In conclusion, our data suggest familial aggregation of high FVIII:C levels, but provides no evidence of inheritance. FVIII:C levels in symptomatic FV Leiden carriers did not enable us to select families in which screening would identify relatives at high risk, due to the concomitance of FV Leiden and high FVIII:C levels.

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Stem Cell Transplantation

Immunological reconstitution after autologous peripheral blood stem cell transplantation in patients with chronic lymphocytic leukemia. Comparison with an historical non-Hodgkin's lymphoma group

The kinetics of immune reconstitution after autologous peripheral blood stem cell transplantation (APBSCT) was examined in a group of 6 patients with chronic lymphocytic leukemia (CLL) and compared to that in an historical group of 12 patients with non-Hodgkin's lymphoma (NHL). Lymphocyte analysis included total lymphocyte count, CD3, CD4, CD8, CD4/8 ratio, CD19, and CD16/56 counts before, on day +15, +30, +60, +90, and +120 and 1 year after transplantation. Immunological recovery in the CLL group was similar to that in the NHL group.

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T-cell dysfunction has been described in CLL and could contribute to both the etiology and the progression of the disease.[1] High dose therapy and stem cell transplantation is increasingly being used for the treatment of CLL.[2] Despite the fact that many data about lymphocyte recovery after unselected PBSCT or selected $CD34^+$ PBSCT have been published so far in lymphoproliferative disorders such as Hodgkin's lymphoma, non-Hodgkin's lymphoma, and multiple myeloma, no data are so far available about lymphocyte recovery after unselected PBSCT for chronic lymphocytic leukemia.[3-7]

Between May 1999 and April 2002, six pretreated adult patients affected by chronic lymphocytic leukemia underwent APBSCT. These patients were compared to 12 patients affected by NHL who were autografted at our institution during the same period. All patients received unselected peripheral blood autografts.

CLL patients were conditioned with MitMel (mitoxantrone 60 mg/m^2 on day –5 and melphalan 180 mg/m^2 on day –2). The median number of $CD34^+$ cell infused was 2.57×10^6/kg. Patients received granulocyte colony-stimulating factor (G-CSF) starting on day +7, until a stable absolute neutrophil count (ANC) > 0.5×10^9/L was achieved for 3 consecutive days. In the control group eight patients were conditioned with BuMel (busulfan 16 mg/kg, from day –6 to –3 and melphalan 140 mg/m^2 on day –2), two patients with BuCy2 (busulfan 16 mg/kg, from day –7 to –4 and cyclophosphamide 60 mg/kg on day –3 and –2) and two with BEAM (BCNU 300mg/m^2 on day –7, etoposide and aracytin 200 mg/m^2 on days –6 to-3, and melphalan 140 mg/m^2 on day –2). The median number of $CD34^+$ cells infused was 5.8×10^6/kg. Only eight patients received G-CSF, which was started on day +7, and continued until a stable ANC > 0.5×10^9/L was achieved for 3 consecutive days.

All results are expressed as median values. A difference was defined as statistically significant when $p<0.05$. Differences between the study groups were analyzed using the Mann-Whitney U-test. A median of 22×10^6/kg and 31.4×10^6/kg (p = ns) of $CD3^+$ T lymphocytes, and a median of 2.48×10^6/kg and 0.84×10^6/kg (p = ns) of $CD19^+$ B lymphocytes were reinfused into the CLL group and the NHL group, respectively. The CLL patients achieved a stable ANC > 0.5×10^9/L and platelet count > 20×10^9/L at day 13 and day 14, respectively. In the NHL group neutrophil and platelet engraftment was achieved on day 13 and day 12, respectively. An absolute lymphocyte count (> 0.5×10^9/L) was obtained on day 30 in the CLL group and on day 18 in the NHL group (p =0.04). Table 1 shows the patients' characteristics and clinical outcome.

