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Brief Report

TRANSPLANTATION

Haploidentical hematopoietic cell and kidney transplantation for hematological malignancies and end-stage renal failure

Yi-Bin Chen,[1,2] Nahel Elias,[2,3] Eliot Heher,[2,4] Jeannine S. McCune,[5,6] Kerry Collier,[1] Shuli Li,[7] Candice Del Rio,[1] Areej El-Jawahri,[1,2] Winfred Williams,[2,4] Nina Tolkoff-Rubin,[2,4] Jay A. Fishman,[8] Steven McAfee,[1,2] Bimalangshu R. Dey,[1,2] Zachariah DeFilipp,[1,2] Paul V. O'Donnell,[1,2] A. Benedict Cosimi,[2,3] David Sachs,[2,3,9] Tatsuo Kawai,[2,3] and Thomas R. Spitzer[1,2]

[1]Blood and Marrow Transplant Program, Massachusetts General Hospital, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]Division of Transplant Surgery and [4]Division of Nephrology, Department of Medicine, Massachusetts General Hospital, Boston, MA; [5]Fred Hutchinson Cancer Research Center, Seattle, WA; [6]Department of Pharmaceutics, University of Washington, Seattle, WA; [7]Dana-Farber Cancer Institute, Boston, MA; [8]Transplant Infectious Disease and Compromised Host Program, Massachusetts General Hospital, Boston, MA; and [9]Center for Translational Immunology, Columbia University Medical Center, New York, NY

KEY POINTS

- **Combined haploidentical HCT/kidney transplantation is safe and feasible with posttransplantation cyclophosphamide.**
- **Fludarabine can be used for conditioning in patients with end-stage renal disease if proper dose adjustments and dialysis are used.**

At Massachusetts General Hospital, we pioneered simultaneous hematopoietic cell (HCT)/kidney transplantation from HLA-identical related donors for the treatment of hematological malignancies with end-stage renal failure. We have now extended this to HLA-haploidentical donors in a pilot trial. Six recipients, 5 of whom were conditioned with fludarabine, cyclophosphamide, and total-body irradiation, underwent combined HCT/kidney transplantation from haploidentical donors; graft-versus-host disease (GVHD) prophylaxis included post-HCT cyclophosphamide, tacrolimus, and mycophenolate mofetil. One patient died as a result of complications of fludarabine neurological toxicity. No neurological toxicity was observed in subsequent patients who received lower fludarabine doses and more intense postfludarabine dialysis. There were no cases of grade 2 to 4 acute GVHD and 1 case of moderate chronic GVHD by 12 months. One patient experienced relapse of multiple myeloma at 30 months after HCT and died 4 years posttransplantation. Overall, 4 of 6 patients remain alive, without disease relapse and with long-term renal rejection–free survival. This trial was registered at www.clinicaltrials.gov as #NCT01758042. (*Blood*. 2019;134(2):211-215)

Introduction

At Massachusetts General Hospital (MGH), we have pioneered combined hematopoietic cell (HCT)/kidney transplantation from the same donor for patients with hematological malignancies and end-stage renal disease (ESRD).[1] The transplanted kidney allows standard graft-versus-host disease (GVHD) prophylaxis, while engrafted hematopoietic cells from the same donor provide immunological tolerance of the transplanted kidney. In a previous study involving HLA-matched sibling donors for patients with multiple myeloma and ESRD,[2] a limiting factor for potential recipients was lack of a fully HLA-matched donor. Recent paradigms of HLA-haploidentical transplantation using posttransplantation high-dose cyclophosphamide (PTCy) for GVHD prevention have illustrated remarkable safety and low rates of GVHD.[3,4] We are conducting a pilot trial of reduced-intensity conditioning with combined HCT/kidney transplantation from haploidentical donors using PTCy. This report describes the first 6 recipients to illustrate the novelty and feasibility of this approach.

Study design

This study was approved by the MGH Institutional Review Board. Informed consent was obtained from all donors and recipients. Eligible recipients were between ages 18 and 70 years with a hematological malignancy. Kidney dysfunction included receiving renal replacement therapy or a creatinine clearance of ≤35 mL per minute. Donors were first-degree haploidentical relatives who met institutional criteria for both hematopoietic cell and kidney donation. Hematopoietic grafts could be either bone marrow (BM) or granulocyte colony-stimulating factor–mobilized peripheral blood stem cells, given the comparable outcomes in patients undergoing conventional haploidentical HCT when receiving PTCy.[5,6] Donors were excluded if donor-specific HLA antibodies were present in the recipient.

