References

1. Hamann J, Fiebig H, Strauss M. Expression cloning of the early activation antigen CD69, a type II integral membrane protein with a C-type lectin domain. J Immunol 1993; 150: 4920-7.
2. Krammer PH. CD95 (APO-1/Fas)-mediated apoptosis: live and let die. Adv Immunol 1999; 71:163-210.
3. Rozman C, Monserrat E. Chronic lymphocytic leukemia. N Engl J Med 1995; 333:1052-7.
4. D'Arena G, Keating MJ, Carotenuto M. Chronic lymphoproliferative disorders: an integrated point of view for the differential diagnosis. Leuk Lymphoma 2000; 36:225-37.
5. Panayiotidis P, Ganeshaguru K, Foroni L, Hoffbrand AV. Expression and function of the FAS antigen in B chronic lymphocytic leukemia and hairy cell leukemia. Leukemia 1995; 9:1227-32.
6. Molica S, Mannella A, Dattilo A, Levato D, Iuliano F, Peta A, et al. Differential expression of BCL-2 oncoprotein and Fas antigen on normal peripheral blood and leukemic bone marrow cells. A flow cytometric analysis. Haematologica 1996; 81:302-9.
7. Gale RP, Caligaris Cappio F, Dighiero G, Keating M, Montserrat E, Rai K. Recent progress in chronic lymphocytic leukemia. International Workshop on Chronic Lymphocytic Leukemia. Leukemia 1994; 8:1610-4.
8. Lucivero G, Prchal JT, Lawton AR, Antonaci S, Bonomo L. Abnormal T-cell functions in B-cell chronic lymphocytic leukemia do not imply T-lymphocyte involvement in the leukemic process: report of a case with demonstrated "polyclonality" of T lymphocytes. J Clin Immunol 1983; 3: 111-6.
9. Tinhofer I, Marschitz I, Kos M, Henn T, Egle A, Villunger A, et al. Differential sensitivity of $CD4^+$ and $CD8^+$ T lymphocytes to the killing efficacy of Fas (APO-1/CD95) ligand + tumor cells in B chronic lymphocytic leukemia. Blood 1998; 91:4273-81.
10. Budd RC. Activation-induced cell death. Curr Opin Immunol 2001; 13:356-62.

Advantages of using thalidomide for the management of patients with refractory myeloma

A group of 11 heavily pretreated patients receiving low-dose thalidomide was compared with a similar group of 10 patients with refractory myeloma treated with a conventional oral chemotherapy. This study shows that thalidomide is not only effective in controlling the neoplastic clone but moreover, thanks to its low toxicity, allows out-patient management of these subjects.

Thalidomide has recently been adopted in the treatment of refractory multiple myeloma patients. From 30 to 50% of patients achieve a response at the dose of 200-800 mg/day.[1-3] Other studies report that thalidomide is also effective at lower dosages (50-100 mg/day) with fewer side-effects.[4-6]

We retrospectively compared two similar groups of patients with refractory myeloma treated with low-dose thalidomide (group I) or with the oral combination regimen CAVD (CCNU, alkeran, vepeside, dexamethasone) (group II). The aim of the study was to evaluate the impact of thalidomide on the management of refractory myeloma patients.

Group I was formed of 11 patients enrolled in a study whose criteria of inclusion were: age less than 75 years, at least two previous lines of therapy, kidney and liver-function tests no more than twice the upper limit of normal levels, no evidence of neuropathies, life expectancy of at least 6 weeks. Thalidomide, kindly supplied by Grünenthal (Aachen, Germany), was administered at a starting dose of 100 mg and escalated, according to tolerance, after two weeks to 200 mg /day.

The dosage of 200 mg/day was reached by all patients, but only 5 maintained this dose for more than 3 months. To improve control of symptoms, four patients also received dexamethasone at the dosage of 20 mg/day for two days every two weeks for the first two months.

Group II comprised 10 patients treated with the oral regimen CAVD, conceived in order to manage them as outpatients. Inclusion criteria were the same as those adopted for the group receiving thalidomide except for presence of neuropathies. The schedule was: CCNU (80 mg/m^2 *per os*) day 1, and melphalan (5 mg/m^2/day *per os*), VP16 (60 mg/m^2/12h *per os*), dexamethasone (8 mg/day *per os*) for 5 days. The chemotherapy was repeated every 4-6 weeks.

The characteristics of the patients of both groups, recorded at

Table 1. Characteristics of MM patients at starting thalidomide or CAVD treatment, and type of response to therapy.

	Thalidomide	*CAVD*
No. of patients	11	10
Median age (range)	59 (52-67)	61 (46-76)
Hb <9 g/dL	6/11 (54%)	3/10 (30%)
Bone marrow plasma cells >50%	6/11 (54%)	6/10 (60%)
β2 microglobulin >3 mg/L	9/11 (82%)	8/10 (80%)
>3 sites of osteolysis	3/11 (27%)	7/10 (70%)
Previous therapy:		
Conventional	7/11 (64%)	5/10 (50%)
High-dose	4/11 (36%)	5/10 (50%)
Type of response		
CR	1/11 (9%)	–
PR	4/11 (36%)	6/9 (66%)
MR	6/11 (55%)	–
NR	0	3/9 (33%)

Table 2. Therapy-related toxicity in patients treated with thalidomide or CAVD.

