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Engraftment of HLA-matched sibling hematopoietic stem cells after immunosuppressive conditioning regimen in patients with hematologic neoplasias

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Abstract

Background and Objective. **The main objective of this pilot study was to assess the possibility of achieving engraftment of HLA-matched sibling donor mobilized hematopoietic stem cells after immunosuppressive non-myeloablative therapy. The second objective was to verify whether high-dose therapy with autologous stem cells *rescue* followed by allografting conditioned by only an immunosuppressive regimen, can be combined in order to achieve the reduction of tumor burden after autografting and the control of residual disease with immune-mediated effects after allografting.**

Design and Methods. **To enter the pilot study the patients had to fulfil the following criteria: advanced resistant disease, presence of an HLA matched sibling donor, no general contraindications to stem cell transplantation. Our data refers to 9 patients: Hodgkin's disease (n=4), non-Hodgkin's lymphoma (n=2), advanced chronic myelogenous leukemia (n=2) (one patient with accelerated phase Ph-negative but p190 BCR-ABL gene positive by RT-PCR and one with Ph-positive blastic phase), refractory anemia with excess of blasts t(1;3) (p36;q21) (n=1). All patients but one received the combined approach. At a median of 40 days (range 30-96), after high-dose therapy and autologous stem cell engraftment, the patients were treated with immunosuppressive therapy consisting of fludarabine and cyclophosphamide (Flu-Cy protocol) and then HLA matched donor mobilized stem cells were infused into the patients. GvHD prophylaxis consisted of cyclosporin and methotrexate.**

Results. **To date, with a median observation period of 4 months (range, 2-10), complete chimerism (100% donor cells) has been achieved in 6 patients. Three patients did not achieve complete chimerism: one patient died of progressive Hodgkin's disease when he reached 55% of donor cells, another patient is now in increasing phase of donor cell engraftment and the last patient (blastic phase-CML) was the only case who appears to have had autologous recovery. Two of the Hodgkin's disease patients, who were in partial remission after autografting, achieved complete remission after allografting and both are disease free 2 and 6 months after. Another Hodgkin's disease patient is alive at 10 months but she has progressive disease. One of the two patients with non-Hodgkin's lymphoma, who achieved partial remission after autografting, obtained complete remission and he is disease free 2 months after allografting. The other patient maintains partial remission obtained after autografting. The accelerated phase-CML patient obtained hematologic and molecular remission; the RAEB patient achieved hematologic and cytogenetic remission. In two patients severe aGVHD (grade II-III) was the single major complication but neither patient died of it. Mild aGVHD was seen in another patient. in only one patient did the ANC decrease to below 1×10^9/L and in no case did platelets decrease below 20×10^9/L. No patients required a sterile room or any red cell or platelet transfusions.**

Interpretation and Conclusions. **Immunosuppressive therapy with a Flu-Cy protocol allowed engraftment of HLA-matched sibling donor stem cells without procedure-related deaths; moreover, we have demonstrated that this combined procedure can be pursued in safety in a serious ill population and some of these patients achieved a complete remission. This procedure is not likely to be curative, but a fascinating step along the path to curing these diseases. Of course, the follow-up is too short to document the incidence of cGvHD.**

Key words: mobilization therapy, high-dose chemotherapy, autografting, immunosuppressive therapy, allografting

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Traditionally the conditioning for allografting has relied on a combination of myeloablative and immunosuppressive therapies which results in substantial morbidity and mortality. By contrast, high dose therapy followed by autografting has less life-threatening toxicity. To circumvent the problems

inherent to the toxicity and treatment related deaths associated with allografting, it has been recently assessed that it is possible to achieve engraftment of donor hematopoietic stem cells after immunosuppressive therapy combined with myelosuppressive but non-myeloablative therapy.[1,2] The observations that non-myeloablative regimens based on fludarabine have resulted in engraftment of allogeneic cells in hematologic malignancies, raises the possibility that such conditioning might even be useful in achieving a graft-versus-tumor effect. In this pilot study we treated 9 patients with resistant malignancies who received high-dose therapy followed by autologous stem cell transplantation as tumor debulking therapy; subsequently, immunosuppressive therapy and infusion of HLA matched sibling donor stem cells were given to the patients in the attempt to induce immune-mediated anti-tumor effect.

