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CORRESPONDENCE

A pilot feasibility study of non-myeloablative allogeneic hematopoietic stem cell transplantation for refractory Crohn Disease

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To the Editor:

Refractory Crohn disease (CD) has been treated with autologous hematopoietic stem cell transplantation (HSCT) using a cyclophosphamide and anti-thymocyte globulin conditioning regimen with or without CD34 selection of the autologous peripheral blood stem cells (PBSC) [1–8]. This regimen provided a treatment-free remission, but histologic evidence of disease activity persisted, and clinical relapses occurred in ~50% and 90–100% by 3 and 5 years, respectively [1–10]. In the only randomized clinical trial to date, the difference between autologous HSCT and the comparator arm in sustained remission defined as a Crohn disease activity index (CDAI) < 150 on no immune drugs and no endoscopic or radiologic evidence of disease was not significant [9, 10]. There have been no reports of sustained 5-year treatment-free remission without clinical, radiologic, endoscopic, or histologic evidence of disease after autologous HSCT.

We undertook a pilot study of non-myeloablative allogeneic HSCT using unselected matched sibling PBSC in three patients and umbilical cord blood (UCB) in six patients when a matched sibling donor was not available. UCB was 6/6 matched in four patients and 5/6 matched in two patients. Two UCB units were available for five patients. The trial was approved by the Institutional Review Board and the Food and Drug Administration and registered with www.clinicaltrials.gov NCT 01288053.

The patients who underwent HSCT were disabled with active inflammatory disease (mean CDAI of 310) despite at least two prior tumor necrosis factor inhibitors. Six patients had fistulae (four perianal, two enterocutaneous), five had strictures, four had prior Crohn-related surgeries, four had total parenteral nutrition, two were refusing a medically recommended total colectomy, one had growth retardation, and one was bedridden from Crohn-related arthralgias. Patients ranged in age from 20 to 41 years old (mean age 26). Forty-four percent (4 of 9) were male. Disease duration before HSCT ranged from 10 to 26 years (mean 15.8 years).

A non-myeloablative conditioning regimen of cyclophosphamide, alemtuzumab, and fludarabine was used to achieve mixed chimerism. Dose escalation of fludarabine and/or alemtuzumab was performed when the prior patients demonstrated minimal or no evidence of donor hematopoietic engraftment (Table 1). During inpatient transplantation, filgrastim, hydration, diuretics, intravenous mesna, and blood product transfusion guidelines were followed as previously reported [1]. Prophylaxis to prevent alemtuzumab-related hives included intravenous methylprednisolone, oral Montelukast, loratadine, chlorpheniramine, diphenhydramine, and acetaminophen. Oral ciprofloxacin and rifaximin were started upon hospital admission and continued until discharge. Intravenous cephalosporin was started on day 0. Intravenous vancomycin was added for a febrile episode. Posttransplant prophylaxis with oral acyclovir, fluconazole, and trimethoprim-sulfamethoxazole was continued for 6 to 9 months. Cytomegalovirus viral load was monitored for 90 days and treated preemptively by switching to oral valganciclovir. For the first 6 to 9 months post HSCT a calcineurin inhibitor was given orally to minimize both graft versus host disease (GVHD) and host verses graft rejection.

No patient died during transplant, and inpatient transplant-related toxicities were NCI grade 3 and due to

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Table 1 Summary.

Patient	Conditioning regimen	Allogeneic $CD34^+$ cells × 10^6/kg	Day of engraftment/day of discharge	Donor chimerism (6 months post HSCT)	GVHD	Crohn disease outcome
Matched sibling						
1	Cy (50 mg/kg × 4) = 200 mg/kg Flu (25 mg/m^2 × 3) = 75 mg/m^2 Alemtuzumab 30 mg × 3 = 90 mg	7.01	13/15	CD3—20% CD33—2%	None	No CD therapy for 5 years, at 5 years no MRI imaging, colonoscopy, or biopsy histologic evidence of disease
2	Cy (50 mg/kg × 4) = 200 mg/kg Flu 30 mg/m^2 × 5 = 150 mg/m^2 Alemtuzumab 30 mg × 2 = 60 mg[a]	9.43	17/17	CD3—30% CD33—1%	Limited chronic	No CD symptoms but on immune suppression for chronic limited GVHD, not complaint with return visits but remained in phone contact
3	Cy (50 mg/kg × 4) = 200 mg/kg Flu 30 mg/m^2 × 5 = 150 mg/m^2 Alemtuzumab 30 mg × 2 = 60 mg[a]	10.36	10/14	CD3—13% CD33—11%	None	Due to pre-HSCT surgery with pancolectomy and short gut syndrome continues to have ostomy bag, remains on immune suppression for renal transplant and TPN for short gut syndrome, 5-year esophagogastroduodenoscopy visually normal
Umbilical cord blood						
4	Cy (50 mg/kg × 4) = 200 mg/kg Flu (25 mg/m^2 × 3) = 75 mg/m^2 Alemtuzumab 30 mg × 2 = 60 mg[a]	2 U = 0.21	13/14	CD3—0% CD33—0%	None	No CD therapy for 5 years, last complete evaluation at 4 years showed no MRI imaging, colonoscopy, or biopsy evidence of disease
5	Cy (50 mg/kg × 4) = 200 mg/kg Flu (25 mg/m^2 × 3) = 75 mg/m^2 Alemtuzumab 30 mg × 3 = 90 mg	2 U = 0.22	12/12	CD3—0% CD33—0%	None	No CD therapy for 5 years, at 5 years no MRI imaging, colonoscopy, or biopsy histologic evidence of disease
6	Cy (50 mg/kg × 4) = 200 mg/kg Flu (25 mg/m^2 × 5) = 125 mg/m^2 Alemtuzumab 30 mg × 2 = 60 mg	1 U = 0.04	11/15	CD3—0% CD33—0%	None	No CD therapy for 5 years, at 5 years no MRI imaging, colonoscopy, or biopsy histologic evidence of disease
7	Cy (50 mg/kg × 4) = 200 mg/kg Flu (25 mg/m^2 × 5) = 125 mg/m^2 Alemtuzumab 30 mg × 2 = 60 mg	2 U = 0.42	13/13	CD3—0% CD33—0%	None	No CD therapy for 5 years, at 5 years no MRI imaging, colonoscopy, or biopsy histologic evidence of disease
8	Cy (50 mg/kg × 4) = 200 mg/kg Flu (25 mg/m^2 × 5) = 125 mg/m^2 Alemtuzumab 30 mg × 3 = 90 mg	2 U = 0.15	10/11	CD3—0% CD33—0%	None	No CD therapy for 5 years, last complete evaluation at 3 years showed no MRI imaging, colonoscopy, or biopsy evidence of disease
9	Cy (50 mg/kg × 4) = 200 mg/kg Flu (25 mg/m^2 × 5) = 125 mg/m^2 Alemtuzumab 30 mg × 3 = 90 mg	2 U = 0.36	18/18	NA	None	Died at 3 months from disseminated adenovirus

