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RAPID COMMUNICATION

Successful Transplantation of HLA-Matched and HLA-Mismatched Umbilical Cord Blood From Unrelated Donors: Analysis of Engraftment and Acute Graft-Versus-Host Disease

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To reduce the morbidity and mortality associated with unrelated donor bone marrow (BM) transplantation and potentially extend the pool of suitable donors, cryopreserved unrelated donor umbilical cord blood was considered as an alternate source of hematopoietic stem cells for transplantation. Patients with leukemia, BM failure syndrome, or inborn error of metabolism were eligible for a phase I clinical trial designed to estimate the risk of graft failure and severe acute graft-versus-host disease after transplantation of umbilical cord blood from unrelated donors. As of December 21, 1995, unrelated donor umbilical cord blood was used to reconstitute hematopoiesis in eighteen patients aged 0.1 to 21.3 years weighing 3.3 to 78.8 kg with acquired or congenital lympho-hematopoietic disorders or metabolic disease. Patients received either HLA-matched (n = 7) or HLA-1 to 3 antigen disparate (n = 11) grafts collected and evaluated by the New York Blood Center (New York, NY). The probability of engraftment after unrelated donor umbilical cord blood transplantation was 100% with no patient having late graft failure to date. The probability of grade III-IV acute graft-versus-host disease at 100 days was 11%. With a median follow-up of 6 months (range, 1.6 to 17 months), the probability of survival at 6 months is 65% in this high risk patient population. We conclude that cryopreserved umbilical cord blood from HLA-matched and mismatched unrelated donors is a sufficient source of transplantable hematopoietic stem cells with high probability of donor derived engraftment and low risk of refractory severe acute graft-versus-host disease. Limitations with regard to recipient size and degree of donor HLA disparity remain to be determined.
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BONE MARROW transplantation (BMT) from HLA-identical sibling donors has been successfully used to treat patients with high-risk or recurrent hematological malignancies, BM failure syndromes and selected hereditary immunodeficiency states and metabolic disorders. A major limitation to the successful use of marrow transplant therapy, however, has been the limited availability of suitable related donors. To increase the availability of marrow transplant therapy for patients who lack closely matched related donors, alternative sources of hematopoietic stem cells have been evaluated.

Since its inception in 1986, the National Marrow Donor Program (NMDP) has identified a pool of 1.92 million potential marrow donors and facilitated 3,965 unrelated donor BM transplants as of December 1, 1995 (personal communication, NMDP). However, there are several important obstacles that limit the successful use of unrelated donor marrow; these include, (1) the long length of the donor search process which is currently a median of 3.5 months (range 1 month to 6 years,[1] (2) limited numbers of donors in certain racial and ethnic subpopulations, (3) donor unavailability at the time of request, and (4) an increased risk of graft rejection, severe graft-versus-host disease (GVHD) and opportunistic infection after the transplant procedure.[1] Various strategies for ameliorating these problems are currently being investigated.

Umbilical cord blood has been used as a source of hematopoietic stem cells in young patients with sibling donors since 1988.[2] Analysis of the clinical results in the first 44 patients showed that umbilical cord blood contains sufficient numbers of hematopoietic stem and progenitor cells to engraft at least small recipients and that the transplantation of these cells was associated with a very low risk of acute and chronic GVHD.[3] As a result of the preliminary successes with the transplantation of umbilical cord blood from sibling donors, pilot programs for the banking of unrelated donor umbilical cord blood were initiated both in the US and in Europe.[4,5] As of December 1995, approximately 5,000 umbilical cord blood grafts have been collected, HLA typed, tested for transmissible infectious diseases and cryopreserved at the New York Blood Center. In order to estimate the toxicity of unrelated donor umbilical cord blood as source of transplantable hematopoietic stem cells, selected high risk patients were considered for a phase I clinical trial to estimate the rate of sustained donor derived hematopoietic reconstitution and risk of severe acute GVHD.

MATERIALS AND METHODS

Eligibility. Patients with high risk leukemia, BM failure syndrome, immunodeficiency state, or inborn error of metabolism were eligible for this phase I clinical trial, if: (1) an HLA-compatible related or unrelated BM donor could not be identified within 4

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months of search request, (2) the nucleated cell count of the umbilical cord blood graft exceeded 1×10^7 per kilogram recipient body weight, and (3) patient and/or guardian consented to the transplant procedure. Protocols for intensive myeloablative therapy and use of unrelated donor umbilical cord blood for transplantation were reviewed and approved by the institutional review boards at the University of Minnesota and Children's Hospital of Orange County.

