


5. Gajewski JL, Khouri I, Champlin RE, Saliba RM, McMannis JD, Donato ML, et al. Anti-thymocyte globulin (ATG) reduces primary graft failure (GF) risk and may reduce acute graft versus host disease (aGVHD) in 212 non-myeloablative blood and marrow transplant (BMT) patients (pts) receiving unrelated or 1 antigen (Ag) mismatched (MM) related donor grafts. Proceedings of ASCO 2002-21:420a[abstract 1676].


8/10 children with recurrence of CC in 6 of them. In 2 children, a significant long-term decrease of MC was documented and AI probably postulated hematologic relapse. This allowed us to perform a second transplantation in both patients. Secondary GvHD grade I–III was seen in 3/4 follow-ups and was fatal in one patient.

We confirmed that patients with increasing MC have a significantly higher risk of hematologic relapse. Continuous CC together with trMC usually proved to be a good prognostic factor, but in our experience had limited value in predicting extramedullary relapse. Detection of HC is a simple, reliable and rapid method and when performed frequently, allows us to identify patients indicated for AI. A graft-versus-leukemia effect of AI in our small cohort was evident in patients with CML and JMML, was less effective in patients with AML, and was questionable in patients with ALL. We speculate that in patients with acute leukemia AI methods are more effective when initiated early before full leukemia recurrence.

References

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Letters to the Editor

Inversion of intron 1 of the factor VIII gene for direct molecular diagnosis of hemophilia A

An intron 1 inversion of the factor VIII gene has been recently described as a consequence of an intrachromosomal recombination involving a 1041 bp specific duplcion inside and outside the gene. We investigated the intron 1 inversion in a cohort of 201 Spanish hemophilia A (HA) families. The inversion was detected in 4 families with severely affected cases of HA and no inhibitor history. The frequency of the inversion among cases of severe HA cases was 5% (4/79), confirming that this inversion is a recurrent mutational event.

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The most frequent mutation in severe hemophilia A patients is an inversion of intron 22 of the factor VIII gene, described 8 years after the cloning of the gene.1,2 In 1996 an inversion breaking intron 1 was detected in two hemophilic monozygotic twins.2 This was originally regarded as a rare event, but 6 years later, the same group in the United Kingdom reported that this inversion was a recurrent event in patients with hemophilia A (HA).3 A 1041-base pair sequence (int1h-1) of the intron 1 was found to be duplicated (int1h-2) and orientated in the opposite direction 140 kb outside the gene between the C6.1A and VBPI genes. This inversion arises from a recombination event between the two homologous sequences int1h-1 and int1h-2 (Figure 1).

One hundred and eighty-five unrelated HA patients and 16 mothers of deceased hemophilic infants, in whom inversion of intron 22 had been excluded, were investigated for the presence of inversion of intron 1. Out of 201 cases, 79 had severe disease, 53 had moderate disease and the remaining 69 had a mild phenotype. For inversion analysis, two polymerase chain reactions (PCR) were performed as previously described4 with slight modifications. In the first reaction, primers specific for int1h-1 (9F, 9cR) plus the primer int1h–2F were used in an amplification reaction that yielded a 1191 bp product from normal DNA and a 1323 bp product if the inversion was present (Figures 1 and 2). In the second reaction, primers specific for int1h-2 (int1h-2F, int1h-2R) plus the primer 9F yielded a 1323 bp product from normal DNA and a 1191 bp product from normal DNA and a 1776 bp product in the presence of an inversion, assuming that the interchange is reciprocal. The pattern of the carriers had both bands (Figure 2). For haplotype analysis, four intragenic (Intron 13 CA repeat, BclI intron 18 and Intron 22 CA repeat by PCR and KpnI/XbaI intron 22 by Southern blot) and two extragenic (DXS52 by PCR and DX13 by Southern blot) markers were used as previously described.5,6

The test was positive in 3 out of 185 HA patients and in one out of the 16 HA mothers. The overall frequency of intron 1 inversion in all hemophiliacs without intron 22 inversion was 4/201 (2%). The calculated frequency was 5% (4/79) when considering only severe cases. Three were familial cases and in

References


