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## Long-Term Follow-Up of Recipients of Combined Human Leukocyte Antigen-Matched Bone Marrow and Kidney Transplantation for Multiple Myeloma With End-Stage Renal Disease

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### Abstract

**Background**—Specific tolerance after combined kidney and bone marrow transplantation for multiple myeloma with end-stage renal disease through mixed lymphohematopoietic chimerism has been achieved, as evidenced by prolonged normal renal function without ongoing immunosuppression.

**Methods**—To achieve potent antimyeloma responses and induce tolerance for the renal allograft, seven patients (median age: 48 years [range: 34–55 years]) with multiple myeloma and end-stage renal disease underwent a combined human leukocyte antigen-matched kidney and bone marrow transplant with lead follow-up time of more than 12 years. Preparative therapy for the transplant consisted of high-dose cyclophosphamide, equine antithymocyte globulin and pretransplant thymic irradiation. Cyclosporine as the sole posttransplant immunosuppressive therapy was tapered and discontinued as early as day 73 posttransplant.

**Results**—All seven patients achieved mixed chimerism. One patient developed acute graft-versus-host disease and two chronic graft-versus-host disease. Five of seven patients are alive, four with no evidence of myeloma from 4 to 12.1 years posttransplant. Three patients have normal or near-normal renal function without needing systemic immunosuppression. Two patients with normal renal function off immunosuppression were returned to immunosuppressive therapy without evidence of rejection because of the occurrence of chronic graft-versus-host disease.

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**Conclusions**—These long-term follow-up data show that sustained renal allograft tolerance and prolonged antimyeloma responses are achievable after human leukocyte antigen-matched kidney and bone marrow transplantation and the induction of mixed lymphohematopoietic chimerism.

## Keywords

Bone marrow; Kidney transplant; Multiple myeloma

The induction of specific allograft tolerance for organ transplantation through mixed lymphohematopoietic chimerism after combined bone marrow and kidney transplantation (KdBMT) has been achieved in small and large animal models (1–4) and more recently in patients with malignancy (multiple myeloma) (5, 6) and without an underlying malignancy (7). Both central (thymic) deletional and peripheral tolerance mechanisms have been invoked, with the latter likely assuming a more important role clinically in the achievement of sustained specific tolerance, given the transient nature of the mixed chimerism in most patients.

Our initial clinical trial for achieving sustained allograft tolerance involved patients with multiple myeloma complicated by end-stage renal disease (ESRD). Renal failure is a common complication of multiple myeloma. Such individuals have historically not been eligible for a kidney transplant because of their malignancy; conversely, allogeneic stem-cell transplants, the only known curative treatment for multiple myeloma, have rarely been performed in patients with ESRD because of prohibitive morbidity and mortality risks. Our strategy of combined KdBMT in this population, therefore, offered an opportunity for durable control of the multiple myeloma, for restoration of normal renal function, and for induction of tolerance of the kidney graft. The preparative conditioning regimen for the combined transplant was based on our murine model and subsequent clinical experience, in which cyclophosphamide (CY) in combination with *in vivo* T-cell depletion and thymic irradiation were used to induce mixed chimerism and to build an immunologic platform for delayed donor leukocyte infusions (DLI) to convert chimerism to full donor hematopoiesis and optimize a graft-versus-tumor effect (8–11).

We described the early outcome of our first patient who received a combined human leukocyte antigen (HLA)-matched KdBMT for multiple myeloma with ESRD (5), then described the outcomes of six patients who received combined HLA-matched KdBMT for multiple myeloma with ESRD, with follow-up ranging from 1.3 to more than 7 years (6). Herein, we describe the long-term follow-up of five surviving patients, four of whom are without recurrent multiple myeloma with lead follow-up time of more than 12 years. The lessons learned from these patients are instructive, both in showing the potential for long-term remission of multiple myeloma with or without sustained lymphohematopoietic chimerism, and for the induction of sustained allograft tolerance, as evidenced by the lack of need for immunosuppressive therapy in three of the patients.

## RESULTS

The clinical outcomes of the six of the seven transplant recipients, with follow-up of 1.3 to 7 years have been previously published (6). Additional details regarding their outcomes are described in Table 1. The current status of the seven patients is described later.