Patients. Eighteen patients received unrelated donor umbilical cord blood transplants for malignant (n = 13) and nonmalignant (n = 5) disorders between July 1994 and December 1995 at the University of Minnesota (n = 13) and Children's Hospital of Orange County (n = 5). The median age and weight of patients was 2.7 years (range, 0.1 to 21.3) and 15.4 kg (range, 3.3 to 78.8), respectively. Ten patients were male and eight were female. The diagnosis and disease status of patients at the time of transplantation are shown in Table 1. Seven patients received grafts that were matched at HLA-A, B, and DRB1 and 11 received grafts that were disparate at one to three HLA loci (see Table 3). Eight patients received sex mismatched grafts (4 male → female and 4 female → male) and 8 patients received umbilical cord blood from ABO-incompatible donors.

Preparative regimen and GVHD prophylaxis. Pretransplant conditioning varied according to the patient's disease and institution. At the University of Minnesota, patients with acute lymphocytic leukemia (ALL) were treated with hyperfractionated total body irradiation (TBI) 1,375 cGy, cyclophosphamide 120 mg/kg and antithymocyte globulin (ATGAM; Upjohn, Kalamazoo, MI) 60 mg/kg; patients with acute myelogenous leukemia (AML) and juvenile chronic myelogeneous leukemia (JCML) were treated with cyclophosphamide 120 mg/kg, fractionated TBI 1,320 cGy and ATGAM 60 mg/kg; patients with BM failure syndromes or metabolic disease were treated with busulfan 320 mg/m^2, cyclophosphamide 120 mg/kg, TBI 750 cGy in a single fraction and ATGAM 60 mg/kg. At Children's Hospital of Orange County, patients with ALL were treated with fractionated TBI 1,200 cGy, etoposide 50 mg/kg, cytosine arabinoside 60 mg/kg, and cyclophosphamide 90 mg/kg; patients with myelodysplastic syndrome (MDS) were treated with etoposide 1,500 mg/m^2 cytosine arabinoside 28 g/m^2, cyclophosphamide 2,700 mg/m^2, and fractionated TBI 1,200 cGy; patients with AML were treated with thiotepa 25 mg/kg, busulfan 12 mg/kg, and cyclophosphamide 120 mg/kg; and patients with metabolic disease were treated as described for those at the University of Minnesota. Prophylaxis for acute GVHD consisted of cyclosporine A alone (n = 1) or in combination with methylprednisolone (n = 14) or methotrexate (n = 3).

Unrelated donor selection. Searches for potential unrelated donor umbilical cord blood grafts were performed by the New York Blood Center. Before transplantation, confirmatory HLA typing of patient and cryopreserved donor specimens were performed using standard serological techniques identifying all WHO-recognized specificities for HLA-A and B antigens. In addition, HLA-DRB1 typing of all 18 donor-recipient pairs was performed using high resolution DNA techniques.

Eighteen patients fulfilled the prescribed eligibility criteria and were offered unrelated donor umbilical cord blood transplantation. For this cohort of patients, the median time between date of initial umbilical cord blood search request and umbilical cord blood transplantation was 65 days (range, 26 to 152). Notably, the median time between date of initial search request and HLA confirmation of the donor graft was 39 days (range, 12 to 109).

Collection and processing of umbilical cord blood. The methods of umbilical cord blood collection and testing have been reported previously.[4] Briefly, the delivered placenta was suspended from a frame with the umbilical cord side down. After cleansing the umbilical cord with ethanol and iodine, the blood was collected by cannulating the umbilical vein with a 16 gauge needle. Blood was collected into a blood collection bag (Baxter, Round Lake, IL) containing approximately 23 mL citrate phosphate dextrose-A (CPD-A). The blood was stored at room temperature and transported to the New York Blood Center for testing and cryopreservation. All grafts were cryopreserved in dimethyl sulfoxide (DMSO) (10% final concentration).

Cryopreserved donor units were delivered to the transplant center from the New York Blood Center via air transportation by overnight express. Before infusion, the umbilical cord blood graft was placed

Table 1. Diagnosis and Disease Status of Patients at Time of Umbilical Cord Blood Transplantation

