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RESEARCH LETTER

Kidney Transplantation After Allogeneic Hematopoietic Cell Transplantation

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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) aims to cure multiple hematologic malignancies, nonmalignant diseases, metabolic disorders, and immune deficiencies. Along with other transplant-related organ toxicities, both acute and chronic kidney disease are common complications of allogeneic HSCT, affecting 10% to 73% and 0% to 60% of patients respectively, depending on the definitions of kidney dysfunction, duration of follow-up and transplant strategies.[S1–S4] The proportion of patients with chronic kidney disease who develop end-stage renal disease is approximately 4%. Among those patients who progress to end-stage renal disease and require hemodialysis, mortality is approximately 90%. Few studies have reported successful kidney transplantation (KT) after HSCT in adults; these were mostly small single-center cohorts often with the same donor for HSCT and kidney, and short follow-up.[1,2] To investigate mortality and the occurrence of severe infections and cancers, we conducted a French multicenter retrospective study of patients who underwent KT, after previous allogeneic HSCT. The details of study methods are shown in the Supplementary Methods.

RESULTS

Nineteen KT patients with a history of HSCT were identified, of whom 3 had received a kidney from the HSCT donor: the remaining 16 patients were included in the analysis (Table 1 and Supplementary Table S1). Patients were allografted between 1986 and 2006, including 12 patients before 2000, at a median age of 31 (9–55) years (3 pediatric patients and 1 patient older than 45 years). The main indication for HSCT was acute leukemia ($n = 11/16$: 8 acute myeloid leukemia and 3 acute lymphoblastic leukemia). Three patients had undergone 2 consecutive HSCT (2 relapses and 1 autologous HSCT before allogeneic HSCT). Myeloablative conditioning ($n = 14/16$) was performed and the graft came from a matched related donor ($n = 12/16$) in the majority of cases. Baseline nephrologic status was partially or fully available for 9 patients. At the time of

Table 1. Patient's characteristics for the hematological period (from hematopoietic cell transplantation to kidney transplant)

Patient no.	Gender	HSCT age (yrs) (HSCT date)	Diagnosis	HSCT Donor	Conditioning	Nephrological status at HSCT	GVHD prevention	Acute GVHD	Chronic GVHD	Acute Kidney Failure	Kidney biopsy	Infectious complications	Neoplastic complications	Comments
1	F	39 (1997)	AML	HLA id-unrelated	MA	No CKD	CsA	No	Yes	No	No	Yes B+	No	
2	F	27 (2005)	MM	HLA id-sibling	non MA	chronic HD	unknown - unknown	No	No	/	Monoclonal Ig deposition disease (before HD)	unknown	No	Previous autologous BMT
3	F	44 (1996)	CML	Mism HLA-unrelated	MA	No CKD	CsA – Cst	Yes	Yes	Yes	No	Yes B+F+	No	
4	M	34 (1996)	AML	HLA id-sibling	MA	CKD2	CsA - MTX	Yes	Yes	Yes	No	Yes B+V+	Yes	1 NMSC /1 squamous cell carcinoma
5	M	36 (1998)	ALL	HLA id-sibling	MA	No CKD	CsA - MTX	No	Yes	Yes	Focal and segmental glomerulo-sclerosis	Yes V+	No	
6	F	18 (1991)	AML	HLA id-sibling	MA	unknown	CsA – MTX	Yes	Yes	unknown	Thrombotic microangiopathy	unknown	No	
7	M	55 (2003)	Myelofibrosis	HLA id-sibling	MA	unknown	CsA - MTX	Yes	Yes	unknown	No	Yes B+	No	
8	F	39 (1992)	AML	HLA id-sibling	MA	No CKD	CsA - MTX	Yes	Yes	No	No	Yes B+	Yes	2 NMSC
9	F	39 (1987)	CML	HLA id-sibling	MA	unknown	CsA	Yes	unknown	unknown	No	unknown	No	
10	M	28 (1996)	AML	HLA id-sibling	MA	No CKD	CsA – MTX	Yes	Yes	Yes	Non-contributive	No	No	
11	M	26 (02/1988) 26 (11/1988)	AML AML	HLA id-sibling HLA id-sibling	unknown MA	unknown unknown	CsA – MTX CsA - MTX	No Yes	unknown unknown	unknown unknown	No Non-contributive	unknown unknown	No No	
12	M	35 (2002)	AML	HLA id-sibling	MA	unknown	CsA - MTX	Yes	No	unknown	No	unknown	No	
13	M	15 (1992)	AML	HLA id-sibling	MA	No CKD	CsA – Cst	No	Yes	Yes	Membranous glomerulopathy	Yes B+F+	No	
14	M	22 (2006) 22 (2008)	ALL ALL	HLA id-unrelated NA-unrelated	MA Non-MA	No CKD chronic HD	CsA – MMF CsA – MMF	Yes No	Yes Yes	Yes /	Acute tubular necrosis /	Yes B+V+ Yes B+V+F+	No No	on long-term HD after HSCT
15	M	9 (1993)	ALL	HLA id-unrelated	MA	CKD2	CsA - MTX	Yes	Yes	No	Calcineurin inhibitor toxicity	Yes B+V+	No	
16	M	16 (1990)	Idiopathic aplasia	HLA id-sibling	MA	No CKD	CsA - MTX	Yes	Yes	Yes	Membranous glomerulopathy	Yes B+V+	No	