The absolute lymphocyte count increased thereafter in

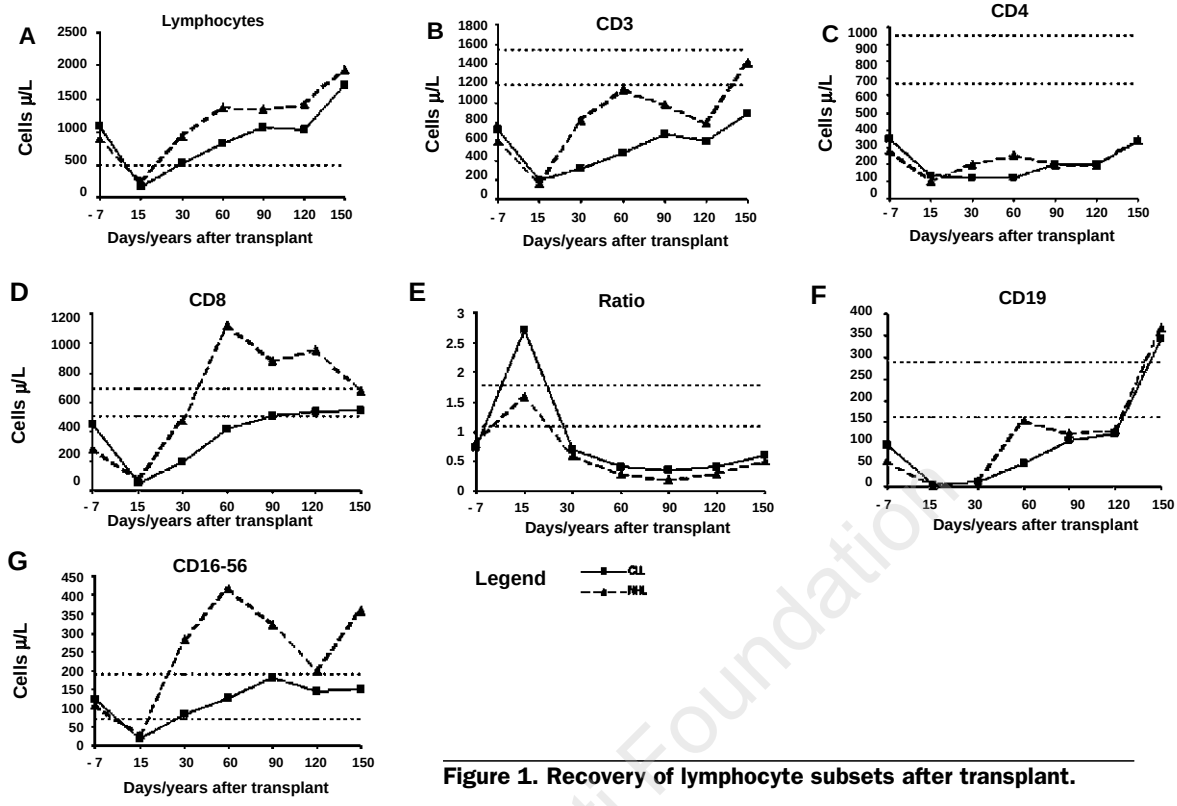

Figure 1. Recovery of lymphocyte subsets after transplant.

Table 1. Patients' characteristics and clinical outcome.