UPN No.	Disease	Age/Sex	Wt	Prep Rx	CBT Date
2,051	ALL CR3	10.9/M	47.7	TBI/CY	07-09-94
2,058	GLD	2.8/M	18.7	BU/CY/TBI	07-29-94
M007	AML REL2	2.5/M	12.1	CY/TBI	03-03-95
2,207	ALL REL3	10.5/M	35.3	TBI/CY	05-03-95
2,214	Blackfan-Diamond	1.4/M	9.1	BU/CY/TBI	05-10-95
2,224	AML REL3	2.1/M	11.2	CY/TBI	05-30-95
2,240	AML CR2	1.0/F	7.5	CY/TBI	06-23-95
2,249	ALL CR2	1.0/F	6.5	TBI/CY	07-04-95
2,270	Osteopetrosis	0.1/M	3.3	BU/CY/TBI	08-11-95
2,293	AML REL2	14.9/F	78.8	CY/TBI	09-26-95
2,297	ALL REL1 Ph1$^+$	10.0/F	29.0	TBI/CY	10-04-95
2,313	FA/RA	21.3/F	49.5	CY/TBI	10-27-95
2,316	JCML	1.1/F	10.0	CY/TBI	11-03-95
141	ALL CR2	3.9/M	21.0	VP16/ARAC/CY/TBI	02-06-95
145	ALL CR2	0.8/F	9.4	TBI/VP16/ARAC/CY	03-24-95
155	AML CR2	1.3/F	11.2	TT/BU/CY	07-03-95
158	RAEB-T	9.7/M	26.4	VP16/ARAC/CY/TBI	07-27-95
160	ALD	21.3/M	53.6	BU/CY/TBI	08-13-95

Patients UPN 2,051 to 2,316 were treated at the University of Minnesota; patients UPN 141 to 160 were treated at Children's Hospital of Orange County.

Abbreviations: Age, age in years; WT, weight in kilograms; Ph1$^+$, Philadelphia chromosome positive; GLD, globoid cell leukodystrophy; ALD, adrenoleukodystrophy; FA/RA, Fanconi anemia with refractory anemia; RAEB-T, refractory anemia with excess blasts in leukemic transformation; CR, complete remission; REL, relapse; CY, cyclophosphamide; BU, busulfan; VP16, etoposide; ARAC, cytosinearabinoside; TT, thiotepa.

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in a sterile bag and then thawed in a 38°C waterbath with gentle agitation. After thawing, an equal volume of dextran/albumin solution was added over 10 minutes, centrifuged at 250*g* for 10 minutes at 10°C and the supernatant removed. The cell pellet was resuspended in dextran/albumin and immediately infused into the patient over 30 minutes to 4 hours.

The median volume of umbilical cord blood collected was 83.1 mL (range, 46.6 to 131 mL) and the median number of nucleated cells per kilogram recipient weight was 4.1×10^7 (range, 1.4 to 40.0).

Supportive care. Patients were hospitalized in single rooms ventilated with high-efficiency particulate air filtration systems. Patients at high risk for the recurrence of herpes simplex (ie, IgG titers $\geq$ 1:8) received prophylactic intravenous acyclovir. Patients at high risk for the recurrence of cytomegalovirus (CMV) (IgG titer $\geq$ 1:8) received prophylactic high dose acyclovir (Minnesota) or ganciclovir (Orange County) until day 100. Broad spectrum antibiotics were administered for fever during aplasia and amphotericin B was added for documented systemic fungal infections or for persistent fever unresponsive to antibiotic therapy. All patients received trimethoprim-sulfamethoxazole twice daily for 2 days each week for prophylaxis of Pneumocystis carinii for 6 months after transplantation and penicillin for prophylaxis of gram positive organisms during treatment of GVHD. Patients with documented CMV infection were treated with ganciclovir and intravenous Ig. Early use of hematopoietic growth factor (sequential use of granulocyte-macrophage colony stimulating factor (GM-CSF) followed by [G-CSF]) was prescribed in all 5 patients transplanted at the Children's Hospital and in none of 13 patients transplanted at the University of Minnesota. Two patients (UPN M007 and UPN 2,293) received hematopoietic growth factor on or after day 21 for delayed neutrophil recovery.

Engraftment. Hematologic recovery was defined as time to absolute neutrophil count (ANC) $\geq 5 \times 10^8$/L (first of 3 consecutive days) and platelet count $\geq 5 \times 10^{10}$/L (first of 7 consecutive days without transfusion support). Donor cell engraftment and remission status were assessed on day 21, 60, 100, 6 months, and 1 year after transplantation and determined by informative recombinant DNA probes that identify restriction fragment length polymorphisms (RFLP) in all instances. Patients were considered evaluable for engraftment if they survived > 30 days. Complete chimerism was defined as the presence of donor hematopoietic cells only; mixed chimerism was defined as the presence of both donor and recipient hematopoietic cell simultaneously.