Materials and Methods

The patients were enrolled from the N.O.A. Hematology and ABMT, Department of Hematology, San Martino Hospital in Genoa. This pilot study was approved by the Ethics Committee of San Martino Hospital and informed consent was obtained from patients and donors. Nine patients were treated, ages 22 to 57 (median age, 36 years) (Table 1). Four had primarily refractory (n=2) or relapsed (n=2) Hodgkin's disease (HD) and two patients had primarily refractory non Hodgkin's lymphoma (NHL); these patients had been treated with first and second line therapies without success. Two patients had chronic myelogenous leukemia (CML), one in accelerated phase (this patient did not have evidence of Philadelphia chromosome at diagnosis, but we found a p190 BCR-ABL gene by the reverse-transcriptase polymerase-chain reaction) and one in myeloblastic transformation with 70% marrow blasts. They were cytogenetically and molecularly resistant to hydroxyurea and interferon-α (5 MU/m^2/die). One patient had refractory anemia with excess blasts (RAEB) with t(1;3) (p36;q21). The median time from diagnosis to mobilization therapy was 28 months (range, 5-49 months). In the first stage of the protocol, autologous peripheral blood stem cells were mobilized from 8 patients, in six after treatment with cyclophosphamide 4 g/m^2 and G-CSF (5 µg/kg/day) and in 2 CML patients with the ICE protocol (blastic phase) or mini-ICE protocol (accelerated phase).[3,4] All but the RAEB patient went on to the next phase of the protocol within 28 days (range, 15-270 days). In preparation for autologous transplant, patients underwent high-dose chemotherapy on protocols appropriate for the underlying disease. CML patients received high-dose busulfan 3 mg/kg/day $\times$ 4 days (accelerated phase) or high-dose mitoxantrone (20 mg/m^2/days $\times$ 3 days) with arabinosylcytosine (1000 mg/m^2/day $\times$ 3 days) (blastic phase). The HD and NHL patients were treated with the BEAM protocol:[5] carmustine 300 mg/m^2 i.v. on day 1, etoposide 200 mg/m^2 i.v. days 2-5, arabinosylcytosine 200

Table 1. Patients and disease characteristics.

	Diagnosis	*Age/sex*	*Previous therapy*	*Status pre-ASCT*	*Interval Auto/Allo (days)*	*CD34+ dose (10^6/kg)*	*D->H*
ZM	HD, MC, IV L+	22/F	MOPP/ABVD DexaBeam	PRD	33	7.8	M/F
BG	HD, NS, IIIA, Med, L+	36/F	EBV/C-MOPP CEP+RT	Rel	40	1.3	F/F
GI	HD, NS, IVB, Med, B+	26/M	MOPP/EBV RT	PRD	96	2.07	F/M
CP	HD, NS, IIA, Med	36/M	MOPP/ABV hybrid RT	Rel	39	3	M/M
BR	NHL, WF:A, IVA	43/M	Flu+IDA CNOP	PRD	40	3.7	F/M
RC	NHL, HG, large cells, IVA, Med, K+, L+, H+	24/F	Mito, VP-16, Cy, CHOP	PRD	40	4.7	M/F
ND	BP-CML	50/F	HU, IFN-α	BP-CML	30	1.6	M/F
ME	AP-CML	55/M	HU, IFN-α	AP-CML	37	1.8	M/M
PM	RAEB, t(1;3)(p36;q21)	57/F	PDN, EPO, Thioguanine mini-ICE	RAEB, t(1;3)	–	5.9	M/F

HD: Hodgkin's disease; L: lung, MC: mixed cellularity; PRD: Primarily refractory disease; M: male; F: female; NS: nodular sclerosis; Rel: relapse; Flu: fludarabine; IDA: idarubicin; K: kidney; H: liver; HU: hydroxyurea; AP: accelerated phase; Med: bulky mediastinum; BP-CML: blastic phase- chronic myelogenous leukemia; H: host; D: donor; Mito: mitoxantrone; VP-16: etoposide; Cy: cyclophosphamide. ASCT: autologous stem cell transplantation.

mg/m^2 b.i.d. on days 2-5 and melphalan 140 mg/m^2 i.v. on day 6. After recovery from autografting, all patients with lymphoma were re-staged by all available imaging techniques (plain radiographic imaging with computed tomographic scan) (Table 2). Patients who had a greater than 50% reduction in measurable disease were considered to be in partial remission; patients who did not achieve complete or partial remission, or who had progression of their disease, were considered to have primarily refractory disease. Three patients with HD and both patients with NHL achieved partial remission. The patients with CML achieved a second chronic phase but all metaphases were still 100% Philadelphia chromosome positive in blastic phase-CML patient and BCR-ABL positive in the accelerated phase-CML patient. The median time from autografting to allografting was 40 days (range, 33-96). The patients received fludarabine (30 mg/m^2/day on days 1-3) with cyclophosphamide (300 mg/m^2/day on days 1-3). GvHD prophylaxis consisted of cyclosporin begun the day before donor stem cell infusion at 1 mg/kg/day by continuous infusion and methotrexate 10 mg/m^2 on days +3 and +5; cyclosporin was continued by i.v. infusion for 12-29 days (median, 16 days), after which it was given by the oral route. The donors were treated with G-CSF at 10 mg/kg b.i.d. for 2 to 4 days and then underwent leukaphereses of stem cells. A median of 3×10^6/kg (range, 1.3-7.8) donor CD34$^+$ cells were obtained and infused fresh into the patient 48 hours after the conclusion of Flu-Cy therapy. Patients' blood samples were serially studied for chimerism.