	Thalidomide	*CAVD*
Need for hospitalization	1/11 (9%)	7/10(70%)
Grade 3-4 infections	1/11 (9%)	3/10(30%)
Transfusion requirement	0	4/10(40%)
Grade 3-4 extra-hematologic toxicity	1/11 (9%)	0
Grade 4 therapy-related neutropenia	0	5/10 (50%)

the time of starting therapy, and response to treatments are reported in Table 1. Response was evaluated according to the EBMT/IBMTR guidelines.[7] All patients treated with CAVD but one were evaluable for response (at least four cycles). The median duration of response was 9 (3-18) months. Seven out of 10 patients did not complete the program of 6 cycles because of treatment-related toxicity. Thalidomide was administered for a median of 210 days (90-460), and the median time to achieve the best response was 60 days (range 30-190). One patient had disease progression after six months of therapy.

Thalidomide-related side effects included grade 2 constipation in 4 patients (36%), grade 2 skin reaction in 1 patient (9%), grade 1-2 neurotoxicity in 6 patients (54%), and a deep venous thrombosis (DVT) in 1 patient (9%). In patients treated with thalidomide, differently from those administered the CAVD regimen, no profound therapy-related cytopenias, septic complications, therapy-related deaths or transfusion requirement were recorded (Table 2). Among patients treated with thalidomide, even those with a minimal response had an improvement of symptoms. Therefore, thanks to the well tolerated side-effects of thalidomide, apart from the case of DVT, all patients were managed in an out-patient care setting.

We did not adopt specific questionnaires to assess quality of life. However, in patients treated with thalidomide the improvement of symptoms, the reduction of transfusion requirements, and the full out-patient management represented clear indicators of an amelioration of quality of life.

In conclusion: 1) thalidomide is an effective therapy for patients with refractory myeloma;[8,9] 2) even patients showing a minimal response can be managed in an out-patient care setting with better compliance to therapy and a better quality of life.

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References

1. Singhal S, Mehta J, Desikan R, Ayers D, Roberson P, Eddlemon P, et al. Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med 1999; 341:1565-71.
2. Yakoub-Agha I, Moreau P, Leyvraz S, Berthou C, Payen C, Dumontet C, et al. Thalidomide in patients with advanced multiple myeloma. Hematol J 2000; 1:186-9.
3. Juliusson G, Celsing F, Turesson I, Lenhoff S, Adriansson M, Malm C. Frequent good partial remission from thalidomide including best response ever in patients with advanced refractory and relapsed myeloma. Br J Haematol 2000; 109:89-96.
4. Palumbo A, Giaccone L, Bertola A, Pregno P, Bringhen S, Rus C, et al. Low-dose thalidomide plus dexamethasone is an effective salvage therapy for advanced myeloma. Haematologica 2001; 86:399-403.
5. Pini M, Baraldi A, Pietrasanta D, Allione B, Depaoli L, Salvi F, Levis A. Low dose thalidomide in the treatment of refractory myeloma. Haematologica 2001; 85:1111-2.
6. Durie BMG, Stephan DE. Efficacy of low dose thalidomide in multiple myeloma. Blood 1999; Suppl 9:1413[abstract].
7. Bladè J, Samson D, Reece D, Apperley J, Björkstrand B, Gahrton G, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Br J Haematol 1998; 102:1115-23.

Genotypic heterogeneity may explain phenotypic variations in inherited factor VII deficiency

Inherited factor VII (FVII) deficiency is a rare autosomal recessive coagulation disorder characterized by a wide genetic heterogeneity and a poor relationship between FVII activity (FVII:C) levels and severity of the hemorrhagic diathesis.[1,2] Given both the rarity and the heterogeneity of this disorder, genotype-phenotype relationships are difficult to clarify. The analysis of three FVII-deficient patients enabled us to offer some explanations.

Here we report the cases of three unrelated factor VII (FVII)-deficient patients having the same FVII:C level and one common FVII mutated allele, but quite different clinical phenotypes. We hypothesize that the clinical bleeding tendency could be related to the different second FVII mutated allele.

Patients A, B and C were three unrelated adult females. Their FVII:C levels were 1% below normal and they all had a compound heterozygous FVII genotype, sharing the common 100Gln→Arg mutation. In contrast, the second FVII mutated allele was different and the three patients presented with different clinical features (Table 1). Patient A, who bore the 100Gln→Arg/331Gly→Ser genotype, was asymptomatic. Patient B, possessing the 100Gln→Arg/97Gly→Cys genotype, showed a mild hemorrhagic diathesis, whereas patient C, with the 100Gln→Arg/49Gln→Stop genotype, presented with severe recurrent hemarthroses. For patients B and C, other potential bleeding etiologies were excluded. As the 353Gln and the 10 base-pair insertion at –323 polymorphic alleles of FVII gene are known to be associated with a decrease in FVII:C levels,[1,2] the haplotype background of each patient was characterized. Only patient B was found to be heterozygote for the 353Gln allele, which may contribute to the decreased FVII expression. However, the four above-mentioned mutations have quite different functional consequences. The common 100Gln→Arg mutation induces an abnormal conformation of the FVII protein leading to a major, but not complete, secretion defect. The small amount of FVII, which is still released from cells, shows a markedly reduced affinity for tissue factor.[3,4] The 49Gln→Stop mutation (patient C) generates a premature termination codon at position 49 in the first EGF domain. Even if the mutant protein is translated, the truncation of the EGF2 and catalytic domains would certainly produce an inactive polypeptide. Thus, this mutation is expected to lead to a total absence of functional FVII protein.[5]

The FVII 97Cys mutant (patient B) results in impaired secretion of the mutant protein due to degradation in the pre-Golgi compartment. The mutant protein, which is still released at low levels, shows impaired tissue factor binding.[4] Finally, the 331Gly→Ser substitution (patient A) occurs within a FVII region that has been demonstrated to be part of a substrate-binding site.[6] Therefore, this mutation may alter substrate binding as