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Allogeneic Hematopoietic Stem Cell Transplantation in Solid Organ Transplant Recipients: A Retrospective, Multicenter Study of the EBMT

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We conducted a questionnaire survey of the 565 European Society for Blood and Marrow Transplantation centers to analyze the outcome of allogeneic hematopoietic stem cell transplantation (alloSCT) in recipients of solid organ transplantation (SOT). We investigated 28 patients with malignant (N = 22) or nonmalignant diseases (N = 6), who underwent 31 alloSCT procedures: 12 after kidney, 13 after liver and 3 after heart transplantation. The incidence of solid organ graft failure at 60 months after first alloSCT was 33% (95% confidence interval [CI], 16–51%) for all patients, 15% (95% CI, 2–40%) for liver recipients and 50% (95% CI, 19–75%) for kidney recipients (p = 0.06). The relapse rate after alloSCT (22%) was low following transplantation for malignant disorders, despite advanced stages of malignancy. Overall survival at 60 months after first alloSCT was 40% (95% CI, 19–60%) for all patients, 51% (95% CI, 16–86%) for liver recipients and 42% (95% CI, 14–70%) for kidney recipients (p = 0.39). In summary, we show that selected SOT recipients suffering from hematologic disorders may benefit from alloSCT and experience enhanced long-term survival without loss of organ function.

Abbreviations: ALL, acute lymphoblastic leukemia; alloSCT, allogeneic hematopoietic stem cell transplantation; AML, acute myelogenous leukemia; BM, bone marrow; CGD, chronic granulomatous disease; CI, confidence interval; CML, chronic myeloid leukemia; EBMT, European Society for Blood and Marrow Transplantation; GvHD, graft-versus-host disease; HSC, hematopoietic stem cell; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; MRD, matched related donor; MUD, matched unrelated donor; OS, overall survival; PBSC, peripheral blood stem cell; PTLD, posttransplant lymphoproliferative disease; RIC, reduced-intensity conditioning; SAA, severe aplastic anemia; SOT, solid organ transplantation; TBI, total body irradiation; TKIs, tyrosine kinase inhibitors; VOD, veno-occlusive hepatic disease

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Introduction

Solid organ transplantation (SOT) is widely used for the treatment of end-stage organ insufficiency. About 30 000 SOTs were performed in the European Union in 2011, comprising approximately 19 000 kidney, 7000 liver and 2000 heart and other, including combined transplants (1) and many more patients are on waiting lists (2). Overall, the number of SOTs is increasing. Survivors of SOT experience many complications, including those related to the hematopoietic system. Development of aplastic anemia after liver transplantation for liver failure caused by viral hepatitis is well documented, and occurs in up to one-third

of children in this situation (3,4). Posttransplant lymphoproliferative disease (PTLD) occurs after 1–3% of liver and kidney, 3–9% of heart and lung and up to 10% of intestinal or multiorgan transplants (5). SOT has also been shown to increase the risk of acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS), observed in about 0.2% of SOT recipients (6). Furthermore, prolonged immune suppression following SOT may cause the relapse of malignancies diagnosed and treated before transplantation. The emergence of hematopoietic complications after SOT requires specific treatment by hematologists, and a proportion of patients may be candidates for allogeneic hematopoietic stem cell transplantation (alloSCT). However, physicians recruiting patients for alloSCT consider SOT recipients to be at significant risk of comorbidities after transplantation. The hematopoietic stem cell (HSC) donor is usually matched based on HLA molecules with the patient, rather than with the solid organ graft; therefore, alloSCT can lead to graft rejection. In contrast, use of a single donor for both stem cells and the solid organ graft may have a tolerogenic effect and decrease the requirement for immune suppression. Exposure to a conditioning regimen, concomitant medications, infections involving the solid organ graft and drops in blood pressure during episodes of septic shock may lead to decreased transplant performance and loss of function. For these reasons, it is not common practice to perform alloSCT in SOT recipients.

Over the last 20 years, several case reports have detailed encouraging results of alloSCT in solid organ transplant recipients (7–21). In a summary of published cases by Chiang and Lazarus (22), 8/10 recipients of alloSCT after SOT were alive at the last follow-up. However, because most currently available data derive from reports of successful alloSCT, these publications may suffer from positive reporting bias; thus, the real outcomes of alloSCT in SOT recipients are unknown.