Evaluation of chimerism

Cytogenetics and DNA polymorphisms by fluorescence-based technology of multiplexed PCR-products (STR) on bone marrow cells were used as a marker for chimerism. Allogeneic stem cells have been monitored with this technique, firstly by multiplex reaction and then by detecting donor/recipient cell population ratios at 10 day intervals the first month and 15 day intervals in the second and in third month after allografting by evaluation peak areas in single-plexed PCR products of each informative marker.

Results

The Flu-Cy protocol was well-tolerated with no severe procedure-related toxicity. No patient required platelet or red cell transfusion. Patients were discharged from the hospital 16 to 28 days (median, 19) after donor stem cell infusion (Table 2). There was evidence of 100% donor cell engraftment in six patients (Table 3). Severe aGvHD was observed in two patients and mild aGvHD in one patient. The first patient was readmitted to the hospital because of fever, herpes zoster and liver grade II aGvHD diagnosed clinically and successfully treated with acyclovir, high-dose methylprednisolone (125 mg/m^2/day) and cyclosporin (2 mg/kg/day). Soon after, the patient developed evidence of GI tract grade II aGVHD, with good clinical response to octreotide, methylprednisolone and cyclosporin. This patient still has liver cGvHD ten months after allografting and progressive HD. The second patient developed GI grade III aGvHD combined with grade II skin disease. Progressive respiratory fail-

Table 2. Treatment results, outcome and survival.

	Diagnosis	*Response to Auto*	*Days ANC <1×10^9/L*	*Day PLT <20×10^9/L*	*Hospitalization (days)*	*aGvHD after Tx*	*Status after Tx (months)*	*Outcome and survival*
ZM	HD	PR	NR	NR	25	Liver (2)	PR	Achieved PR, liver cGvHD. Alive in progressive disease, (10+)
BG	HD	PR	NR	NR	20	none	CR	Achieved CR. Alive in CR, (6+)
GI	HD	PD	NR	NR	19	none	PD	Never achieved CR. Died from progressive disease day 65.
CP	HD	PR	NR	NR	16	Skin (2), GI (3)	CR	Achieved CR. Alive in CR, (4+)
BR	NHL	PR	NR	NR	19	none	CR	Achieved CR. Alive in CR ,(2+)
RC	NHL	PR	NR	NR	18	none	PR	Maintained PR. Alive in PR, (3+)
ND	BP-CML	2nd CP	NR	NR	26	none	2nd CP	Achieved 2nd chronic phase. Alive in 2nd CP, (7+).
ME	AP-CML	2nd CP	NR	NR	17	Skin (1),GI (1)	CMol.R	Achieved molecular remission. Alive in CR, (4+).
PM	RAEB, t(1;3)	---	3	NR	28	none	CCyR	Achieved cytogenetic remission. Alive in CR, (2+)

RAEB: refractory anemia with excess of blasts; 2nd CP: second chronic phase; CCyR: complete cytogenetic remission; CMol.R: complete molecular remission. NR: never reached; Tx: allografting; PR: partial remission; PD: progressive disease; BP: Blastic phase; AP: accelerated phase;

Table 3. Chimerism analysis after immunosuppressive non-myeloablative regimen and allogeneic HSC transplantation.

