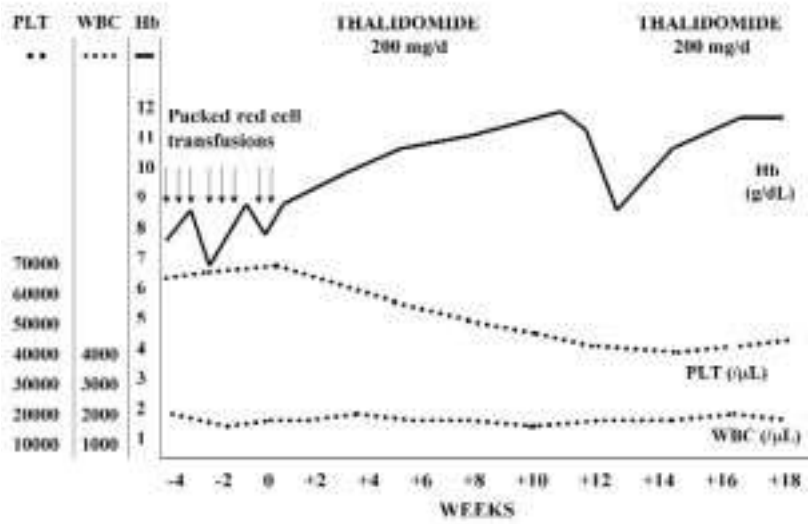

Figure 1. Modifications of hemoglobin in a representative 62-year old male patient with refractory anemia treated with thalidomide. Note the decrease of hemoglobin after interruption of thalidomide therapy and the new response when the drug was given again.

transfusion-dependent, younger MDS patients with a recent diagnosis, normal karyotype and no excess of marrow blasts. In fact, despite the overall response rate being 20% on an intention-to-treat analysis, 5 out of 7 (71.4%) patients with these characteristics responded to the treatment in our series. It is also interesting to note that we obtained erythroid responses in 4 transfusion-dependent subjects with initial serum levels of endogenous erythropoietin > 200 miu/L, a subset of MDS patients with a very low chance of responding to treatment with recombinant erythropoietin, alone or in combination with G-CSF.[9,10] Elderly patients, however, tolerated the drug poorly, despite the dose used in our study being lower than those employed in other trials.

The mechanism (s) by which thalidomide acts in MDS remains unclear. Zorat *et al.*[5] extensively investigated this aspect, examining marrow apoptosis and angiogenesis in 30 MDS patients treated with thalidomide, reaching heterogeneous results and no firm conclusion. Bertolini *et al.*[3] have reported that plasma levels of angiogenic growth factors and the number of activated endothelial cells in bone marrow significantly decrease in MDS patients responding to thalidomide. In contrast, preliminary data from our[4] and other laboratories (*Dr. A. List, personal communication*) indicate that circulating molecules with angiogenic activity, such as vascular endothelial growth factor, hepatocyte growth factor and basic fibroblast growth factor, often appear to be increased, rather than decreased, in MDS patients treated with thalidomide. Furthermore, microvessel density on trephine biopsy also increased in two of our responders under thalidomide therapy (*unpublished data*). These observations do not support a possible anti- angiogenic effect of thalidomide in MDS. Another interesting finding that emerged from our study was the progressive increase of HbF and serum erythropoietin values during thalidomide treatment in some of the responders (Table 1). Whether these aspects may really contribute to the improvement of anemia in MDS patients receiving thalidomide warrants further and larger investigations.

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Morphologic characterization of acute myeloid leukemia with cytogenetic or molecular evidence of t(8;21), t(15;17), inv(16) and 11q23 abnormalities

We reviewed the morphology of 110 acute myeloid leukemias (AML) with recurrent cytogenetic/molecular translocations. The t(8;21) cases had some pseudolymphoid blasts and severe dysgranulopoiesis. Acute promyelocytic leukemia showed atypical promyelocytes in peripheral blood and maturation of abnormal granulocytes. The atypical eosinophils were exclusive to inv(16). The cases with 11q23-abnormalities had blasts of monocytic appearance.

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The WHO classification[1] has divided AML into four categories, one of which includes the well established types of AML with recurrent cytogenetic/molecular translocations: AML with t(8;21), AML with t(15;17) and variants, AML with inv(16) and variants, and AML with 11q23 abnormalities. These AML have some degree of correlation with morphology, together with prognostic influence.[2-8] We reviewed the morphologic and laboratory characteristics of 110 cases of these AML subtypes diagnosed in seven hospitals in Catalonia from January 1994 to December 1999. The aim was to know whether the morphologic findings associated with these cytogenetic/ molecular abnormalities were as constant as stated in the literature. Table 1 shows the main clinical and laboratory data. Leukocytosis was significantly higher in 11q23 than in the other types. Cases with t(15;17) and M3 variant morphology had a mean (SD) leukocyte count of 28.5 (27.2) $\times 10^9$/L, higher than those with classical M3 [9.7 (24.8) $\times 10^9$/L], but the difference was of borderline significance (p=0.05). The percentage of blasts in peripheral blood (PB) was significantly higher in 11q23 than in the other types, and in bone marrow (BM), higher in 11q23 and t(15;17). Eosinophils in BM were present in an appreciable amount in inv(16) and in t(8;21). Table 2 shows the main morphologic data.

