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Unsuccessful allogeneic and autologous transplants after prolonged interferon-α treatment in a pediatric patient with chronic myeloid leukemia

Recombinant or partially pure human leukocyte interferon-α (IFN-α) has shown promising activity in the treatment of chronic myeloid leukemia (CML).[1,2] However, IFN-α might inhibit self-renewal of the progenitor cells in CML3 and may result in irreversible alterations of the marrow microenvironment.[4,5] This pediatric case report seems to confirm the negative impact of prolonged IFN-α treatment on subsequent stem cell transplantation.

Sir,

A 13-year old girl, diagnosed as having Ph1-positive CML at another hospital, had received hydroxyurea for three months and IFN-α (5 MU/daily) for 27 months before she was referred to our hospital, still with chronic phase CML, for unrelated cord blood cells transplant with two incompatible loci (B, DR).

The number of cord blood mononuclear cells was 2.7×10^7/kg and that of $CD34^+$ cells 13.5×10^6/kg. Conditioning consisted of busulfan 16 mg/kg over 4 days, cyclophosphamide 60 mg/kg/d for 2 days, antithymocyte globulin 15 mg/kg/d for 6 days and steroids 1 mg/kg/d for 6 days. The girl received 10 µg/kg G-CSF from day +40 to +46. On day +46 engraftment had not been achieved and a marrow biopsy showed complete aplasia.

On day +48 from the first hematopoietic progenitor cell transplant (PCT), previously harvested autologous bone marrow was infused (TNC 10.3×10^7/kg, GFU-GM 13.8×10^4/kg). On day +41 after the second PCT engraftment had not been achieved.

A third transplant with peripheral stem cell $CD34^+$ selection from a sibling with two mismatched HLA loci (B, DR) was performed. Conditioning consisted of antithymocyte globulin and steroids at the same doses used for the unrelated cord blood cells transplant. The number of $CD34^+$ cells infused was 1.5×10^5/kg.

On day +32 after the third PCT without marrow engraftment, 5 µg/kg GM-CSF was administered for 12 days. The patient developed bilateral pneumonia; *Candida albicans* was isolated from her sputum and despite treatment with intravenous amphotericin B, she died 45 days after her third PCT, still with no evidence of marrow engraftment.

There are contradictory reports on the effects of prior IFN-α therapy on the outcome of PCT for CML patients. Tomás *et al*.[6] and Zuffa *et al*.[7] found that previous IFN-α exposure had no adverse effects on the outcome of HLA identical sibling donor PCT for adult patients with CML. However, the Essen group observed that IFN-α therapy for more than one year can compromise PCT results, with a greater transplant-related mortality, more delay and graft failure, and lower survival. Graft failure was only observed in PCT with unrelated donors.[8]

Prolonged IFN-α treatment, together with the long interval between diagnosis and first transplant, and the HLA disparity of both grafts may explain the inability of stem cells to repopulate after the allogeneic transplants in our patient. Since children with Ph1- positive CML in the first chronic phase are initially all candidates for allogeneic PCT from a related or unrelated donor, it would be wise to avoid the use of IFN-α as front line cytoreductive therapy in these patients.[9,10]

César Pérez-Caballero, Mª Soledad Maldonado, Rocío Tamariz, Jaime Pérez de Oteyza, Arturo Muñoz*

*Departments of Pediatrics and *Hematology, Ramón y Cajal Hospital, University of Alcalá, Madrid, Spain*

Key words

Chronic myelogenous leukemia, interferon-α, hematopoietic progenitor cells transplant, graft failure.

Correspondence

A. Muñoz Villa, MD, Dept. of Pediatrics, Ramón y Cajal Hospital, Ctra. de Colmenar km. 9.100, 28034 Madrid, Spain. Phone: international +34.91.3368091 – Fax: international +34.91.3368417.

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Prophylactic use of desmopressin in surgery of six patients with symptomatic heterozygous factor XI deficiency

From January 1998 to March 1999, we followed 6 symptomatic heterozygous factor XI (FXI) deficient patients undergoing surgery. There were 4 males and 2 females. Their mean age was 39.8 years (range 6-67 years). Three of the 6 patients were members of the same family. The investigation of additional coagulation abnormalities (e.g. bleeding time, platelet aggregation, other clotting factors levels and von Willebrand factor level) was negative in all 6 patients. This report shows that desmopressin can be used successfully to prevent surgical bleeding in these patients.

Sir,

Patient #1 was a 56-year old female undergoing endoscopic cholecystectomy. Her mother had died at the age of 61 of a post-cholecystectomy hemorrhage. The patient had suffered severe bleeding, which required multiple blood transfusions, after a tonsillectomy at the age of 10. She had had 2 pregnancies, 1 with severe post-partum hemorrhage. At the age of 42 the patient underwent a total hysterectomy and was successfully treated with fresh frozen plasma in order to avoid hemorrhagic complications.

Patient #2, a 65-year old male, the first patient's brother, was transfused aged 60 because of hemorrhagic complications after a prostatectomy.

Patient #3, a 29-year old male, the second patient's son, had received blood transfusions for haemorrhagic complications following splenectomy after road accident trauma. Patients #2 and #3 were scheduled for arthroscopic reconstruction of knee ligaments.

Patient #4, a 67-year old nulliparous female, was to undergo right leg saphenectomy. This patient had suffered from menorrhagia and reported bleeding complications during left leg saphenectomy 2 years previously.

Patient #5, a 6-year old male child, had received blood transfusions at the age of 3, for post-tonsillectomy hemorrhage: he was hypospadic and needed reconstruction of his urethra.

Patient #6, a 16-year old male, suffered from excessive and prolonged bleeding after two dental extractions. He was undergoing hydrocele surgery.

Before surgery, each patient was tested for the response to a subcutaneously injected dose of 0.3 µg/kg of DDAVP. In all patients the desmopressin injection led to normalization of the APTT, a slight increase in FXI activity (mean 12.0 U/dL; range 9-14 U/dL), a marked increase in FVIII:C (mean 147.8 U/dL; range 132-162 U/dL), vWF:Ag (mean 89.3 U/dL; range 68-123 U/dL) and vWF:Ricof (mean

Table 1. Hemostatic parameters before and 60 minutes after subcutaneous DDAVP injection.

Patients	*Before DDAVP*					*60 minutes after DDAVP*				
	APTT (ratio)	*FXI:C (U/dL)*	*FVIII:C (U/dL)*	*vWF:Ag (U/dL)*	*vWF:RiCof (U/dL)*	*APTT (ratio)*	*FXI:C (U/dL)*	*FVIII:C (U/dL)*	*vWF:Ag (U/dL)*	*vWF:RiCof (U/dL)*
Patient #1	1.34	32	104	89	130	1.08	46	260	180	210
Patient #2	1.25	42	130	96	102	1.08	54	275	190	190
Patient #3	1.28	40	87	107	118	1.11	52	249	230	210
Patient #4	1.19	45	117	107	107	0.91	54	270	175	210
Patient #5	1.35	36	117	104	110	1.11	50	256	188	205
Patient #6	1.32	34	108	94	104	1.07	45	240	170	175

Normal range: APTT = 0.8-1.15 (ratio); FXI:C = 60-140 U/dL; FVIII:C 50-150 U/dL; vWF:Ag = 60-150 U/dL; vWF:RiCof = 50-145 U/dL.