The European Society of Blood and Marrow Transplantation (EBMT) registry database constitutes a rich source of data on alloSCTs performed in European countries. We assessed a cohort of patients from this database who underwent at least one alloSCT after SOT to gather information on clinical outcomes in this group.

Materials and Methods

Study design

First, a questionnaire was sent to all centers registered with the EBMT ($n = 565$) requesting information on cases of HSC transplantation after SOT. The centers were asked to report all cases of autologous and allogeneic HSC transplantation performed after SOT. Based on these reports, patients' data were identified in the EBMT registry database. Second, the centers were asked to complete a detailed questionnaire, including missing information on SOT and alloSCT. In this study we enrolled only patients who had undergone at least one alloSCT after SOT. All the patients gave their informed consent for alloSCT, data analysis and publication, according to the EBMT rules. The institutional review board approval was unnecessary for the study.

Statistical analyses

Nonpaired and normally distributed data were compared using the two-sided Student's t-test, whereas nonnormally distributed data were analyzed using the Mann–Whitney test. Categoric data were compared using the chi-squared or Fisher's exact tests, as appropriate. The outcomes included terminal solid organ graft failure and patient survival. In liver transplant recipients, terminal transplant failure was defined as death due to impaired organ function or organ replacement. In renal transplant patients, terminal transplant failure was determined by retransplantation or return to dialysis. Solid organ graft rejection was diagnosed by the reporting physicians based on clinical features and, where possible, histopathologic analysis.

Survival estimates were calculated using the Kaplan–Meier method, and the curves were compared using the log-rank test. Approximate 95% confidence intervals (CI) were calculated using Greenwood's formula. Cumulative incidence was used to estimate terminal transplant failure; death and second transplantation were considered competing risks for transplant failure. Cumulative incidences were compared using the Gray test (23). Acute graft-versus-host disease (GvHD) was graded according to the criteria of Glucksberg et al (24), whereas chronic GvHD stage was determined according to the Seattle criteria (25). Engraftment failure was defined as a lack of stable regeneration of neutrophils $>0.5 \times 10^9$/L and platelets $>20 \times 10^9$/L, unless survival time was less than 1 month. All statistical analyses were performed using the statistical software SPSS (PASW Statistics versions 18.0 and 19.0; IBM Corporation, Armonk, NY) and R version 2.12.2 with the ''survival'' package (http://www.r-project.org/foundation).

Results

Of the 565 EBMT centers, 101 responded to the survey (18%). The response rate among the centers performing alloSCT was 90/357 (25%). Eighteen of the responding alloSCT-performing centers (20%) reported a total of 28 patients who had undergone SOT and subsequent alloSCT. The patients had undergone a total of 31 alloSCTs (Patients 10, 17 and 26 underwent double alloSCT after SOT).

Solid organ transplantations

The SOT recipients included 12 patients with kidney, 13 with liver and 3 with heart transplants. Detailed patient characteristics are shown in Table 1. Nineteen of the patients were men (68%), and nine were women (32%). Their median age at SOT was 25 years (range, 1–62 years): 33 years (range, 9–50 years) for kidney and 19 years (range, 1–62 years) for liver recipients ($p = 0.297$). The group included nine patients aged <18 years at SOT. The median year in which SOT was performed was 2002 (range, 1974–2011). Kidney transplants were performed earlier (median year 1997; range, 1974–2006) than liver transplants (median year 2007; range, 1993–2011; $p = 0.005$). The indications for SOT are listed in Table 1. For solid organs, data concerning HLA typing were largely unavailable, except when the donor was related (haploidentical for one kidney and two liver transplant recipients, where the donors were the parents of the patient; fully matched sibling for one kidney recipient and one liver recipient). One heart transplant recipient received an organ for which 4/8 HLA antigens were matched, and one kidney was fully

Table 1: Characteristics of patients in the context of solid organ transplantation