GVHD. Patients were evaluated daily for acute GVHD during hospitalization and at least once weekly as an outpatient during the first 100 days. Diagnosis of acute GVHD was based on clinical signs with histopathologic confirmation when possible. Patients were considered evaluable for GVHD if they engrafted with donor cells and survived > 30 days. Overall staging was based on published criteria.[6] Patients with clinical grade II disease in any organ were treated with methylprednisolone $\geq$ 48 mg/m^2 intravenously. Except for 3 patients (UPN 2,249, UPN 2,316, and UPN 160) who received antithymocyte globulin for treatment of recurrent cutaneous disease (UPN 2,249 and UPN 2,316) or multiorgan disease (UPN 160), all other patients responded to steroids alone.

Statistical analysis. The major statistical end points of this phase I toxicity trial were probabilities of neutrophil recovery, acute GVHD and survival at 3 and 6 months after transplantation. Event times were measured from date of transplantation to date of neutrophil recovery and acute GVHD with censoring at time of death or last contact when it occurred before the specific event. Probability of engraftment, acute GVHD and survival curves were estimated by the product-limit method.[7] Event times were analyzed as of December 21, 1995.

RESULTS

Hematopoietic recovery and engraftment. Thirteen of 18 patients surviving > 30 days were considered evaluable for hematopoietic recovery with five patients dying on days 10, 19,

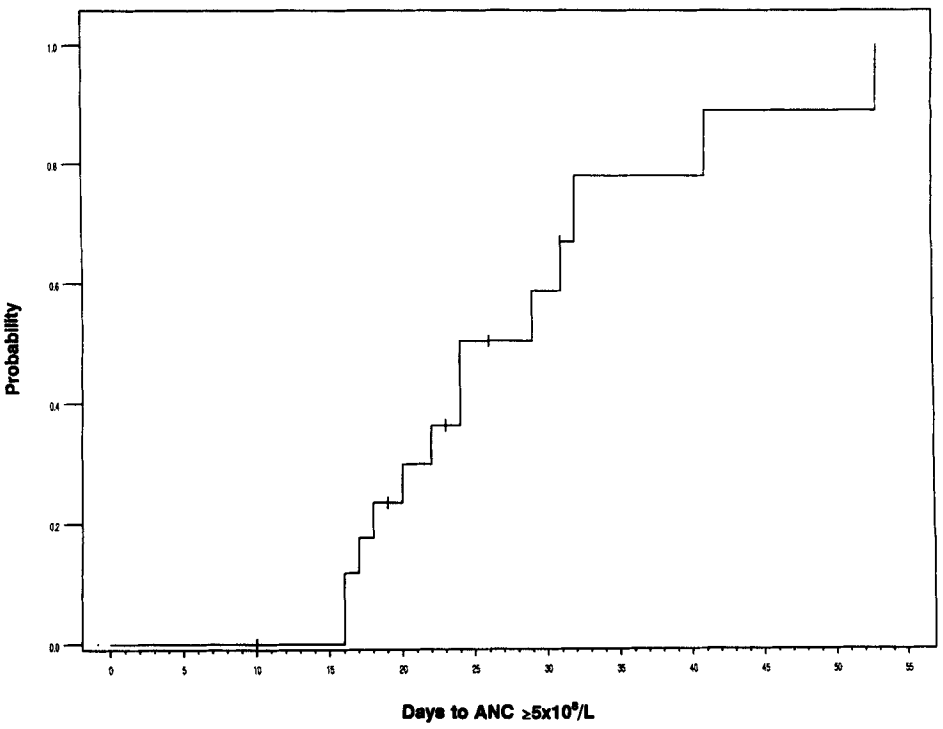

Fig 1. Actuarial probability of neutrophil recovery (defined as days to achieve an absolute neutrophil count $\geq 5 \times 10^8$/L) for thirteen recipients of unrelated donor umbilical cord blood surviving > 30 days. Tic marks indicate the day of death for five recipients dying before day 30 without neutrophil recovery.

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Table 2. Characterization of the Umbilical Cord Blood Graft and Hematopoietic Recovery

UPN No.	UCB Graft Vol (mL)	nuc/kg (× 10^7)	ANC ≥ 5 × 10^8/L	PLT ≥ 5 × 10^{10}/L	Chimerism
2,051	94	3.8	NE	NE	75-99
2,058	64	3.5	20	88	100
M007	57	3.0	41	NA†	100
2,207	97	4.1	NE	NE	NE
2,214	88	7.8	22	111	100
2,224	47	4.1	NE	NE	25-50*
2,240	56	10.1	29	67	100
2,249	53	16.0	31	65	100
2,270	83	40.0	24	120	100
2,293	88	1.4	53	TX	100
2,297	56	3.0	17	61	100
2,313	104	2.0	NE	NE	NE
2,316	86	10.4	32	TX	100
141	75	2.2	16	99	100
145	90	18.2	18	55	100
155	57	6.6	16	61	100
158	131	8.3	NE	NE	NE
160	83	1.7	24	TX	100

Abbreviations: NE, parameter not evaluable because of early death; TX, platelet transfusion dependent.