Five of the 6 patients received a conditioning regimen of fludarabine, cyclophosphamide, and 200 cGy of total-body irradiation. The first patient received rabbit antithymocyte globulin

(ATG; Thymoglobulin) at 1.5 mg/kg per day on days −4, −3, and −2 in place of fludarabine. The next 2 patients received fludarabine at 24 mg/m^2 per day on days −6 through −2 (total, 120 mg/m^2) with standard hemodialysis starting between 6 and 12 hours after each dose. The subsequent 3 patients received fludarabine at 24 mg/m^2 per day on days −4, −3, and −2 (total, 72 mg/m^2) and underwent longer hemodialysis (6 hours) with a larger dialyzer (F-200).

Kidney transplantation was performed according to standard techniques, using an iliac fossa extraperitoneal approach. Hematopoietic cells were infused immediately after revascularization of the kidney allograft. Peripheral blood stem cell grafts were collected at least 1 week before transplantation and cryopreserved (4×10^6 to 5×10^6 CD34$^+$ cells per kilogram of recipient's body weight). BM donors underwent marrow and kidney donation on the same day (4×10^8 total nucleated cells per kilogram of recipient's ideal body weight). GVHD prophylaxis comprised PTCy (50 mg/kg per day IV on days +3 and +4), along with tacrolimus (target trough level, 5-10 ng/dL; tapered after day +100) and mycophenolate mofetil (15 mg/kg 3 times per day to day +35, then tapered through day +100). Fludarabine pharmacokinetic analysis to determine the plasma concentration of 9-β-D-arabinofuranosyl-2-fluoroadenine area under the curve as previously described[7] was conducted on blood samples from the most recent 3 patients. Safety and adverse events were monitored and assessed by an independent data safety monitoring board.

Results and discussion

Table 1 lists characteristics and transplantation outcomes. All recipients had chemotherapy-sensitive disease control at the time of transplantation, and 4 had undergone prior autologous stem cell transplantation. All participants had prior renal disease requiring renal replacement therapy. All 6 recipients experienced successful initial donor neutrophil engraftment within the first 30 days. The first patient, who received ATG in place of fludarabine, experienced secondary hematopoietic graft rejection when presenting at day +24 with fever, fatigue, and myalgias. Chimerism analysis confirmed loss of donor hematopoiesis and subsequent autologous recovery. With fludarabine in conditioning, all other patients experienced durable donor hematopoiesis.

In the first 6 months after transplantation, 2 patients developed grade 1 acute GVHD; both demonstrated stage II skin disease and responded promptly to corticosteroids. There were no cases of grade 2 to 4 acute GVHD. Five of the 6 recipients survived through 12 months. All 5 surviving patients had an underlying diagnosis of multiple myeloma and were free of disease at 12 months. Patient 1 remained on low-dose tacrolimus for kidney rejection prevention, given autologous-derived hematopoiesis. Patient 5 remained on low-dose tacrolimus and prednisone for chronic GVHD. The remaining 3 living patients were free of immunosuppression at 12 months. Subsequently, 1 patient developed chronic GVHD at 18 months, which did not require systemic immunosuppression. At 3 years after transplantation, patient 2 was found to have relapsed multiple myeloma, which ultimately resulted in kidney allograft failure and death 1 year later. The remaining 4 patients were alive and free of myeloma at 73, 46, 34, and 12 months after transplantation, respectively. The prolonged remission of our first patient despite hematopoietic graft rejection is compelling, given our past observations of durable remissions in certain patients with refractory malignancies who also experienced haploidentical hematopoietic graft rejection after nonmyeloablative conditioning.[8]

In terms of significant attributable adverse events, patient 1 experienced, along with the aforementioned secondary hematopoietic graft rejection, significant fluid retention resulting from a transient decrease in ejection fraction thought to be from high-dose cyclophosphamide. During hematopoietic graft rejection, renal function remained intact, which is in contrast to our prior experience with tolerance trials involving combined haploidentical BM and kidney transplantation for patients without an underlying malignancy, where hematopoietic rejection after mixed chimerism led to significant renal dysfunction.[9] Patient 3 experienced grade 4 renal toxicity in the week after transplantation and required transient renal replacement therapy. At 1 month, he experienced the onset of cortical blindness, progressive weakness of all extremities, and seizures, symptoms consistent with fludarabine neurotoxicity, from which he died on day +142. All other patients experienced adverse events consistent with standard reduced-intensity haploidentical HCT. There were no observed cases of renal allograft rejection.