Patient #	Age at SOT/sex	SOT donor type	Primary disease	SOT rejection prophylaxis	Rejection episodes
Heart transplantation					
1	19/F	Deceased	Acute postanthracyclin failure	GCS/CSA/Sir	(++)
2	12/M	4/8, deceased	Dilative cardiomyopathy	CSA	(−)
3	Unkn/M	Deceased	Severe insufficiency, post MI	GCS/CSA/Aza	unkn
Kidney transplantation					
4	41/M	Deceased	Chronic GN	GCS/Tacro	(−)
5	13/M	Unkn	Terminal kidney insufficiency, unkn	GCS/CSA	(−)
6	36/M	Unkn	Unkn	Unkn	(−)
7	32/M	Deceased	Chronic GN	CSA/Aza/Tacro/MMF/Evero	(+)
8	25/M	Deceased	Terminal kidney insufficiency, unkn	CSA	(−)
9	25/M	Deceased	Pyelonephritis	GCS/CSA	(−)
10	9/F	Parent	Pyelonephritis	GCS/Tacro/MMF	(+)
11	33/M	Deceased	Tubulo-interstitial nephropathy	GCS/CSA/Aza/Lg	(+)
12	34/F	6/6 sibling	Terminal kidney insufficiency, unkn	Tacro	(−)
13	50/F	6/6 matched, living unrelated	Polycystic kidney disease	GCS/Tacro/MMF	(−)
14	45/M	Living	Pyelonephritis	Unkn	unkn
15	33/F	Deceased	Diabetes type I	CSA	(−)
Liver transplantation					
16	1/M	Parent	Hepatoblastoma	CSA	(−)
17	26/F	Deceased	Acute chemotherapy-induced failure	GCS/Tacro	(−)
18	12/F	Deceased	Idiopathic failure	CSA	(−)
19	39/F	Deceased	HBV/HDV hepatitis	GCS/Tacro	(+)
20	39/M	Deceased	HCV hepatitis	GCS/Tacro/Aza	(+)
21	9/M	Deceased	NASH	GCS/Tacro/Aza	(−)
22	5/M	Parent (split)	Hepatoblastoma	GCS/Tacro/Basil	(−)
23	54/M	6/6 sibling	HBV hepatitis, HCC	Unkn	(−)
24	3/M	Deceased	NANBNC hepatitis	CSA	(−)
25	62/M	Deceased	NASH, HCC	GCS/Tacro/MMF	(−)
26	19/M	Deceased	Sclerosing cholangitis	GCS/Tacro/MMF	(−)
27	17/F	Deceased	Idiopathic failure	Unkn	(+)
28	23/M	Deceased	Idiopathic cirrhosis	GCS/Tacro	(−)

The list of immunosuppressive agents contains all the agents used between SOT and SCT.
4/8, matched in 4/8 HLA antigens; 6/6, matched in 6/6 HLA antigens; Unkn, unknown; F, female; M, male; MI, myocardial infarction; GN, glomerulonephritis; NASH, nonalcoholic steatohepatitis; NANBNC, non-A non-B non-C; HCC, hepatocellular cancer; GCS, glucocorticosteroids; CSA, cyclosporine A; Sir, sirolimus; MMF, mycophenolate mofetil; Aza, azathioprine; Tacro, tacrolimus; Evero, everolimus; Lg, lymphoglobulin; Basil, basiliximab.

matched with the recipient. The patients were treated with various immunosuppressive regimens (Table 1) and, in 7/26 patients with available data, rejection episodes occurred after SOT and before alloSCT. These were resolved by increasing immune suppression.