* RFLP analysis revealed 75% to 99% donor derived cells in the peripheral blood and 25% to 50% donor derived cells in the marrow with recurrent leukemia diagnosed by morphologic examination on day 21.

† NA = died before achieving a platelet count >5 × 10^{10}/L, although platelet transfusion independent.

23, 26, and 30 before achieving an ANC ≥ 5 × 10^8/L. For the 13 patients surviving > 30 days, the probability of neutrophil donor-derived recovery at 60 days after transplantation was 1.00 ± 0.00 with a median time to an ANC ≥ 5 × 10^8/L of 24.0 days (range, 16 to 53) (Fig 1). Moreover, donor-derived hematopoiesis in the marrow was documented in 15 patients, including 2 patients failing to achieve an ANC ≥ 5 × 10^8/L at the time of death before day 30. Thirteen showed complete chimerism and two showed mixed chimerism (Table 2). Mixed chimerism in one patient (UPN 2,224) was caused by persistent disease.

Platelet recovery was remarkably delayed as compared to that observed after unrelated donor BMT.[1] Of 13 evaluable

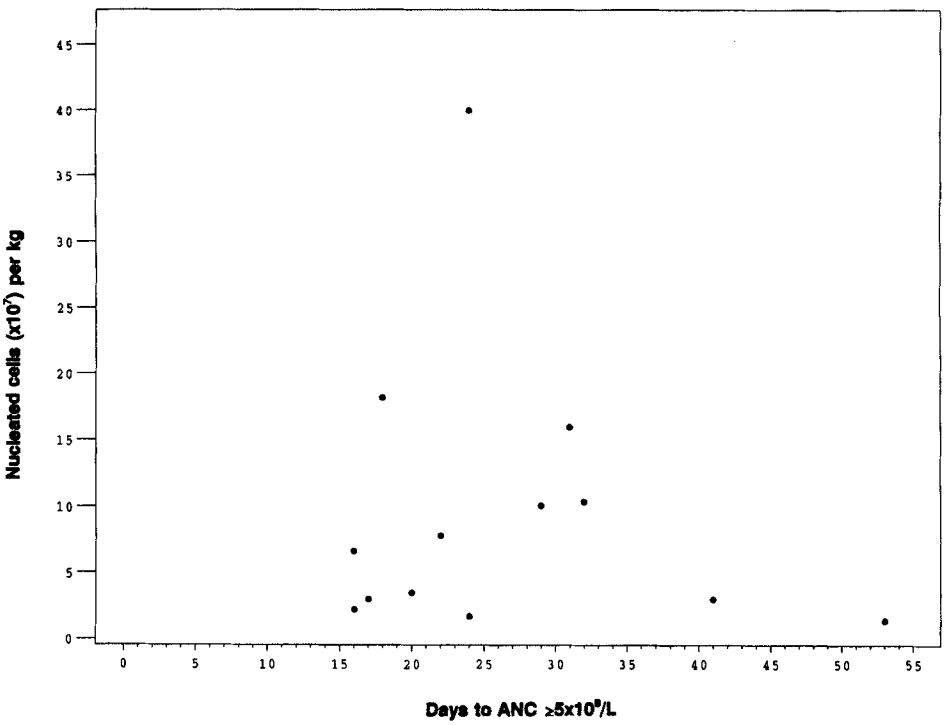

Fig 2. Comparison between number of nucleated cells per kilogram recipient body weight and time to neutrophil recovery (ANC ≥ 5 × 10^8/L) after umbilical cord blood transplantation were assessed using the Spearman rank method.