### Patient 1 (Unique Patient Number [UPN] 277)

UPN 277 was a 55-year-old woman who underwent a combined HLA-matched KdBMT in September 1998. She is currently alive 12.1 years posttransplant with stable renal allograft function on no immunosuppressive therapy. She has had a gradually rising level of kappa-

free light chains since 2006 (most recently 137 ng/mL). Serial bone marrow examinations (most recently in October 2010) have most recently shown small populations (1%–2% clonal plasma cells by flow cytometry) of plasma cells with monoclonic kappa immunoglobulin light-chain expression. She has had no clinical evidence of recurrent multiple myeloma.

#### **Patient 2 (UPN 407)**

UPN 407 was a 51-year-old woman who received a combined HLA-matched KdBMT in August 2000. She remained well and off immunosuppressive therapy until 2003 (2.9 years posttransplant) when she was determined to have recurrent multiple myeloma. She received three subsequent DLI without a response or restoration of donor chimerism. She received multiple salvage therapies for her myeloma and ultimately expired 7.7 years posttransplant due to progressive multiple myeloma. She had normal renal function off of immunosuppression until the relapse of her myeloma.

#### **Patient 3 (UPN 454)**

UPN 454 was a 34-year-old man who received an HLA-matched KdBMT in August 2001. He remained in complete remission until 2005 when he was found to have a right conjunctival hematoma after local trauma. A subsequent biopsy showed a plasmacytoma with lambda light-chain restriction. This was treated with local radiation therapy. In 2007, he had a systemic relapse of his disease, which was treated with lenalidomide with achievement of a complete remission. In 2010, he was found to be in relapse with elevated serum lambda light chains and new findings on positron emission tomography scan consistent with recurrent myeloma. He received bortezomib with achievement of another clinical remission but was recently found to be in relapse based on a rising free lambda light-chain level. Throughout his complicated myeloma course, renal allograft function has remained stable.

#### **Patient 4 (UPN 528)**

UPN 528 was a 35-year-old woman who underwent a combined HLA-matched KdBMT in June 2002. Given loss of chimerism despite two DLI and progressive myeloma, and normal renal function after her first transplant, she underwent a second myeloablative HLA-matched peripheral blood stem-cell transplant (from the same original bone marrow/kidney donor) in July 2004. This posttransplant course was complicated by chronic hepatic graft-versus-host disease (GVHD) and polymyositis. Serial chimerism studies for 3 years after her second transplant have shown full donor hematopoiesis. Her chronic GVHD has responded well to medical therapy, and her corticosteroids have been discontinued.

#### **Patient 5 (UPN 566)**

UPN 566 was a 35-year-old woman who received a combined HLA-matched KdBMT in March 2003. Postoperatively she initially had a normalization of her creatinine (to 1.2 mg/dL). Seven days posttransplant, her creatinine was 2.1 mg/dL. She underwent a renal biopsy 1 week posttransplant, which showed recurrent cast nephropathy. Her renal function progressively worsened, and she required resumption of hemodialysis. In 2006, she was diagnosed with therapy-related myelodysplastic syndrome, which progressed in 2007 to acute myeloid leukemia. She died in 2007 from progressive therapy-related acute myeloid leukemia.

#### **Patient 6 (UPN 615)**

UPN 615 was a 57-year-old male patient who underwent a combined HLA-matched KdBMT in December 2003. His posttransplant course was complicated by transient acute

cellular rejection, type II, which was reversed by therapy with corticosteroids and cyclosporine. His immunosuppression was discontinued approximately 1.5 years later, and he has had no evidence of allograft rejection since then. In April 2009, he was noted to have a slightly elevated serum kappa-free light-chain level. His most recent kappa light-chain level in October 2010 was 97 mg/dL. A recent bone marrow examination showed a small (0.15%) population of plasma cells with monotypic kappa light-chain expression. He is without clinical evidence of recurrent myeloma.