Allogeneic stem cell transplantation

The reason for the first alloSCT was most commonly a malignant disorder (22/28, Table 2). The most common cause of alloSCT was AML (n = 8), followed by acute lymphoblastic leukemia (ALL; n = 4), nonHodgkin's lymphoma (n = 3; two patients with PTLD and one with γδ T cell lymphoma), chronic myeloid leukemia (CML; n = 4), severe aplastic anemia (SAA) or otherwise unexplained bone marrow (BM) failure (n = 4), inherited disorders (n = 2; primary immunodeficiency and chronic granulomatous disease [CGD]), MDS (n = 1), chronic myelomonocytic leukemia (n = 1) and hepatoblastoma (n = 1). In eight patients, the diagnosis that led to alloSCT was known before SOT (AML, CML, 2 × ALL, CGD, hepatoblastoma, primary immunodeficiency and SAA). In the remaining 20 patients, the disease was diagnosed a median of 50 months after SOT (range, 2–294 months). Second alloSCTs were performed for ALL relapse (n = 2) or primary graft failure (n = 1). The median time between SOT and alloSCT was 37 months (range, 1–315 months) and SCTs were performed a median of 15 months (range, 0.4–207 months) after diagnosis of the disease. Two patients underwent autologous SCT before alloSCT: Patient 16 for treatment of hepatoblastoma, and Patient 7 for ALL.

The median year of alloSCT was 2006 (range, 1990–2012) in all patients, 2001 (range, 1990–2009) in kidney recipients and 2010 (range, 1994–2012) in liver recipients. At alloSCT, the median patient age was 29 years (range, 3–65 years).

Table 2: Characteristics of patients in the context of hematopoietic stem cell transplantation

Patient #	Events leading to SCT	Disease status at SCT	Diagnosis to SCT (months)	SOT to SCT (months)	Year of SCT	Age at SCT	Donor	F/M graft	Graft source	Conditioning intensity	Conditioning regimen	GvHD proph.	Blood group match (SCT / organ donor)	CMV status match (SCT / organ donor)
Heart transplantation														
1	AML/MDS	CR1	7	2	2003	19	mMUD	(−)	PB	MAC	Cy/TBI	CSA/MTX	A/O	Pos/pos
2	PTLD	unkn	17	150	2001	25	MRD	(−)	BM/PB	RIC	TBI/ATG	CSA/MTX/ATG/Tacro/Sir	A/O	Unkn/unkn
3	AML	CR1	8	unkn	1999	61	MRD	(+)	PB	RIC	Flu/TBI	CSA/MMF	A/unkn	Unkn/unkn
Kidney transplantation														
4	AML	Rel1	21	33	2006	43	MRD	(+)	PB	RIC	Unkn, no TBI	GCS/Tacro/MMF	A/unkn	Unkn/unkn
5	CML	CP1	21	315	2001	40	MUD	(−)	BM	RIC	Flu/Bu	GCS/CSA/MTX	O/unkn	Unkn/unkn
6	AML	Rel2	34	84	1998	43	MUD	(+)	BM	RIC	Bu/Cy/ATG	CSA/MTX	Unkn/unkn	Neg/unkn
7	Acute leukemia	Rel1	11	84	2008	39	haplo	(+)	PB	MAC	Flu/Thio/TBI/ATG	Sir	O/unkn	Neg/unkn
8	PLTD (Burkitt's type)	CR1	7	43	1992	28	MRD	(+)	BM	MAC	Cy/Ida/TBI	CSA	Unkn/AB	Neg/pos
9	CML	AccP	15	3	1990	25	MRD	(+)	BM	MAC	AraC/Cy/TBI	CSA/MTX	A/O	Pos/neg
10	ALL Ph+	unkn	17	1	2006	9	haplo	(−)	PB	MAC	Flu/MEL/Thio/Campath	GCS/Tacro/MMF	A/A	Pos/pos
10 2nd SCT	ALL Ph+	Rel	20	4	2006	9	haplo	(+)	PB	RIC	Flu/Thio/ATG/Campath	GCS/MMF	Unkn/unkn	Pos/unkn
11	CML	CP1	22	50	1999	37	MUD	(+)	BM	MAC	Cy/TBI/ATG	CSA/MTX	B/A	Pos/neg
12	CGD	NA	207	1	2001	35	MRD	(−)	PB	RIC	Flu/Bu/ATG	Tacro/MMF	B/unkn	Neg/unkn
13	ALL	CR1	4	69	2004	56	MUD	(−)	PB	RIC	TBI	Unkn	Unkn/O	Unkn/unkn
14	MDS	MR	7	56	2009	49	MUD	(−)	BM	RIC	Flu/TBI/ATG	CSA/MMF	O/A	Pos/unkn
15	CML	CP1	15	39	1999	37	mMUD	(−)	PB	MAC	Cy/TBI/ATG	CSA/MTX	A/unkn	Pos/unkn
Liver transplantation														
16	AML	CR2	13	127	2010	12	haplo	(+)	PB	MAC	MEL/Thio/Clo	CSA/Tacro	O/O	Neg/pos
17	ALL	PR2	35	33	2009	29	MUD	(−)	PB	MAC	Eto/TBI	GCS/Tacro/MMF	O/O	Unkn/neg
17 2nd SCT	ALL	Rel	52	50	2011	30	MUD	(−)	PB	MAC	Flu/MEL	GCS/CSA/MTX/Tacro	O/O	Pos/unkn
18	SAA	NA	0.4	5	2007	12	MRD	(−)	BM	MAC	Flu/Cy/ATG	CSA/MTX	B/unkn	Pos/pos
19	AML	CR1	8	59	2010	44	MUD	(−)	PB	RIC	Flu/Bu/ATG	CSA/MMF	A/A	Neg/neg
20	CMML	Pref	7	162	2008	53	mMUD	(+)	PB	MAC	Flu/MEL/Amsa/AraC/ATG	Tacro/MMF	O/A	Pos/unkn
21	BM failure	NA	0.4	3	2008	9	MRD	(−)	BM	RIC	Cy/TLI	CSA/MTX	A/unkn	Neg/pos
22	Hepatoblastoma	CR	11	5	2010	5	haplo	(−)	PB	MAC	Flu/MEL/Thio/Campath	MMF	A/A	Unkn/pos
23	ALL	CR1	6	110	2011	63	MRD	(−)	PB	MAC	Flu/Bu/ATG	CSA/MTX	O/unkn	Unkn/unkn
24	BM failure	NA	5	7	1994	3	MRD	(+)	BM	MAC	Cy/ATG	CSA/MTX	A/O	Neg/unkn
25	AML	CR2	24	35	2012	65	MUD	(−)	PB	RIC	Flu/Bu/ATG	CSA/MMF	O/unkn	Neg/unkn
26	Primary ID	NA	138	3	2009	18	MRD	(−)	PB	RIC	AraC/MEL	CSA/MMF	Unkn/unkn	Unkn/unkn
26 2nd SCT	Graft failure	NA	153	18	2010	19	MUD	(−)	PB	MAC	Flu/Treo	CSA	A/unkn	Neg/unkn
27	γδ T cell NHL	Pref	6	75	2002	23	MRD	(−)	PB	MAC	TBI	CSA	O/unkn	Neg/unkn
28	SAA	NA	111	8	2012	24	MUD	(+)	PB	RIC	Flu/Bu/ATG	Tacro/MTX	Unkn/unkn	Neg/unkn