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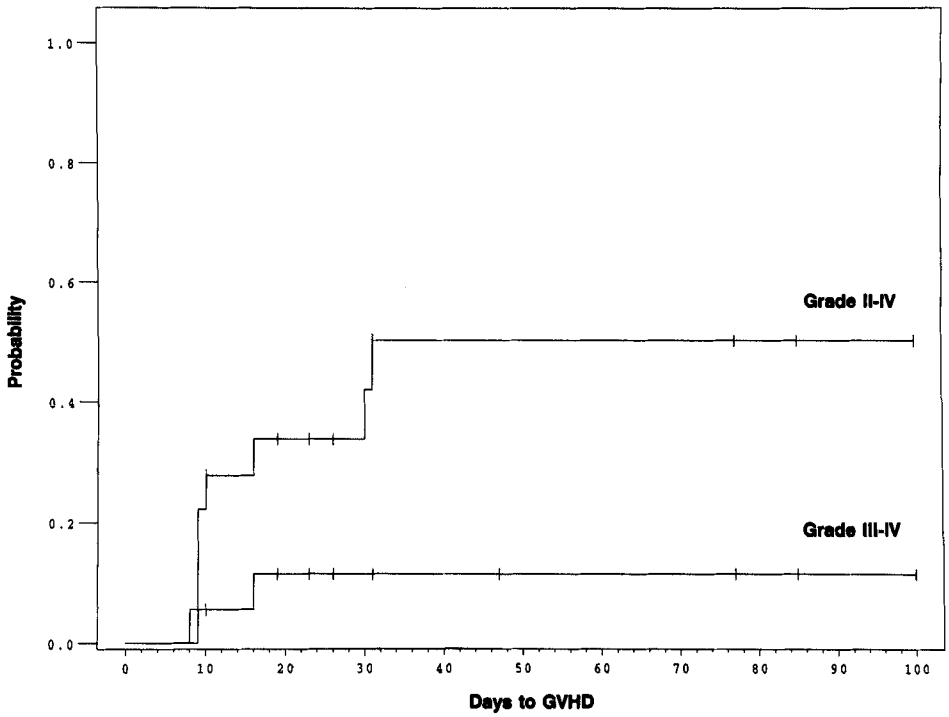

Fig 3. Probability of grade II-IV and III-IV acute GVHD.

patients, 10 became platelet transfusion independent. For these patients, the median time to achieve a platelet count $\geq 2 \times 10^{10}$/L (n = 10) and $\geq 5 \times 10^{10}$/L (n = 9) was 54 days (range, 39 to 130) and 67 days (range, 55 to 120) after transplantation, respectively (Table 2).

As reported for recipients of sibling donor umbilical cord blood, time to neutrophil recovery did not correlate with the number of nucleated cells infused (correlation coefficient, −0.135) based on recipient body weight (Fig 2). Insufficient data were available for a correlation of engraftment with numbers of GM-colony forming cells infused.

In an attempt to reduce the potential risks of hemoglobinuria and DMSO toxicity, all patients received washed, buffy coated umbilical cord blood cells before transplantation. No adverse effect on engraftment by this procedure was observed. Of eight patients receiving ABO-incompatible umbilical cord blood, no transfusion reaction was observed.

GVHD. For these recipients of HLA identical and HLA-1 to 3 antigen disparate umbilical cord blood grafts, the probability of having grade II-IV acute GVHD by 100 days after transplantation was 0.50 ± 0.13 (Fig 3). In all but three cases (UPN 2,297, UPN 2,316, and UPN 160), the disease was responsive to steroid therapy alone. However, two patients developed grade III-IV acute GVHD. In one case (UPN 141), histopathologic evaluation of the skin and lower gastrointestinal tract failed to document GVHD and the patient responded promptly to steroid therapy alone. In the other case (UPN 160), GVHD was documented in the skin, gastrointestinal tract and liver; unlike all other cases, GVHD was unresponsive to various agents, including antithymocyte globulin, anti-interleukin-2 receptor, methotrexate, and low dose cyclophosphamide. The probability of grade III-IV acute GVHD by 100 days after transplantation was 0.11 ± 0.08. Notably, the two recipients of HLA 2 antigen disparate unrelated umbilical cord blood grafts had only grade II disease and both responded to steroid therapy alone (Table 3).

Survival. The probability of survival at 3 and 6 months after transplantation is 0.65 ± 0.12 (Fig 4). Causes of death in the seven patients were early fungal sepsis (n = 2, UPN 2,051 and UPN 2,207), chemotherapy related toxicity/multiorgan failure (n = 2, UPN 2,313 and UPN 158), relapse (n = 2, UPN M007 and UPN 2,224) and grade IV GVHD (n = 1, UPN 160). Of the two patients relapsing after unrelated donor umbilical cord blood transplant, both had AML in relapse at the time of transplant with one (UPN M007) having previously relapsed after autologous marrow transplantation.

DISCUSSION

The use of umbilical cord blood as a source of transplantable hematopoietic stem cells was first suggested by Prof Edward A. Boyse (University of Arizona, Tucson) in 1983, tested in an animal model in 1984,[8] and used clinically to successfully treat a patient with Fanconi anemia in 1988.[2] As a result of early successes with umbilical cord blood from sibling donors, umbilical cord blood banks, including the Placental Blood Program at the New York Blood Center, were established in February 1993. The purpose of this phase I clinical trial was to document the engraftment potential of cryopreserved HLA-matched and mismatched unrelated donor umbilical cord blood in recipients with lympho-hematopoietic malignancy, BM failure syndrome or inborn errors of metabolism at high risk of disease progression or opportunistic infection.