[a]Patient received only one dose of alemtuzumab (30 mg) due to drug induced hives. CD3 = T-cell marker, CD33 = neutrophil marker.

Cy cyclophosphamide, *Flu* fludarabine, *GVHD* graft versus host disease, *HSCT* thematopoietic stem cell transplantation, *NA* not available.

electrolyte abnormalities, alemtuzumab-related hives, or infections with one case each of diarrhea due to *clostridium difficile*, and blood cultures positive for *Escherichia coli, enterococcus faecalis*, and extended broad spectrum beta-lactamase producing *E. coli*. The risk of bacteremia during neutropenia was increased due to Crohn-related intestinal ulcerations. No patient had acute GVHD, one matched sibling donor recipient developed chronic limited GVHD manifest as dry eyes and mouth.

One death occurred after transplantation in an UCB recipient due to disseminated adenovirus infection occurring after exposure to an otherwise healthy sibling with adenoviral conjunctivitis 3 months after discharge to home. The conditioning regimen was cyclophosphamide 200 mg/kg and the maximal dose escalation of fludarabine 125 mg/m^2 and alemtuzumab 90 mg (Table 1). Following the patient's death, enrollment was voluntarily terminated while the remaining cohort was monitored.

All three HLA-matched sibling transplants had donor T-cell (CD3) engraftment from 13% to 30% at 6 months (Table 1). One matched sibling completed yearly follow-up for 5 years with no CD symptoms or GVHD and since transplant has remained in clinical, MRI imaging, endoscopic, and histologic remission on no medications. At 5 years, stable mixed chimera persisted at 4.3% donor CD3+ T cells. The other two matched sibling recipients, both from out-of-state, refused to return for re-evaluation after the 6 month assessment. Both denied CD symptoms over the 5-year interval since transplant. However, one remains on immune suppression for chronic limited GVHD, while the other matched sibling recipient is on immune suppression due to a renal transplant following dehydration and calcineurin inhibitor-induced renal failure. The canonical interpretation of these findings is that mixed chimerism results in remission of CD.

Of the five evaluable allogeneic UCB recipients, none had GVHD and none had CD3+ or CD33+ donor engraftment at 6 months. Without donor engraftment, calcineurin inhibitors were also discontinued at 6 months. Thereafter, all UCB recipients have remained free of any immune suppressive or CD drugs and have had no clinical, radiographic, endoscopic, or histologic biopsy evidence of disease (Table 1). In opposition to the conclusion from the matched sibling transplants, the UCB results indicate that donor engraftment is not necessary to achieve long-term, treatment-free remission of CD.

Possible explanations for the effectiveness of UCB despite failure to engraft are (1) the conditioning regimen and 6 months of maintenance tacrolimus may, by itself, be sufficient for long-term remission, (2) transient donor graft versus autoimmunity [11] occurred before the donor graft vanished at the 6 month blood draw for chimerism, or (3) the donor UCB unit provided non-hematopoietic cells such as mesenchymal stem cells that may have facilitated a durable remission. UCB mesenchymal stem cells when infused as a solitary treatment have, in a randomized trial, demonstrated partial benefit for CD [12].

This is the first study for CD to demonstrate durable 5-year follow-up with no clinical, imaging, endoscopic, or histologic evidence of disease. To determine the mechanism of action, a trial could be performed with the safer lowest dose of the non-myeloablative conditioning regimen utilized herein followed by 6 months of low dose tacrolimus in which the patient is randomized to receive or not receive an UCB stem cell infusion on day zero. Although the conditioning regimen with cyclophosphamide (200 mg/kg) and the lowest dose of infused fludarabine (75 mg/m^2) and alemtuzumab (30 mg) was safe, autologous PBSC that normally contain significant numbers of host lymphocytes should be mobilized and cryopreserved before transplantation as a safety backup in the event of a severe lymphopenia-mediated viral infection during the first year after HSCT. The conditioning regimen described herein supplemented with allogeneic UCB infusion is the first treatment to result in sustained and complete CD remissions without evidence of disease. These results, while unexpected because engraftment did not occur, are fortuitous in that donor hematopoietic graft failure with reconstitution of host hematopoiesis mitigates the risk of GVHD. Further study of allogeneic UCB infusion after a non-myeloablative regimen should be considered for refractory cases of CD.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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