SCT, stem cell transplantation; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; PTLD, posttransplant lymphoproliferative disease; CML, chronic myeloid leukemia; ALL, acute lymphoblastic leukemia; CGD, chronic granulomatous disease; SAA, severe aplastic anemia; CMML, chronic myelomonocytic leukemia; BM, bone marrow; ID, immune deficiency; NHL, nonHodgkin's lymphoma. CR, complete remission; unkn, unknown; NA, not applicable; CP, chronic phase; MR, minor response; PR, partial remission; Pref, primary refractory; mMUD, mismatched unrelated donor; MRD, matched related donor; MUD, matched unrelated donor (''matched'' refers to 10/10 HLA match at allele level); haplo, haploidentical; F/M, female to male; BM, bone marrow; PB, peripheral blood; MAC, myeloablative conditioning; RIC, reduced intensity conditioning; Cy, cyclophosphamide; TBI, total body irradiation; ATG, anti-thymocyte globulin; Flu, fludarabine; Bu, busulphan; Thio, thiotepa; Ida, idarubicin; AraC, cytosine arabinoside; MEL, melphalan; Clo, clofarabine; Eto, etoposide; Amsa, amsacrine; TLI, total lymphoid irradiation; Treo, treosulphan; CSA, cyclosporine A; MTX, methotrexate; MMF, mofetil mycophenolate; GCS, glucocorticosteroids; Tacro, tacrolimus; Rel, relapse; Pos, positive (IgG+IgM−); Neg, negative (IgG−IgM−).