Similar to the results observed in recipients of umbilical

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Table 3. GVHD

UPN No.	HLA Disparity†	CMV Stat	GVHD Proph	GVHD Grade				Survival
				Skin	Liv	GI	Overall	
2,051	6/6	+	MC	NE	NE	NE	NE	26
2,058	5/6 (DR)	+	CP	II	0	0	II	509*
M007	5/6 (B)	+	MC	I	0	0	I	252
2,207	6/6	+	CP	NE	NE	NE	NE	10
2,214	4/6 (B, DRB1)	+	CP	0	0	II	II	224*
2,224	6/6	+	CP	0	0	0	0	30
2,240	4/6 (B, DRB1)	–	CP	II	0	0	I	180*
2,249	5/6 (A)	–	CP	III	0	0	II	170*
2,270	5/6 (A)	–	CP	II	0	0	II	131*
2,293	6/6	+	CP	II	0	0	I	85*
2,297	5/6 (DRB1)	+	CP	I	0	0	I	77*
2,313	3/6 (B, B, DRB1)	–	CP	NE	NE	NE	NE	23
2,316	6/6	–	CP†	III	0	0	II	47*
141	6/6	–	C	III	II	II	III	317*
145	6/6	+	MC	0	0	0	0	271*
155	5/6 (DR)	–	CP	II	0	0	II	170*
158	4/6 (B, DR)	–	CP	NE	NE	NE	NE	19
160	5/6 (DR)	–	CP	0	0	III	II	88

Abbreviations: CMV status, patient's cytomegalovirus status by serology; C, cyclosporin A; M, methotrexate; P, prednisone/methylprednisolone.

* HLA antigen disparities between donor and recipient are shown in parentheses.

† Cyclosporin A was temporarily discontinued day 15 to 24 because of renal toxicity.

cord blood from sibling donors, a high rate of engraftment was documented after unrelated donor umbilical cord blood transplantation. In this study, all patients surviving > 30 days showed donor-derived hematopoiesis with early evidence of hematopoietic recovery observed in three additional patients dying before day 30. Thirteen patients achieved an ANC $\geq 5 \times 10^8$/L at a median of 24, days which is similar to that observed after sibling donor umbilical cord blood

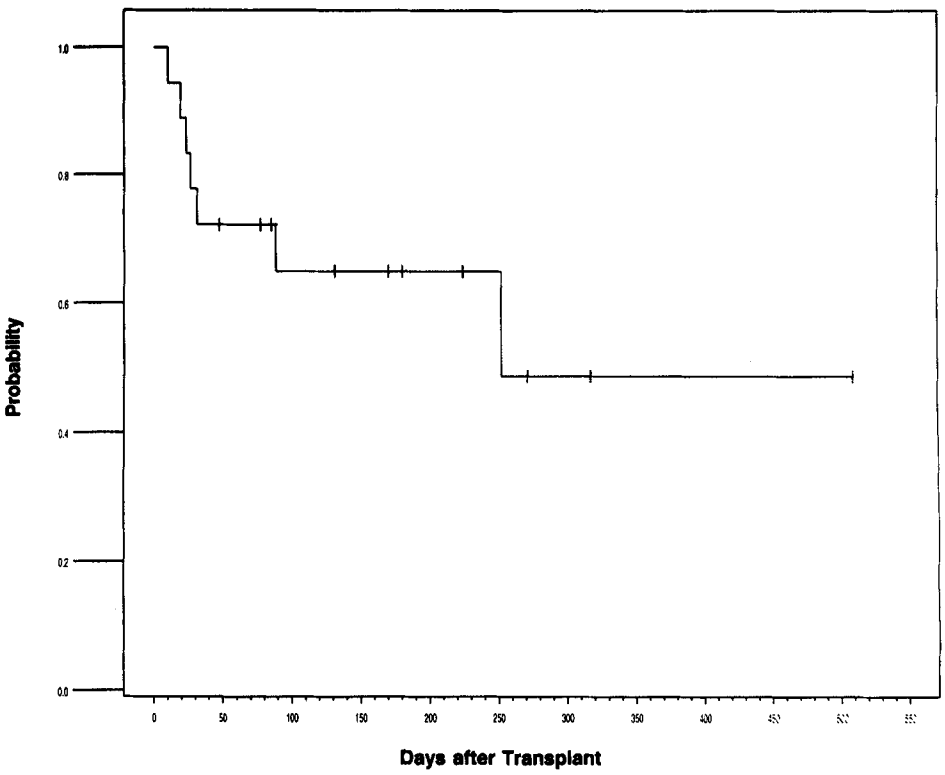

Fig 4. Probability of survival after transplantation of unrelated donor umbilical cord blood.