After patient 3 developed presumed fludarabine neurotoxicity despite dose modifications, fludarabine pharmacokinetic analysis was conducted in the subsequent 3 patients (Figure 1). Our most recent adjustments, both in fludarabine dose and method of dialysis, allowed us to achieve fludarabine areas under the curve similar to those of HCT patients who have normal renal function and receive standard-dose fludarabine.

Combining solid organ transplantation and HCT to achieve tolerance first arose from anecdotes of HCT recipients who later developed ESRD. They were observed to accept, rejection free, kidney transplants from the original HCT donors without immunosuppression.[10,11] Numerous preclinical animal experiments have explored these observations,[12-14] leading to the development of innovative simultaneous combined protocols designed to either achieve specific solid organ tolerance or allow patients with concurrent hematological malignancies and advanced kidney disease access to both solid organ transplantation and HCT.

Use of HCT solely to achieve specific tolerance has been conducted in the United States predominantly at 3 centers. At MGH, this concept evolved from the ability of transient mixed hematopoietic chimerism to engender renal allograft tolerance without immunosuppression. Other approaches have included total lymphoid irradiation/ATG preparative therapy for combined HLA-matched BM and kidney transplantation at Stanford University[15] and the use of facilitating cells to enhance engraftment and limit the risk of GVHD after HLA-mismatched combined transplantation at Northwestern University.[16]

In patients with underlying hematological malignancies, the goal is not just solid organ tolerance but also durable full donor chimerism to cultivate a potentially curative graft-versus-malignancy effect. Our prior experience with 10 fully HLA-matched donor-recipient pairs was recently updated, now 20 years after

Table 1. Clinical characteristics of recipients (n = 6) and outcomes after transplantation

	Patient					
	1	2	3	4	5	6
Age, y	65	56	38	51	57	62
Sex	F	F	M	M	M	M
Disease	Myeloma	Myeloma	NHL	Myeloma	Myeloma	Myeloma
Renal disease	Myeloma	Myeloma	Unknown	Myeloma	Myeloma	Myeloma
RRT	Yes	Yes	Yes	Yes	Yes	Yes
Prior ASCT	Yes	Yes	No	Yes	No	Yes
Disease status	CR	VGPR	CR	CR	VGPR	CR
Time since diagnosis, mo	27	24	44	55	12	30
Conditioning	ATG/Cy/TBI	Flu/Cy/TBI	Flu/Cy/TBI	Flu/Cy/TBI	Flu/Cy/TBI	Flu/Cy/TBI
Donor	Son	Sister	Mother	Brother	Son	Sister
HLA match	3/6	3/6	3/6	3/6	3/6	3/6
HSC source	Marrow	Marrow	Marrow	Marrow	PBSCs	Marrow
CD34 per kg	2.62×10^6	2.06×10^6	4.58×10^6	1.67×10^6	3.01×10^6	0.94×10^6
Engraftment, d						
Neutrophils	15	17	26	22	20	28
Platelets	48	31	—	41	32	39
Return to RRT	No	No*	Yes	No	No	No
d-30 chimerism, %†						
All cell	<10	>97	>98	100	100	96
$CD3^+$	<2	NA‡	>96	100	100	NA‡
d-100 chimerism, %†						
All cell	0	100	>97	100	NA‡	NA‡
$CD3^+$	0	100	NA‡	100	NA‡	NA‡
1-y chimerism, %†						
All cell	0	100	—	NA‡	100	100
$CD3^+$	0	100	—	NA‡	100	100
Acute GVHD	No	Grade 1	No	No	Grade 1	No
Chronic GVHD	No	No	—	Moderate	Moderate	No
1-y OS	Alive	Alive	Died (d 142)	Alive	Alive	Alive
1-y disease status	CR	CR	—	CR	CR	CR
IST	Yes	No	—	No	Yes	No
1-y serum Cr, mg/dL	0.87	0.92	—	1.04	1.12	1.45
Follow-up, mo	73	48 (died)	—	46	34	12
Most recent serum Cr, mg/dL	0.78	—	—	1.04	1.00	1.45

Abbreviations: ASCT, autologous stem cell transplantation; CR, complete remission; Cr, creatinine; Cy, cyclophosphamide; Flu, fludarabine; HSC, hematopoietic stem cell; IST, immunosuppressive therapy; NA, not applicable; NHL, non-Hodgkin lymphoma; OS, overall survival; PBSC, peripheral blood stem cell; RRT, renal replacement therapy; TBI, total-body irradiation; VGPR, very good partial response.