For double alloSCTs, the second transplantations were performed 3 (Patient 10), 16 (Patient 26) or 17 (Patient 17) months after the first alloSCT. The alloSCTs were performed with peripheral blood stem cells (PBSCs; n = 21), BM (n = 9) or both (n = 1). PBSC transplantation was more frequent in liver transplant recipients (12/15, 80%) than in kidney transplant recipients (7/13, 54%; p = 0.017). The donors were HLA-identical siblings (n = 12), matched (8/8 HLA molecules at allele level; n = 11), and mismatched (n = 3) unrelated, or haploidentical (n = 5), and their distribution did not differ markedly among the groups. The mismatched unrelated donors were mismatched at single HLA-DRB1 (allelic level, Patient 1), single HLA-DQB1 (antigen level, Patient 20) and at HLA-B (single mismatch at antigen level), HLA-DRB1 and HLA-DQB1 (single mismatches at allelic level, Patient 15).

Three patients (Patients 10, 16 and 22) received haploidentical stem cells from the same donors as the solid organs (Patient 10 received double alloSCT from the donor). There was an unfavorable (female-to-male transplantation) sex mismatch between donor and recipient in 12/31 (39%) transplantations. The intensity of the conditioning was standard (myeloablative, MAC, n = 17) or reduced (reduced-intensity conditioning, RIC, n = 14) and included total body irradiation (TBI) in 12 patients, but the regimens were heterogeneous (Table 2). Fifty-four percent of alloSCTs in kidney recipients were performed after RIC, and the same proportion of patients received TBI. In liver transplant recipients, RIC was used in 33%, but only two (13%) conditioning regimens included TBI. In most cases (20/29), T cell depletion was performed (*in vivo*, n = 15; *ex vivo*, n = 2; and *in vivo* and *ex vivo*, n = 3). The most common GvHD/solid organ graft rejection prophylaxis was based on cyclosporine A and methotrexate (n = 12), followed by cyclosporine A and mycophenolate (n = 5) and tacrolimus with mycophenolate (n = 5), but the regimen frequently included other immunosuppressive drugs, especially steroids (Table 2).

Outcomes

Hematopoietic engraftment was achieved after 25/26 evaluable transplantations (96%) but, in two patients, the hematopoietic graft was subsequently lost (Table 3). In one patient, HSC graft loss was due to progression of the primary disease (MDS), whereas the reason in the second patient was unclear. Five patients died without achieving hematopoietic reconstitution, and only one lived longer than 1 month. In the evaluable patients, the time to neutrophil recovery ($>0.5 \times 10^9$/L) was 13.5 days (range, 9–37, n = 22). In five patients, the platelet count never dropped below 20×10^9/L, and in the remaining patients, the median time to achieving a platelet count $>20 \times 10^9$/L was 17 days (range, 10–103 days). Patient 2 died of hemorrhage 16 months after alloSCT, still without a platelet count $>50 \times 10^9$/L. Acute GvHD was observed after alloSCT in 17/31 patients, including eight with clinically significant Grade II–IV disease (details in Table 3). Chronic GvHD occurred after alloSCT in seven patients, but was mostly of limited stage (5/7).

The cumulative incidence of solid organ graft failure was 25% (95% CI 10.0–42.1%) at 3 months and 32.8% (95% CI, 16.1–50.7%) at 12 months. No further transplant failures occurred between 12 and 60 months after the first alloSCT (Figure 1A), although Patient 5 experienced chronic kidney rejection that led to graft failure 11 years after alloSCT. In total, transplant failure occurred in nine patients after 31 alloSCTs: 1/3 in heart recipients (33%); 3/15 (20%) in liver recipients; and 5/13 (38%) in kidney recipients. There was a trend toward a higher cumulative incidence of solid organ graft failure in kidney transplant recipients than liver transplant recipients (p = 0.06; Figure 1B). The median time from first alloSCT to solid organ graft failure was 1.8 months (range, 0–131 months). In Patient 26, transplant failure occurred 1.7 months after the second alloSCT. Five of nine cases of failure were described as solid organ graft rejections: 1/1 heart, 3/5 kidney and 1/3 liver failures (Table 3). A detailed description of the graft failures can be found in Table S1.

