the time of starting therapy, and response to treatments are reported in Table 1. Response was evaluated according to the EBM T/IBM TR guidelines. 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, as 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; 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

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 and clinical heterogeneity and a poor relationship between FVII activity (FVII:C) levels and severity of the hemorrhagic diathesis.

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 compound heterozygous FVII genotype, 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 Italian 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 hemorrhages. For patients B and C, other potential bleeding etiologies were excluded. As the 331Gly 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, the haplotype background of each patient was characterized. Only patient B was found to be heterozygote for the 331Gly 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. 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.

The FVII 97Gly and the 331Gly substitutions (patients A and C) occur within a FVII region that has been demonstrated to be part of a substrate-binding site. Therefore, this mutation may alter substrate binding as
well as the previously described 331Gly → Asp mutation. In addition, as the FVII antigen level remains normal, the FVII 331Ser mutant protein seems to continue to be secreted. Together, these data are consistent with the hypothesis that the severity of bleeding could be related to the amount of FVII or activated FVII that is still produced. Thus, we suggest that a very small amount of FVII is sufficient to prevent the occurrence of a severe bleeding phenotype and that conventional FVII:C measurement fails to differentiate this gradual decrease in residual FVII activity.

Furthermore, the severity of bleeding could be related to the amount of FVII or activated FVII that is still produced. Thus, we suggest that a very small amount of FVII is sufficient to prevent the occurrence of a severe bleeding phenotype and that conventional FVII:C measurement fails to differentiate this gradual decrease in residual FVII activity.

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References


A novel case of immunodeficiency, centromeric instability, and facial anomalies (the ICF syndrome): immunologic and cytogenetic studies

The immunodeficiency, centromeric instability, and facial anomalies (ICF) syndrome is characterized by hypogammaglobulinemia and recurrent bacterial infections. Here we report a novel case of ICF syndrome with hypogammaglobulinemia and an inverted CD4/CD8 ratio. Cytogenetically abnormal cells, that were identified in both CD4+ and CD8− peripheral blood lymphocytes, retained their ability to proliferate in vitro following polyclonal stimulation. A primitive defect of B-cell differentiation was detected.

The ICF syndrome is a rare autosomal recessive disorder; to date, approximately 20 cases have been reported. Patients with ICF syndrome suffer from recurrent respiratory and/or gastrointestinal infections, and have facial anomalies, as well as mental retardation of variable degree. They display hypogammaglobulinemia involving two or more isotypes and, rarely, lymphopenia or an inverted CD4/CD8 ratio. Juxtapcentromeric abnormalities involving chromosomes 1 and 16 and, to a lesser extent, chromosome 9 are the diagnostic hallmarks of the disease. The majority of ICF cases display mutations in the DNA methyltransferase 3B (DNMT3B) gene.

Here we report a new case of ICF syndrome with hypogammaglobulinemia and an inverted CD4/CD8 cell ratio.

The propositus, a male, was born in 1981 in a small village in the south of Italy. He is the second child of healthy non-consanguineous parents. The pregnancy and delivery at full term were uneventful, and the child’s weight at birth was 2950 g. At the age of 3 months, the propositus manifested bronchiolitis and recurrent respiratory infections. He was hospitalized at the age of 14...