		% Donor*											
		+10	*+20*	*+30*	*+45*	*+60*	*+75*	*+90*	*+115*	*+150*	*+210*	*+250*	*+280*
ZM	HD	25	65	80	80	88	88	88	88	95	100	100	100
BG	HD	28	50	70	92	92	98	100	100	100	100		
ND	BP-CML	5	5	8	8	5	7	0	0				
ME	AP-CML	6	6	15	20	10	55	95	100				
GI	HD	20	20	60	55	Died							
CP	HD	5	20	25	40	40							
BR	NHL	15	15	80	100								
RC	NHL	5	20	30	35	70	100						
PM	RAEB	45	50	65	60	80	100						

**Percentage based on results by Short Tandem Repeat Polymorphisms via PCR; HSC: hematopoietic stem cells.*

ure due to bilateral pneumonia in the presence of *Pseudomonas aeruginosa*, *Klebsiella oxytoca*, *Staphylococcus coagulase negative*, *Candida Albicans* and *Aspergillus* was demonstrated by BAL. Specific antibiotic therapy (third generation cephalosporin and aminoglycosides combined with vancomycin in continuous i.v. infusion) and amphotericin B (subsequently substituted by liposomal derivatives) produced a complete resolution. In another patient there was a suggestion of grade I aGVHD of the skin (erythema) and diarrhea (500 cc/die) which disappeared after therapy with octreotide, corticosteroids and oral cyclosporin.

Disease response

Two of the HD patients, who were in partial remission after autografting, achieved a complete remission after allografting and both are disease-free 2 and 6 months after. Another HD patient is alive after 10 months but she is in progressive disease and the fourth patient died of progressive disease on day 65. One of the two patients with NHL who achieved partial remission after autografting, is disease-free 2 months after allografting. The other patient remains in partial remission. The blastic phase-CML patient continues in a second Ph-positive chronic phase 7 months after allografting; in contrast, the patient with accelerated phase disease, who obtained a second chronic phase after autografting, achieved complete disappearance of BCR-ABL hybrid transcript and he is now in complete hematologic and molecular remission with 100% donor cells in the marrow on day 108 (Table 5). The patient with RAEB with t(1;3) achieved complete hematologic and cytogenetic remission with 100% donor cells and she is disease free 2 months after (Table 4). All patients, but the Hodgkin's disease who progressed and died after allografting, are alive between 2 and 10 months (median, 4 months) post-allografting.

Table 4. Laboratory values and cytogenetic response in RAEB with t(1;3) patient.

Variables	*Before HSCT*	*D+20 after HSCT*	*D+45*	*D+53*	*D+63*
Hemoglobin (µg/L)	7.6	10.5	10.5	10.9	12.6
White cell count ($\times$ mm^3)	3100	2600	2900	3000	3000
Platelet count ($\times$ mm^3)	275,000	143,000	145,000	147,000	150,000
Cytogenetics on BM					
46,XX,t(1;3)(p36;q21)	100%	42%	27%	0	0
46,XY	0%	58%	73%	100%	100%
STR* on BM	---	50%	60%	80%	100%

**Percentage based on results by Short Tandem Repeat polymorphism via PCRHSCT: allogeneic hematopoietic stem cell transplantation.*

Table 5. Accelerated phase-CML: quantitative competitive RT-PCR and STR evaluation after allografting.

	Days	*BCR-ABL/ABL ratio*	*STR* (%)*
	d -10	0.1	---
Allografting	d 0	---	---
	d +20	ND	6
	d +30	0.01	15
	d +45	0.01	20
	d +75	0.003	55
	d +90	0.001	95
	d +108	0.0008	100
	d +122	0.0001	100

**Percentage based on results by Short Tandem Repeat polymorphisms via PCR.*

Discussion

Myeloablative chemo-radiotherapy regimens, generally considered a mandatory first step in the preparation of allografting, are associated with substantial toxicity and mortality rates particularly in older patients. Recently, it was demonstrated that fludarabine, as for other purine analogs, has substantial immunosuppressive activity, inducing long-lasting T-cell lymphopenia when used in the treatment of patients with lymphoproliferative disorders and when administered to patients with chronic lymphocytic leukemia as part of their primary therapy before allografting.[6] Fludarabine may modulate the host immune system, thereby reducing the severity of GvHD;[7,8] moreover, transfusion-associated GvHD appears to be more frequent in fludarabine-treated patients, because of the profound $CD4^+$ and $CD8^+$ T-cell depletion induced by the drug.[9]

The efficacy of this drug in combination with other myelosuppressive drugs in allowing engraftment of HLA matched sibling donor stem cells was recently demonstrated.[1,2] These teams used nonmyeloablative but myelosuppressive drugs in their regimens. Because of this, major hepatic toxicity was seen combined with neutropenia[2] or neutropenia alone.[1] Five patients died of infections and multiorgan failure in Houston and four patients died of severe aGvHD in Jerusalem. Furthermore, in no case was cytogenetic and/or molecular evidence of remission documented. In contrast, the Flu-Cy protocol employed by our team is free of myelosuppressive drugs but immunosuppressive enough to allow the engraftment of donor cells without potential side effects. None of our cases showed hepatic toxicity and only one patient had a neutropenia lower than 1×10^9/L. To date, with the exception of the blastic phase-CML patient who appears to have had autologous recovery, complete chimerism (100% donor cells) has been demonstrated in six patients and one patient is now on the way to achieving it; another patient died of progressive disease on day 65 (STR 55% of donor cells) (Table 3).