ALL, acute lymphoid leukemia; AML, acute myeloid leukemia; B+, bacterial infection requiring hospitalization; BMT, bone marrow transplant; CKD, chronic kidney disease; CML, chronic myeloid leukemia; CsA, cyclosporine A; Cst, corticosteroids; F, female; F+: fungal infection; GVHD, Graft-versus-host disease; HD, hemodialysis; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; id, identical; Ig, immunoglobulin; M, male; MA, myeloablative; mism, mismatch; MM, multiple myeloma; MMF, mycophenolate mofetil;
MTX, methotrexate; NA, not available; NMSC, nonmelanoma skin cancer; V+, viral infection

Table 2. Patient's characteristics for the nephrological period (after KT)

Patient no.	Time from HSCT to ESRD (yrs)	Age at KT (yrs)	Kidney Donor / HLA mm	Induction IS	Maintenance IS	Kidney rejection	Infectious complications	Neoplastic complications	Follow-up period after KT (mos)	Vital status at last follow-up	Comments
1	11.8	56	Deceased / full match	ALG	MMF-Cst	No	Yes B+	No	37	Alive	
2	/	33	Deceased / unknown	ALG	FK-MMF-Cst	T Cell Rejection	Yes B+V+	No	64	Alive	
3	0.4	54	Deceased / unknown	Anti-CD25	FK-Cst	No	Yes B+V+F+	Yes	117	Alive	1 NMSC / 1 Merkel cell Carcinoma
4	13	50 / + Liver Transplant	Deceased / unknown	Anti-CD25	FK-MMF-Cst	No	Yes B+F+	No	4	Died	Died on HD (sepsis)
5	5.8	45	Deceased / unknown	Anti-CD25	CsA-MMF-Cst	No	No	No	113	Alive	
6	3.8	30	Deceased / unknown	Anti-CD25	FK-MMF-Cst	unknown	Yes B+	unknown	32	Alive	
7	8.4	66	Deceased / unknown	Anti-CD25	FK-MMF-Cst	No	Yes B+V+	No	27	Alive	
8	12.1	58	Deceased / unknown	Lc depl Ag	FK-MMF-Cst	No	Yes B+	Yes	25	Alive	1 NMSC
9	22.3	63	Deceased / unknown	Lc depl Ag	FK-MMF-Cst	No	No	No	20	Alive	
10	13.4	43	Deceased / unknown	Anti-CD25	FK-MMF-Cst	No	No	No	72	Alive	
11	10.6	38	Deceased / unknown	Lc depl Ag	FK-MMF-Cst	No	Yes B+	Yes	135	Died	Death caused by NH Lymphoma
12	0.3	40 / + Heart Transplant	Deceased / unknown	Anti-CD25	FK-MMF-Cst	No	Yes V+	No	98	Alive	
13	6.4	24	Deceased / unknown	Lc depl Ag	CsA-MMF-Cst	No	Yes B+	No	178	Alive	
14	0.1	23	Deceased / unknown	Anti-CD25	CsA-MMF-Cst	T Cell Rejection	Yes B+V+	No	76	Alive	
15	7	20	Deceased / unknown	Anti-CD25	FK-MMF-Cst	No	Yes B+	No	146	Alive	
16	12	28	Alive / different from BMT Donor	Unknown/ CsA-mTor inh-Cst		No	No	No	162	Alive	

ALG, antilymphocytes globulins; anti-CD25, anti-CD25 antibodies; B+, bacterial infection requiring hospitalization; BMT, bone marrow transplant; CsA, cyclosporine A; Cst, corticosteroids; ESRD, end-stage renal disease; F+, fungal infection; FK, tacrolimus; HD, hemodialysis; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; IS, immunosuppression; KT, kidney transplantation; MMF, mycophenolate mofetil; mTor inh, mTor Inhibitor; NH, Non-Hodgkin; NMSC, nonmelanoma skin cancer; V+, viral infection.