#### Patient 7 (UPN 801)

UPN 802 was a 47-year-old woman who presented in 2001 with acute renal failure due to immunoglobulin A kappa multiple myeloma. After initially achieving a complete remission, she had two subsequent skeletal relapses. In 2006, she presented with worsening renal failure. She underwent a combined HLA-matched KdBMT in October 2006. Cyclosporine was tapered and discontinued on transplant day 105. For persistent mixed chimerism, she received DLI consisting of  $5 \times 10^5$ /kg and  $1 \times 10^6$ /kg CD3<sup>+</sup> T cells on days 135 and 208 posttransplant. She is in a clinical complete remission as evidenced by a normal bone marrow examination and serial serum protein electrophoresis and serum light-chain evaluations. Serial chimerism studies have shown sustained multilineage mixed chimerism with a persistently high level of granulocyte ( $\geq 80\%$ ) chimerism and CD3<sup>+</sup> T-cell chimerism of  $\geq 30\%$ . She has xerophthalmia likely due to chronic GVHD but requires no immunosuppressive therapy.

## DISCUSSION

The feasibility of combined HLA-matched KdBMT for multiple myeloma with ESRD has been well established, and sustained allograft tolerance and myeloma remissions have been demonstrated even in some patients who lost their donor bone marrow chimerism. Such patients may have a state of “split tolerance” to donor minor histocompatibility antigens expressed on the kidney, as cytotoxic T-cell responses to donor hematopoietic cells, but not to cultured donor renal tubular epithelial cells, were observed in several of those who lost chimerism (6).

These follow-up data for the first seven patients treated with combined HLA-matched KdBMT demonstrate longterm remissions in three of the patients (albeit in two patients with small but stable elevations of serum kappa light chains at  $>6$  and  $>10$  years posttransplant), with a fourth achieving a durable remission after a second, myeloablative transplant, and the sustained normal or near-normal renal function despite being off all antirejection medications in three of the surviving five patients. Transient renal allograft rejection was experienced by only one patient, and he has subsequently been off all immunosuppressive medications for more than 5 years with no further evidence of rejection. The small number of patients during this 12+-year time period is reflective of a number of obstacles including, in some cases, insurance reimbursement for the procedure, substantial comorbidities in some of the patients, and the frequent lack of a suitable HLA-matched-related donor.

The loss of donor hematopoietic cell chimerism at approximately day 100 posttransplant in our first two patients was an unexpected observation, as were the remissions from 2.9 to 12.1 years that followed their transplants. We subsequently showed, in a group of patients with chemorefractory hematologic malignancies, that antitumor responses were achieved in 41% of cases after nonmyeloablative stem-cell transplants using similar conditioning regimens for the induction of mixed chimerism, despite only transient engraftment of the bone marrow graft (12). To discern the mechanism of these antitumor responses, murine transplants were carried out by Sykes and coworkers (13–15) in which mixed lymphohematopoietic chimerism was induced after nonmyeloablative major

histocompatibility complex-mismatched donor bone marrow transplantation followed by intentional hematopoietic graft rejection using recipient lymphocyte infusions (RLIs). Prolonged survival was seen among mice challenged with several host strain-specific tumor cell lines after the induction of mixed chimerism and RLI-induced or spontaneous graft rejection (compared with mice treated with conditioning alone, conditioning and RLI, or conditioning and bone marrow transplantation without RLI, thus showing the importance of the initial induction of mixed chimerism followed by graft rejection). Antitumor responses were determined to be mediated by RLI-derived interferon- $\gamma$ -producing CD8 T cells and recipient CD4 cells and were associated with development of tumor-specific cytotoxicity (16).

Several unique observations have been made in this long-term follow-up of our combined transplant patients.

1. The occurrence of a plasmacytoma in the site of a traumatic conjunctival hematoma in a patient who had been in remission for years after his transplant, suggesting a trophism of clonal plasma cells to the site of earlier injury and bleeding.
2. The pathological demonstration of myeloma kidney (cast nephropathy) and progressive kidney failure within 1 week of transplantation in a patient who had primary refractory myeloma at the time of her transplant. To our knowledge, this unfortunate observation of renal failure in a normal transplanted kidney within such a short time has not been previously demonstrated and shows how toxic, and in such a short time, myeloma-related light chains can be to a normal kidney.
3. After kidney transplantation in which renal graft tolerance has been achieved, patients may be candidates for a second myeloablative transplant if there is progression of the myeloma (as demonstrated by UPN 528).
4. Gradually rising levels of serum-free light chains and small populations of light-chain-restricted plasma cells in the bone marrow can exist posttransplant in the absence of detectable donor lymphohematopoietic chimerism or recurrent myeloma, even in patients who had a significant myeloma disease burden before their transplant (as demonstrated by UPN 277).

