with ICF syndrome. Finally, hypogammaglobulinemia was found to depend in part on a primary B-cell defect.

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Second allogeneic hematopoietic stem cell transplantation in hematologic malignancies in children: long-term results of a multicenter study of the Spanish Working Party for Bone Marrow Transplantation in Children (GETMON)

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 and disease-free with a probability of event-free survival at 5 years of 32%. These results show that this procedure offers a chance to a subset 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 intitial 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 32%. 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,

Table 1. Patients' characteristics.

Number of patients	24
Median age at second HSCT (range)	9 (2-16 years)
Sex (M/F)	13/11
Diagnosis	
ALL	11
AML	10
CML	3
Duration of remission after first HSCT	
< 12 months	11
≥ 12 months	13
Time between HSCT	
< 12 months	8
≥ 12 months	16

Abbreviations: HSCT = hematopoietic stem cell transplantation.

Table 2. Transplant-related data.

	HSCT 1	*HSCT 2*
Conditioning regimen		
fTBI + CT	18	5
CT alone	6	19
GVHD prophylaxis		
CsA + MTX	22	5
CsA	2	19
GVHD grade		
Grade 1-2	8	0
Grade 3-4	0	3

Abbreviations: fTBI = fractionated total body irradiation; CT = chemotherapy; GvHD = graft-versus-host disease; CsA = cyclosporin A; MTX = methotrexate.

respectively. The 5-year probability of transplant-related mortality was 32%.

These results corroborate that although transplant-related mortality is high, as previously reported in adults,[3,4] a second HSCT can lead to prolonged EFS in patients relapsing more than 12 months after a first HSCT.[3,5,6] An interval between both transplantations of less than one year and the use of very intensive conditioning at second transplantation (*e.g.* repeat fractionated TBI) are associated with high toxicity and should be avoided.[6-8]

DLI is another treatment option. However, it has been demonstrated to be ineffective in adults with ALL and AML[9] and there is limited experience in children.[10]

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