Twenty-two cases were AML-t(8;21), 4 M1 and 18 M2, coinciding with the FAB subtypes usually described.[1-3,9] Dysgranulopoiesis was severe in all cases, with constant abnormal nuclear segmentation (hyposegmentation or bizarrely segmented nuclei) and hypo or hypergranulation. Two types of blasts were observed in 9 (41%) cases in PB and 13 (59%) cases in BM, one type being of myeloid appearance, and the other one of pseudolymphoid appearance (high nuclear-cytoplasmic ratio, irregular nucleus, scant cytoplasm and moderate basophilia). Although the WHO review states that the small blasts are predominantly found in PB, we found them more frequently in BM. The myeloblasts had fine granulation, frequent Auer rods, and in some cases pseudo-Chediak granules, in agreement with the WHO report. Though uncommon in the other subtypes, cytoplasmic vacuolization was

Table 1. Comparison of the main clinical and laboratory results of the four types of AML. Results expressed as mean (SD).

Cytogenetic anomaly/ N. cases	*t(8;21) N=22*	*t(15;17) N=52*	*inv16 N=27*	*11q23 N=9*	*p*
Age (years)	48 (17)	42 (16)	41 (17)	58 (23)	0.04
Hemoglobin (g/L)	85 (25)	92 (23)	86 (22)	108 (32)	0.07
Platelets ($\times 10^9$/L)	39 (22)	45 (41)	50 (42)	61 (37)	0.4
Leukocytes ($\times 10^9$/L)	12.1 (7.1)	12.6 (25.6)	45.5 (49.2)	85.3 (53.4)	<0.001
Blasts in peripheral blood (%)	42.8 (25)	42.2 (34)	42.7 (33)	69.3 (32)	0.03
Blasts in bone marrow (%)	50.4 (19.9)	74.8 (17.3)	54.4 (19)	82.4 (14.8)	0.001
Eosinophils in bone marrow (%)	2.1 (2.9)	0.1 (0.5)	13 (9.6)	0.6 (1.7)	<0.001

Table 2. Main morphologic data in the four types of AML wih recurrent cytogenetic abnormalities.

Cytogenetic anomaly	*t(8;21) n (%)*	*t(15;17) n (%)*	*inv16 n (%)*	*11q23 n (%)*	*p*
Peripheral blood					
Granulocytes					
Abnormal granulation	17/18 (94)	5/30 (16)	16/23 (70)	1/7 (14)	<0.0001
Abnormal segmentation	18/18 (100)	3/30 (10)	17/23 (74)	3/7 (43)	<0.0001
Single Auer rods	0/18 (0)	1/30 (3)	3/23 (13)	0/7 (0)	ns
Hybrid eosinophils	0/22 (0)	0/50 (0)	8/27 (30)	0/9 (0)	0.008
Red cells					
Dysplasia	1/21 (5)	13/49 (26)	3/22 (13)	2/9 (22)	ns
Platelets					
Dysplasia	0/19 (0)	2/42 (5)	2/26 (7)	2/9 (22)	ns
Bone marrow					
Dyserythropoiesis	2/17 (12)	3/39 (7)	3/22 (13)	0/5 (0)	ns
Dysmegakaryopoiesis	2/15 (13)	0/17 (0)	2/18 (11)	0/5 (0)	ns
Granulocytes					
Abnormal granulation	21/21 (100)	22/30 (73)	19/24 (79)	1/6 (16)	<0.0001
Abnormal segmentation	21/21 (100)	14/30 (46)	17/24 (71)	0/6 (0)	<0.0001
Single Auer rods	5/21 (24)	2/30 (6)	5/24 (21)	0/6 (0)	ns
Vacuoles	8/21 (38)	1/30 (3)	1/24 (4)	0/6 (0)	0.001
Hybrid eosinophils	0/22 (0)	0/50 (0)	27/27 (100)	0/9 (0)	<0.001
Blast characteristics					
Irregular or bilobed nuclei	11/22 (50)	40/50 (80)	20/27 (74)	3/9 (33)	0.001
Fine granulation	15/22 (68)	8/50 (16)	18/27 (66)	5/9 (55)	0.0001
Large granulation	4/22 (18)	42/50 (84)	1/27 (4)	0/9 (0)	0.0001
Pseudo-Chediak granules	6/22 (27)	7/50 (14)	1/27 (4)	0/9 (0)	ns
Single Auer rods	16/22 (73)	8/50 (16)	7/27 (26)	2/9 (22)	0.002
Faggots	0/22 (0)	46/50 (92)	1/27 (4)	0/9 (0)	<0.0001