With this relatively small number of patients, it is not clear what the optimal fate of the hematopoietic cell graft, both in achieving renal allograft tolerance and sustained remission of the myeloma, should be. In keeping with our preclinical transplant models in which even transient hematopoietic cell chimerism was associated with sustained allograft tolerance, we have demonstrated that sustained renal allograft tolerance is achievable in humans even after chimerism lasting for as little as 105 days. The minimum duration of chimerism to achieve such tolerance is uncertain. We have demonstrated that detectable donor chimerism for as little as 7 days is associated with apparent specific tolerance of the kidney after combined HLA-mismatched KdBMT in patients without an underlying malignancy (7). With such transient chimerism, central (thymic) deletional tolerance may play less of a role than it does in our murine and large animal models of tolerance induction. In all likelihood, peripheral mechanisms of tolerance induction are operative in our patients, including an enrichment for CD4<sup>+</sup>, CD25<sup>+</sup> FoxP3-expressing T-regulatory cells (17).

Although the usual intent of an allogeneic hematopoietic stem-cell transplant is to achieve sustained donor lymphohematopoietic chimerism and to optimize a graft-versus-tumor effect, this strategy may be associated with untoward risks such as acute and chronic GVHD and their associated morbidity and mortality risks. Perhaps, the ideal outcome is one of sustained mixed lymphohematopoietic chimerism (Fig. 1), which virtually assures renal allograft tolerance and is associated with protection from GVHD, as demonstrated by UPN

801. The goal of our strategy has been to achieve durable mixed chimerism and to administer DLI later, which results in optimal antitumor effects without GVHD in animal models (18, 19).

Our experience with combined HLA-matched KdBMT for patients with multiple myeloma with ESRD is promising for achieving durable disease-free survival and achieving sustained kidney allograft tolerance in patients who otherwise would not be candidates for allogeneic bone marrow transplant or kidney transplant options and for whom durable myeloma remission are not likely achievable by any other means, and should, therefore, be considered in younger patients who have HLA-matched donors. Future strategies will consider alternative, perhaps more selectively T-cell depleting conditioning regimens to achieve a more stable state of mixed lymphohematopoietic chimerism as a platform for subsequent adoptive cellular immunotherapy to optimize the long-term antitumor effects of the transplant.

## MATERIALS AND METHODS

### Patients

Seven patients at a median age of 48 years (34–55 years) with multiple myeloma and ESRD received a combined HLA-matched sibling donor KdBMT at the Massachusetts General Hospital between 1998 and 2006. An eighth patient developed CY-induced cardiac toxicity on transplant day –5 and did not receive the combined transplant. The first two patients were treated on an institutional review board-approved innovative treatment plan, five patients were enrolled on an Immune Tolerance Network-sponsored clinical trial, and the most recent patient was treated according to an institutional treatment plan (with institutional review board approval to review and report the clinical data). The clinical characteristics of the patients are described in Table 2.

Preparative therapy for the transplant consisted of CY 60 mg/kg/day on days –5 and –4 (with dose based on actual or ideal body weight, whichever was less) with hemodialysis 14 hr after each CY dose, equine antithymocyte globulin 15 to 20 mg/kg on transplant days –1,+1, +3, and +5, and thymic irradiation (700 cGy) on day –1. Cyclosporine for GVHD prophylaxis was tapered and discontinued as early as day 73 posttransplant in the absence of GVHD.

On the day of the transplant, the donors underwent bone marrow harvesting and subsequent nephrectomy under general anesthesia. Transplant recipients then received their kidney transplant, followed, once the anastomoses were complete, by the infusion intraoperatively of the donor bone marrow. As the marrow product contained 15,000 units of heparin, protamine 50 to 75 mg was given intra- and postoperatively to prevent heparin-induced hemorrhage.