HSCT, the 2 most recently allografted patients, the only ones to receive nonmyeloablative conditioning regimen, were already on hemodialysis. Two patients were with stage 2 chronic kidney disease and 5 had no kidney failure.

Excluding patients on dialysis at the time of HSCT, patients reached end-stage renal disease requiring dialysis or transplantation within a median of 8.4 (0.1–22.3) years after allogeneic HSCT ($n = 13$). Of these patients, 2 required dialysis during the first year. One patient developed infections related to the dialysis technique (sepsis). The median time from HSCT to KT was 11 (1–24) years and the median age at transplantation was 41.5 (20–66) years (Table 2). The transplanted kidney came from a deceased donor in 94% of cases and was fully human leukocyte antigen-matched in 1 patient. The median follow-up time after KT was 6 (0.3–15) years with good overall survival (OS [95% confidence interval]: 94% (83%, 100%) at 5 years; Supplementary Figure S1). At the end of follow-up, 15 patients had a functional kidney transplant. Two patients died: 1 died early, 4 months after combined liver/KT, of sepsis (mucormycosis), with a nonfunctional kidney graft; the other died 12 years after KT with a functional graft, following an Epstein Barr virus (EBV)-negative post-kidney transplant malignant non-Hodgkin's lymphoma. Of the case series, no other patient returned to dialysis during the follow-up period.

Eleven patients (69%) developed bacterial infections, 5 (32%) developed severe viral infections and 2 (12.5%) developed fungal infections. No parasitic infections were reported. Bacterial infections were mainly of urinary tract and pulmonary origin. Viral infections were due to cytomegalovirus, herpes simplex virus, influenza A virus, BK virus and EBV. Fungal infections were *Candida albicans pneumonia* and facial mucormycosis. Oncologic complications occurred in 3 patients: 1 patient developed fatal non-EBV non-Hodgkin's lymphoma, 1 developed a Merkel cell carcinoma and nonmelanoma skin cancer, and 1 developed a nonmelanoma skin cancer. The skin cancers occurred within 5 years of KT. Five patients did not develop severe infection or cancer during follow-up.

DISCUSSION

This study, of a cohort of 16 French KT patients who received a kidney from a donor different from the HSCT donor, is the first to address oncologic and infectious complications after deceased donor KT. Previous case reports and studies have reported successful KT after HSCT,[1-6,S5–S12] but only 1 was a large multicenter study,[7] and none had that large, deceased donor recruitment. Brockmann *et al.*[1] analyzed the outcomes of 53 HSCT recipients undergoing a subsequent kidney transplant in a recent review combined with a single-center analysis.[1] The study revealed an actuarial patient survival of 85%, death-censored graft survival of 81% after a mean follow-up of approximately 4 years. To note, the mainly involved patients transplanted from living donors and an undetermined number of graft failures may not have been published, which introduces a data selection bias. Nevertheless, the overall survival reported is close to that observed in our study. In another single-center cohort, Jurdi *et al.*[2] described a 1-, 5-, and 10-year overall survival of 100%, 85%, and 58%, respectively, in 13 HSCT patients receiving a kidney graft.

In the review of Brockmann *et al.*,[1] 7 of 53 (15%) kidney transplant patients died because of infectious complications ($n = 3$), malignancies ($n = 2$), and myocardial infarction or cardiac death ($n = 2$).[1] Jurdi *et al.*[2] reported 4 deaths in 13 patients, due to infectious complications ($n = 2$; secondary graft failure after polyomavirus infection and bacterial infection), malignancy relapse (n=1), and diabetes mellitus-related complications. Infectious complications, and malignancies were also responsible for 2 deaths in our cohort. These rates of fatal infections and malignancies could be related to high immunosuppression or long-term exposure to immunosuppressive agents.

These data can be paralleled in patients with no history of HSCT. In a population of 46,471 adults with KTs between 1995 and 2003, a retrospective US study identified an infection rate of 74.7% in the first year posttransplantation, decreasing to 33.1% in the second year and 29.6% in the third year.[8] Regarding malignancies, a cohort review of more than 30,000 KT recipients without a history of HSCT found a 15% incidence of cancer, mostly nonmelanoma skin cancers, over a median follow-up period of 16 years.[9] In our study, the incidence is 20%, with 3 patients developing cancers.

