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 occurrence of a severe bleeding phenotype and that conventional FVII:C measurement fails to differentiate this gradient of severity explains the different phenotypic expressions observed in the three probands.

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 hemarthrosis.

Table 1. Genotypic and phenotypic characteristics of patients A, B and C.

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Sex</th>
<th>FVII:C/FVII:Ag allele 1</th>
<th>FVII:C/FVII:Ag allele 2</th>
<th>PVR</th>
<th>Polymorphic sites</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>F/62</td>
<td>&lt;1% 100Gln→Arg + 331Gly→Ser ++</td>
<td>ALA1 - M1M1</td>
<td>asymptomatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>F/66</td>
<td>&lt;1% 8% 100Gln→Arg + 97Gly→Cys</td>
<td>ALA1 - M1M2</td>
<td>epistaxis, menorrhagia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>F/52</td>
<td>&lt;1% 7% 100Gln→Arg + 49Gln→Stop</td>
<td>ALA1 - M1M1</td>
<td>recurrent hemarthrosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The FVII coagulant activity (FVII:C) was assayed by a one-stage method based on the prothrombin time using a recombinant human tissue factor (Instrumentation Laboratory, Lexington, USA). The FVII antigen (FVII:Ag) was determined by an enzyme-linked immunosorbent assay using the Association for Blood Coagulation (ABCC) Antisera, Paris, France. The FVIIR genotypes were characterized by direct sequencing as previously described. A1 and A2 correspond to the presence or absence, respectively, of the 16 base-pair insertion at -323 in the promoter region of FVII gene. M1 and M2 correspond to the 323Arg and 353Gln alleles, respectively. FVIIIR denotes the "presumed residual amount of FVII."
months because of bronchopneumonia and measles. Hypogammaglobulinemia, hepatosplenomegaly and failure to thrive were found. A liver biopsy did not provide any diagnostic information and hepatomegaly was no longer detected in the subsequent clinical course of the patient.

The patient was first referred to our hospital at the age of 13 years because of chronic bronchopneumonia and bronchiectasis in the absence of hematologic abnormalities. Immunoglobulin serum levels were the following: IgM = 124 mg/dL (normal range for the age = 40-230 mg/dL), IgG = 380 mg/dL (normal range for the age = 550-1600 mg/dL), IgA = 20 mg/dL (normal range for the age = 40-230 mg/dL). His weight and height were 32 kg and 146 cm (10th centile), respectively; head circumference was 54 cm. He showed epicanthus, hypertelorism, a flat nasal bridge, low set ears, an asymmetrical thorax and slight splenomegaly (2 cm below the left costal margin). Mental retardation (IQ= 61) was also documented; at that time, the patient was attending the first class of secondary school. Cytogenetic studies supported the diagnosis of ICF syndrome. Associations and interchanges in the juxtacentromeric region among homologous or non-homologous chromosomes, deletions of whole arms, chromatids and isochromatids, breaks in the juxtacentromeric region and multibranched configurations formed by a variable number of arms of the same or different chromosomes were detected in peripheral blood mononuclear cells (MNC) stimulated with phytohemagglutinin (PHA) for 72 h (Figure 1A). In these experiments, 69/212 T-cell blasts displayed chromosomal abnormalities. Interphase FISH analysis demonstrated that both CD4+ and CD4- lymphocytes, freshly isolated by immunomagnetic bead manipulation, contained 92/400 and 25/200 cytogenetically abnormal cells, respectively.

Immunophenotypic analyses performed at different times, in the absence of active infectious or inflammatory disorders at least 2 weeks before and after testing, showed a stable inversion of the CD4/CD8 ratio, cytogenetically abnormal T-cells were able to divide and clonally expand following stimulation, suggesting that such cells are functional in vivo. This finding fits with the unusual manifestations of defective cell-mediated immunity in patients with ICF syndrome and an age-matched normal control were separated into T- and non-T-cells by E-rosetting and cultured in the presence of PWM. Cultures were harvested after 7 days and supernatants were tested for the presence of IgG and IgA by ELISA. Results are expressed as ng/mL. p indicates the patient, c indicates the control subject.
with ICF syndrome. Finally, hypogammaglobulinemia was found to depend in part on a primary B-cell defect.

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Key words: immunodeficiency, juxtacentromeric abnormalities, ICF syndrome, FISH.

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Twenty-four children with acute leukemia (21) or chronic myeloid leukemia (3) who relapsed after a first hematopoietic stem cell transplantation (HSCT) underwent a second allogeneic HSCT. Sixteen patients died from relapse or transplant-related causes and 8 are alive. The event-free survival rate is 32%. This study shows that this procedure offers a chance to a set of these patients.

Relapse is the most frequent cause of therapeutic failure in patients with hematologic malignancies undergoing allogeneic hematopoietic stem cell transplantation (HSCT).1 The optimal treatment strategy for these patients remains an open question. Conventional chemotherapy (CT) can achieve complete but generally brief remission. Other treatment options are donor leukocyte infusions (DLI) or a second HSCT.2 The results of GETMON in children with hematologic malignancies undergoing second allogeneic HSCT are reviewed.

From May 1985 to April 1998, 24 children (13 males, 11 females) with hematologic malignancies received a second HSCT. All patients were in complete clinical and hematologic remission (CR) achieved by conventional CT (acute leukemias) or in second chronic phase (chronic myeloid leukemia). The same HLA identical sibling donor was used for both transplants, except in two cases in which another HLA identical sibling was used. From 1985 to 1996, HLA typing of donors and transplant recipients was performed by serology and by DNA techniques thereafter. There were 11 cases of acute lymphocytic leukemia (ALL), 10 of acute myeloid leukemia (AML), and 3 of chronic myeloid leukemia (CML). The median age at second transplantation was 9 years (range 2-16) (Table 1). Conditioning for the first HSCT consisted of fractionated total body irradiation (TBI) plus CT (18 cases) or CT alone (6 cases). At second transplant, 19 patients received CT alone and 5 received fractionated TBI plus CT. Four patients received fractionated TBI in both conditionings. Graft-versus-host disease (GVHD) prophylaxis at first HSCT was performed with cyclosporin A (CsA) at an initial dose of 5 mg/kg/day intravenously in two cases and CsA plus methotrexate (MTX) at a dose of 10 mg/kg on alternate days for a total of 4 days in the remaining cases. At second HSCT 19 patients received CsA at an initial dose of 3 mg/kg/day intravenously and 5 received CsA plus MTX at the same standard dose as in the first HSCT (Table 2). Twenty-two patients achieved a stable graft at second transplantation. Eight patients presented acute GVHD grade 1-2 at first transplant and 7 developed acute GVHD > grade 1 (> grade 3-4 in three patients) at second HSCT.

Eight of the 24 patients are alive and event-free at a median follow-up of 82 months (range 38-142). The probability of event-free survival (EFS) at 5 years was 53%. Eight of thirteen patients who relapsed more than 12 months post-HSCT are alive and event-free. All 11 patients who relapsed < 12 months post-HSCT have died (p = 0.001). Sixteen patients died after their second HSCT: 8 from relapse, 8 from transplant-related causes [graft failure (2), acute GVHD (2), veno-occlusive disease (1) and interstitial pneumonia (3)]. The interval between transplants was less than 12 months in 7 of the 8 patients who died from toxicity. The three patients who died from interstitial pneumonia received fractionated TBI in both transplants. The two cases of graft failure had ALL and received an infusion of 2.5×10^6/kg and 5.0×10^6/kg CD34+ cells.