Postoperative supportive care included standard institutional antiinfective prophylaxis. Red blood cell and platelet transfusional support was given, and all blood products were irradiated using a Cesium irradiator to a dose of 2500 cGy, and leukocyte was reduced using third generation leukocyte filters. Febrile neutropenia was managed with broad spectrum antibiotics (usually vancomycin and cefepime).

Chimerism analyses were performed using a variable number of tandem repeat sequence or short tandem repeat sequence analysis, as described previously (5, 20, 21). Chimerism was evaluated weekly posttransplant for the first 100 days, then periodically as dictated by the protocol or as clinically indicated. DLI were considered for patients with mixed chimerism or loss of chimerism or persistent or progressive multiple myeloma even in the absence of

detectable donor chimerism based on previous data suggesting that DLI may enhance antitumor effects even after lymphohematopoietic graft rejection (12). DLI were either collected and infused the same day (three infusions) or, in instances where donors did not live locally, cryopreserved for later infusion (eight infusions).

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TABLE 1

## Clinical outcomes

UPN	Chimerism max, MMM				GHVD		IS	Creat (mg/dL)	DFS (yr)	OS (yr)	Cause of death
	Granulocyte (%)	T cell (%)	Duration	Response	Acute	Chronic					
277	70-90	70-90	105 d	CR <sup>a</sup>	None	None	None for >11 yr	0.63	12.1	12.1	
407	1-10	30-50	95 d	CR	None	None	None for >2 yr	—	2.9	7.7	Progressive myeloma
454	>99	>99	9.2+yr	CR→relapse→CR→relapse	None	Skin, conjunctivae, lung	Prednisone	1.42	4.6	9.2	
528	25-40	10-25	63 d	PD	None	None					
	>99 (after second SCT)	>99	(6.2+yr)	(CR after second SCT)	None	Liver, polymyositis (after second SCT)	Tacrolimus	0.90	6.2 (after 2nd SCT)	8.3	
566	>99	>99	4.2 yr	PD	Grade II		Prednisone	—	None	4.2	tAML
615	15-25	1-15	91 d	CR <sup>a</sup>	None	None	None for >5 yr	1.70	6.8	6.8	
801	70-85	25-40	4.0+yr	CR	None	Conjunctivae	None for >3 yr	1.14	4.0	4.0	

<sup>a</sup> Gradually increasing serum<sup>κ</sup> light chains.

CR, complete response; PD, progressive disease; DFS, disease-free survival; OS, overall survival stable; IS, immunosuppressive therapy; Creat, most recent serum creatinine; tAML, therapy-related acute myeloid leukemia; SCT, stem-cell transplantation; GHVD, graft-versus-host disease.

TABLE 2

Pretransplant patient characteristics

UPN	Gender	Age (yr)	Remission status	HD	Prior therapy	Renal Biopsy
277	F	55	$\kappa$ <sub>1</sub> LC/PR	Y	MEL/PRED, DEX	Cast nephropathy
407	F	51	$\kappa$ <sub>1</sub> LC/PR	Y	VAD	ND
454	M	34	$\kappa$ <sub>1</sub> LC/CR	Y	VAD, MEL	LCDD
528	F	35	$\kappa$ <sub>1</sub> LC/1° PR	N	VAD	Cast nephropathy
566	F	35	$\lambda$ <sub>1</sub> LC/1° refractory	Y	THAL/DEX, CY	Cast nephropathy
615	M	57	$\kappa$ <sub>1</sub> LC/CR	Y	THAL/DEX	LCDD
801	F	47	IgA/CR2	N	THAL/DEX/Dox HD MEL/AuSCT	Cast nephropathy
					THAL/XRT	
					THAL/CY	
					B/L-Dox/DEX	

$\kappa$ <sub>1</sub>LC, kappa light chain;

$\lambda$ <sub>1</sub>LC, lambda light chain;

PR, partial remission; CR, complete remission; MEL, melphalan; DEX, dexamethasone; THAL, thalidomide; Cy, Cytoxan; HD, high dose; AuSCT, autologous stem-cell transplantation; VAD, vincristine, Adriamycin, dexamethasone; B, bortezomib; Dox, doxorubicin; L-Dox, liposomal doxorubicin; LCDD, light-chain deposition disease; ND, not done; HD, hemodialysis pretransplant; Ig, immunoglobulin; F, female; M, male; Y, yes; N, no.