The second objective of our pilot study was to verify whether autologous and allogeneic transplantations can be combined in order to harness the reduction of tumor burden following autografting and the immune-mediated effects on minimal residual disease after allografting without high general toxicity and/or procedure-related deaths. We have demonstrated that this approach can be pursued in safety in a serious ill population. No patient experienced procedure-related deaths; the patients did not require a sterile room or any red cell or platelet transfusions. None needed hyperalimentation and none of them suffered mucositis. At a median of 19 days, the patients were discharged from the hospital and were followed-up as an outpatient. Two patients showed > grade II aGvHD but neither of them died. Seven of 8 patients (88%) treated by autografting followed by allografting are alive and 4 of them achieved complete remission.

Of particular interest are the results achieved in the patients with RAEB and accelerated phase-CML. In the first case, the patient was pretreated with high-dose erythropoietin followed by corticosteroids and chemotherapy without success. In the last months she was receiving red cell transfusions every week to maintain a hemoglobin level between 7-8 g/dL. All metaphases contained t(1,3) (p36;q21). On day 63 after allografting, karyotype showed only 46 XY without evidence of 1;3 translocation. Reticulocytosis of 12% was shown on day 40 and was followed by an increase in hemoglobin to 12.6 g/dL by day 63 (Table 4). No sign of aGvHD was observed.

The second patient had CML diagnosed in 1996 without evidence of Ph-chromosome but with p190 BCR-ABL gene detected by RT-PCR. He was treated with hydroxyurea and interferon-α (5 MU/m^2/d) for 6 months but the RT-PCR remained positive and WBC and platelets increased. In October 1997, the disease was considered to be in an accelerated phase; WBC 105×10^9/L and platelets 1200×10^9/L. He was treated with the mini-ICE protocol[4] and, while recovering from aplasia, he underwent leukaphereses, which yielded only PCR-positive cells with a BCR-ABL/ABL ratio of 0.1. The patient received autografting but no change in the BCR-ABL/ABL ratio was seen and WBC and platelets increased. He had a 69-year-old HLA-matched brother and after Flu-Cy protocol, mobilized donor hematopoietic stem cells were infused. Granulocytes and platelets never decreased below 1×10^9/L and 20×10^9/L, respectively. He was discharged on day 14 and followed as an outpatient. Complete chimerism was achieved on day 108 (100% donor cells) with the BCR-ABL/ABL ratio 0.0008. On day 122 the complete chimerism was confirmed with BCR-ABL/ABL ratio being 0.0001 (Table 5).

In conclusion, the long term benefit of this treatment has yet to be determined. The five patients who share normal performance status with disease remission 2 to 7 months from allografting are reasons for cautious optimism. Considering that our patients were all at high-risk, we think that such a sequential procedure could represent a new approach for a large variety of clinical situations with an indication for allografting.

Addendum

In July 1998 the outcome of our patients was the following:
ZM: alive in PD (liver) with cGvHD (100% donor cells);
BG: alive in CR (100% donor cells);
CP: died in CR of brain hemorrhage following aspergillus infection; morevoer, cGvHD in the liver (40% donor cells);
BR: alive in CR (100% donor cells);
RC: alive in progressive lymphoma (100% donor cells);
ND: alive in myeloblastic phase-CML (100% donor cells);
ME: alive in hematologic and molecular remission (BCR/ABL-ABL ratio < 0.0001 at 7 months) (100% donor cells);
PM: alive with 50% of t(1;3) (20% donor cells).

Contributions and Acknowledgments

AMC and AB were the principal investigators. AMC/EL wrote the paper, designed the study, obtained ethical approval, directly supervised and had day-to-day contact with participants, performed the analysis and interpretation of data. FF, AD, LC, RB, AG, MV, LT and GPa were involved in clinical assessment of the patients. MTC developed and carried out the molecular biology assays. FB and OF carried out the flow cytometry analyses. CP developed and carried out the cytogenetics analyses. PC, GF, GL, MVa, GPi and MP coordinated and analyzed CD34+ cell collection by leukapheresis. LCa and FDS collaborated in the study design and developed and carried out the STR analyses. All the authors gave their critical contribution to the manuscript and approved its final version.

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Disclosures

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