Our study has some limitations. Indeed, this retrospective case series certainly involves a highly selected population with a survival bias and many data were missing, especially on the hematological period. Like other authors in the literature, our data do not allow us to make recommendations on the period of hematologic malignancy recurrence-free survival required before KT approval.

In conclusion, this study although retrospective shows that KTs are feasible in recipients of an allogeneic hematopoietic cell transplantation and that their outcomes are comparable to those who did not have a hematopoietic cell transplantation. Indeed, this relatively large cohort of KT recipients with a kidney donor different from the HSCT donor shows excellent

overall and graft survival. Clinical outcomes were satisfactory, compared with those previously reported for patients without a history of HSCT. Similarly, our case series describing outcomes of patients who received a graft from a deceased donor (15/16) shows overall survival as good as those including patients who underwent KT from a related living-donor.[1,7] We believe that these very good results may encourage hematologists and nephrologists to open access to KT for these patients.

If our data are exhaustive about patients concerned by KT over this 15-year period, it is difficult to determine the number of patients with a history of HSCT who need dialysis and are offered a transplant. The number of such patients seems low given our series, despite the good results described in the literature and in our study. It would seem necessary to set up a study in France to collect this data on an ongoing basis.

DISCLOSURE

All the authors declared no conflicting interests.

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AUTHOR CONTRIBUTIONS

MJZ and CC contributed to conception and design of the study. MJZ organized the database. MJZ, CC, and CV performed the statistical analysis. MJZ and CV wrote the first draft of this manuscript. All authors contributed to the revision of the manuscript, read, and approved the submitted version.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure 1. Kaplan–Meier curve of overall and graft survival.
Table S1. Diabetes and hypertension status at HSCT.
Supplementary Methods.
Supplementary References.

REFERENCES

1. Brockmann JG, Broering DC, Raza SM, et al. Solid organ transplantation following allogeneic haematopoietic cell transplantation: experience from a referral organ transplantation center and systematic review of literature. *Bone Marrow Transplant*. 2019;54:190–203. https://doi.org/10.1038/s41409-018-0255-9
2. Jurdi NE, DeFor T, Adamusiak AM, Brunstein CG, Pruett T, Weisdorf DJ. Hematopoietic Cell and Solid Organ Transplantation in the same patient: long term experience at the University of Minnesota. *Transpl Cell Ther*. 2021;27:87.e1–87.e6. https://doi.org/10.1016/j.bbmt.2020.09.005
3. Jacobsen N, Taaning E, Ladefoged J, Kvist Kristensen J, Pedersen Freddy K. Tolerance to an HLA-B,DR disparate kidney allograft after bone-marrow transplantation from same donor. *Lancet*. 1994;343:800. https://doi.org/10.1016/S0140-6736(94)91881-3
4. Butcher JA, Hariharan S, Adams MB, Johnson CP, Roza AM, Cohen EP. Renal transplantation for end-stage renal disease following bone marrow transplantation: a report of six cases, with and without immunosuppression. *Clin Transplant*. 1999;13:330–335. https://doi.org/10.1034/j.1399-0012.1999.130409.x
5. Beitinjaneh A, Burns LJ, Majhail NS. Solid organ transplantation in survivors of hematopoietic cell transplantation: a single institution case series and literature review. *Clin Transplant*. 2010;24:E94–E102. https://doi.org/10.1111/j.1399-0012.2009.01155.x
6. Fangmann J, Kathrin Al-Ali H, Sack U, et al. Kidney transplant from the same donor without maintenance immunosuppression after previous hematopoietic stem cell transplant. *Am J Transplant*. 2011;11:156–162. https://doi.org/10.1111/j.1600-6143.2010.03352.x
7. Koenecke C, Hertenstein B, Schetelig J, et al. Solid organ transplantation after allogeneic hematopoietic stem cell transplantation: a retrospective, multicenter study of the EBMT. *Am J Transplant*. 2010;10:1897–1906. https://doi.org/10.1111/j.1600-6143.2010.03187.x
8. Snyder JJ, Israni AK, Peng Y, Zhang L, Simon TA, Kasiske BL. Rates of first infection following kidney transplant in the United States. *Kidney Int*. 2009;75:317–326. https://doi.org/10.1038/ki.2008.580
9. Collett D, Mumford L, Banner NR, Neuberger J, Watson C. Comparison of the incidence of malignancy in recipients of different types of organ: a UK registry audit. *Am J Transplant*. 2010;10:1889–1896. https://doi.org/10.1111/j.1600-6143.2010.03181.x