	CLL group (range)	*NHL group (range)*	*Mann-Whitney U test*
Number of patients	6	12	
Male/Female	4/2	7/5	
Median age	50 (46-60)	52 (30-62)	p = ns
Prior chemotherapy (pts)			
	Fludarabine/CTX 4	MACOP-B/MiCMA 5	
	CHOP/CTX 1	PROMACE/MiCMA 4	
	CHOP/MiCMA 1	CHOP/MiCMA 3	
Disease status at PBSCT			
CR (pts)	2	5	
PR (pts)	4	7	
no. $CD34^+$ cells $\times 10^6$/kg	2.57 (1.91-4.63)	5.8 (2.3-16.0)	p = 0.02
total $CD3^+$ cells $\times 10^6$/kg	22 (5.7-49.4)	31.4 (10.7-45.1)	p = ns
total $CD19^+$ cells $\times 10^6$/kg	2.48 (0.54-3.25)	0.84 (0.11-2.4)	p = ns
days to ANC >0.5 $\times$ 10^9/L	13 (10-14)	13 (8-18)	p = ns
days to PLTS >20 $\times$ 10^9/L	14 (8-31)	12 (8-28)	p = ns
days to ALC >0.5 $\times$ 10^9/L	30 (15-60)	18 (12-26)	p = 0.04
Days of fever (>38°C)	3 (1-6)	3 (0-11)	p = ns
Days of antibiotic therapy	9.5 (0-15)	8 (5-25)	p = ns
Days of hospitalization	21.5 (20-25)	22 (18-30)	p = ns
Sepsis	0	2 (*E. Coli; S. Aureus)*	p = ns
Single donor platelet units	1 (0-3)	0.5 (0-1)	p = ns
Red blood cell units	0 (0-2)	0 (0-3)	p = ns

both groups, reaching median values of 1×10^9/L on day + 90 without statistically significant differences (Figure 1A). The CD3$^+$ subset recovered slowly in both groups during the study period achieving median values with the normal range at 1 year only in the NHL group (Figure 1B).[7] The number of CD4$^+$ T-lymphocytes was stable and $<200\times10^6$ cells/L during the first four months after transplant (except on day +60 in the lymphoma group). Thereafter, a slow recovery of the T helper subset was observed in both groups up to 1 year (p = ns) (Figure 1C). In both groups the CD8$^+$ subset increased rapidly starting from day +15, reaching median values above the normal range from day +60 (p = 0.04) in the lymphoma group and normal values from day +90 in the CLL group (Figure 1D). After day +30 the CD4/CD8$^+$ ratio remained constantly below 0.6 in both groups (p = ns) (Figure 1E). There was a marked deficiency of CD4$^+$ T cells during the study period, according with prior observations that CD3$^+$ and CD8$^+$ subsets recovered promptly while CD4$^+$ abnormalities persisted for several year after transplantation.[8-10] Starting from day +30 the numbers of CD19$^+$ B-lymphocytes tended to normalize, reaching median values above the normal range only at 1 year, in both groups (Figure 1F).

During the study period, the values of CD16/56$^+$ NK cells recovered to normal in the CLL group starting from day +30 while they were constantly above the normal range in the lymphoma group, this difference being statistically significant on day +30 and +60 (Figure 1G).

In conclusion, the immunological recovery after PBSCT was similar in the two groups of patients with different lymphoproliferative disorders and seemed not to be influenced by the disease itself or by the concomitant T-cell dysfunction typical of CLL. However, given that functional studies of T cells were not done and our sample size was small, these conclusions need confirmation.

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Stem Cell Transplantation

Hematopoietic abnormalities persist for more than six years after autologous peripheral blood stem cell transplantation in patients with non-Hodgkin's lymphoma

We used cell culture assays in 22 lymphoma patients who underwent autologous peripheral-blood stem-cell transplantation (PBSCT) in order to assess whether hematopoietic damage persists during a long-term follow-up. We found that hematopoietic and stromal cell compartments are impaired even six years after transplantation, although some parameters (CFU-E, CFU-GM, hemoglobin and white cell counts) seem to improve from the fourth year.

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Abnormalities in both hematopoietic and stromal bone marrow compartments have been described after allogeneic and autologous stem cell transplantation.[1-6] In the present study we used cell culture assays in order to ascertain whether this damage persists 1-6 years after PBSCT, to establish at what level it occurs and to measure its evolution over time.

Twenty-two patients with non-Hodgkin's lymphoma (NHL) who had received a peripheral blood stem cell transplant (PBSCT) were included in this study. Their median age was 43 (16-63) years, with a male/female ratio of 9/13. The median dose of progenitor cells infused was 3.3 (1.2-