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transplantation (median 22.5 days[3]) and comparable to that observed after unrelated donor marrow transplantation.[1] However, platelet recovery was markedly delayed, as observed in sibling donor umbilical cord blood transplant recipients.[3] Although longer follow-up is required for some patients enrolled in this trial, donor-derived hematopoiesis has been sustained with late graft failure yet to be observed.

Of considerable interest, engraftment was also observed in the largest recipient weighing 78.8 kg. Rates of neutrophil and platelet recovery, however, were exceedingly slow. Although trilineage hematopoiesis of donor origin was documented in the BM as early as 21 days after transplantation, neutrophil recovery in the peripheral blood was not observed until day 40. Notably, no correlation between nucleated cell content of the umbilical cord blood graft and interval to neutrophil recovery could be discerned despite the wide range of cell doses infused in this cohort. Based on data from a preclinical model,[9] lack of correlation might suggest that the number of progenitors in an umbilical cord blood graft well exceeds that threshold needed for engraftment in small recipients. Further, such data would suggest that umbilical cord blood grafts may be sufficient for engraftment in adults. Whether the marked delay in recovery in the single adult size recipient will be a consistent finding remains to be determined.

Hematopoietic growth factors have been used after marrow transplantation to reduce the time to neutrophil recovery. In this analysis, prophylactic use of hematopoietic growth factor varied between the two institutions. The median time for neutrophil recovery was 17 days (range, 16 to 24) for patients treated with growth factor beginning on the day of transplantation as compared to 26 days (range, 17 to 53) for patients not treated with growth factor before day 21. Although these results suggest a role for hematopoietic growth factor early after the transplantation of umbilical cord blood, this observation contrasts with that reported for recipients of sibling donor umbilical cord blood. Of 44 children transplanted with umbilical cord blood from sibling donors as reported to the *International Cord Blood Transplant Registry,*[3] time to neutrophil recovery was no different between those receiving hematopoietic growth factor and those that did not.

The second major endpoint of this phase I clinical trial was to estimate risk of grade II-IV and grade III-IV acute GVHD after unrelated donor umbilical cord blood transplantation. In this series, the incidence of grade II-IV GVHD was 50%. However, most patients had limited disease responsive to first line therapy with methylprednisolone alone, which is especially notable in view of the fact that most patients had HLA mismatched donor grafts. Notably, two patients did develop grade III-IV disease with one responsive to initial therapy and the other refractory to multiple agents. Nonetheless these results compare favarably with those reported for young recipients of unrelated donor BM. Balduzzi et al[10] have recently reported an incidence of grade III-IV acute GVHD of 37% and 63% in recipients of HLA matched (n = 46) and HLA mismatched (n = 41) unrelated donor BM, respectively. Although case controlled studies must be performed to verify the benefit of unrelated donor umbilical cord blood in terms of GVHD risk, these results indicate that in some cases umbilical cord blood lymphocytes are capable of inducing a graft-versus-host response.

Beyond the important immunological aspects of umbilical cord blood transplantation, there are several other practical benefits associated with banked umbilical cord blood: (1) rapid availability, (2) absence of donor risk,[11] (3) absence of donor attrition, and (4) very low risk of transmissible infectious diseases, such as cytomegalovirus[12,13] and Epstein-Barr virus.[14] The results of this trial support the argument that umbilical cord blood grafts are more rapidly available. Compared to the median of 3.5 months to acquire marrow from an unrelated donor, umbilical cord blood was available a median of 69 days after search request. Even with this reduction in search time, current delays in the search process were often a reflection of the small bank size. Although searches frequently failed to identify a suitable umbilical cord blood donor initially, HLA compatible grafts were identified weeks to months later as new grafts were registered. Nonetheless, this decreased time to acquire a donor graft may have an important impact on overall treatment outcome because a significant proportion of patients either relapse or die of infection while completing a marrow donor search or develop complications, which increase the risk of transplant-related mortality.

In summary, we have shown that cryopreserved umbilical cord blood from unrelated donors is a safe source of transplantable hematopoietic stem cells for clinical transplantation. The high rate of engraftment and low rate of grade III-IV acute GVHD even in recipients of HLA disparate grafts are remarkable. Future phase II and III clinical trials will be required to further characterize the advantages of umbilical cord blood from unrelated donors as a source of hematopoietic stem and progenitor cells for both pediatric and adult recipients as well as to define the degree of HLA matching required for successful transplantation.

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