*Required RRT after 3 y because of relapse of multiple myeloma.

†Chimerism is expressed as percentage of cells that are of donor origin.

‡NA refers to time points where purity of cell population was inadequate to perform assay or it was not performed.

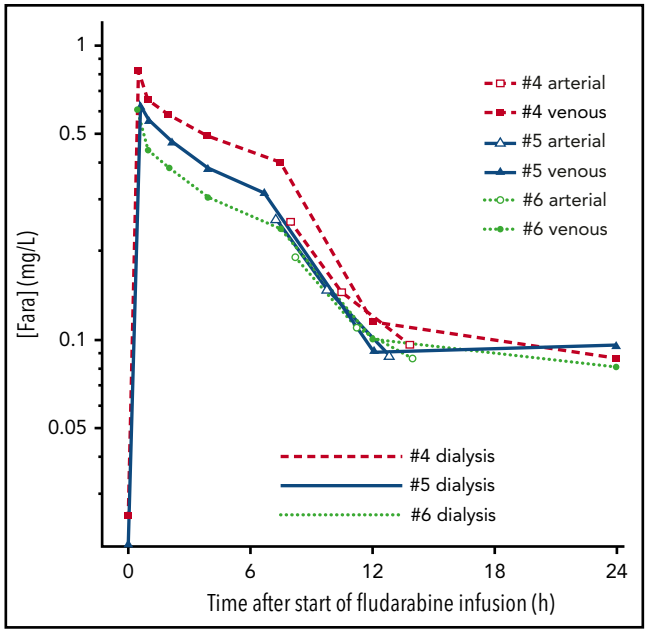

Figure 1. Fludarabine pharmacokinetics for the most recent 3 patients (patients 4, 5, and 6). F-ara, 9-β-D-arabinofuranosyl-2-fluoroadenine.

the first procedure, with continued efficacy in immunosuppression-free renal allograft survival and myeloma control.[2,17]

As we evaluated candidates for this trial, inherent ethical issues arose. Early mortality and discussions regarding overall prognosis for a recipient are inherently different for each discipline when determining candidacy. Frankly, the question is: what prognosis from an HCT standpoint justifies eligibility for a kidney transplant? In addition, use of staged approaches (ie, kidney transplantation first, then delayed HCT from the same donor) may be safer and more feasible. Nevertheless, the continued evolution of these approaches has allowed a life-changing and potentially lifesaving therapy for patients whose prior prognosis was dismal.

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Authorship

Contribution: Y.-B.C., N.E., E.H., N.T.-R., P.V.O., A.B.C., D.S., T.K., and T.R.S. participated in initial conception, enrolled participants, and wrote and approved the final manuscript; J.S.M. performed correlative studies and approved the final manuscript; K.C. and C.D.R. managed the study and database, conducted research assessments, and approved the final manuscript; S.L. helped to design the trial; and A.E.-J., W.W., J.A.F., S.M., B.R.D., and Z.D. enrolled participants, helped to conduct the trial, and approved the final manuscript.

Conflict-of-interest disclosure: Y.-B.C. has served as a consultant for Takeda, Magenta, Incyte, Kiadis, and Equillium; Z.D. has received research funding from Incyte; and T.R.S. has served on a scientific advisory board for ITB-Med. The remaining authors declare no competing financial interests.

ORCID profiles: Y.-B.C., 0000-0002-9554-1058; N.E., 0000-0001-6466-7347; J.S.M., 0000-0002-0795-497X; Z.D., 0000-0002-7994-8974.

Correspondence: Yi-Bin Chen, 0 Emerson Place, Suite 118, Boston, MA 02114; e-mail: ychen6@partners.org.

Footnotes

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Protocols and datasets are available by email to corresponding author.

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