At the last follow-up, 13/28 patients were alive (46%; 8/13 patients after liver, 5/12 after kidney and none after heart transplantation). The estimated overall survival (OS) was 75% at 3 months (95% CI, 59–91%), 60.2% at 12 months (95% CI, 41.8–78.5%), 45.1% at 36 months (95% CI, 25–65.3%) and 40.1% at 60 months (95% CI, 19.1–60.3%) after the first alloSCT (Figure 2A). The transplant-related mortality at 3 months after first alloSCT was 25% (95% CI, 11–42%). The difference in median OS between liver and kidney transplant recipients did not reach statistical significance (Figure 2B). The median duration of observation was 14.4 months from the first alloSCT (range, 0.3–243 months). Deaths occurred after a median of 3.6 months (range, 0.3–38.5 months) after the first alloSCT (two patients died 9.2 and 12.3 months after their second alloSCT).

Nine deaths (60%) were directly related to infection (Patients 3, 4, 11, 14, 17, 21, 22, 23 and 27); in six patients, transplant failure directly contributed to death (40%; Patients 1, 4, 9, 11, 21 and 22). Patients 2, 7 and 9 died as a consequence of hemorrhagic complications, whereas veno-occlusive hepatic disease (VOD) directly contributed to the deaths of Patients 6 and 11. The deaths of Patients 7 and 9 were also related to the development of GvHD in the gut. Within the group of patients after liver transplantation no cases of VOD were reported and single case of liver aGvHD was described (Patient 24). Within the observation period, the relapse of malignant hematologic disease was observed in Patients 10 (ALL), 17 (ALL) and 15 (CML), while Patient 14 (MDS) never achieved complete remission. The median time to relapse was 11.8 months (range, 3.3–28.2 months).

The intensity of conditioning, type of stem cell donor and source of HSCs are factors known to have an impact on the

Table 3: Outcomes of allogeneic stem cell transplantation in recipients of solid organ transplants

Patient #	Time to Neu>0.5	Time to Plt>20	aGvHD max. grade	cGvHD	SOT failures (weeks after SCT)	Survival (months after SCT; D, dead, A, alive)	Comments
Heart transplantation							
1	NR	NR	0	NA	(+), Rejection (1)	0.3/D	Died 9 days after SCT due to subacute SOT rejection (confirmed by histpat)
2	19	19	0	(−)	(−)	16.1/D	Died of hemorrhage (never reached Plt 50×10^9/L) and MOF. Experienced transient episode of heart rejection 2 months after alloSCT treated successfully with tacrolimus and GCS
3	18	NB	II	(+), Limited	(−)	38.5/D	Died of infection—pulmonary Aspergillosis with good SOT function (no rejection, checked by histpat)
Kidney transplantation							
4	13	unkn	II (Skin 3)	(−)	(+) (18)	4.6/D	Died of infection and MOF with features of terminal SOT dysfunction
5	20	16	I (Skin 1)	(+), Limited	(+), Rejection (569)	141/A	Alive in CR after chronic SOT rejection, on dialysis program
6	NR	NR	0	NA	(−)	0.3/D	Died 9 days after SCT of VOD with impaired SOT function, which occured on day +4
7	13	NR	III (Gut 3)	NA	(−)	0.9/D	Died of gut GvHD with GI bleeding
8	18	103	I (Skin 2)	(+), Limited	(+), Rejection (45)	243.4/A	Alive after SOT rejection and 18 years after kidney re-transplantation, with good graft function, in CR
9	NR	NR	III (Skin 3, liver 3, gut 2)	NA	(+), Rejection (day 0)	0.7/D	Died 19 days after alloSCT of GI hemorrhage and pulmonary insufficiency due to aspiration, aGvHD and hyperacute kidney rejection which occured on day 0
10	9	unkn	0	(−)	(−)	3.1A	Relapsed, 2nd alloSCT after 3 months from same donor as SOT, at thetime of alloSCTalive, with good SOT function
10 2nd SCT	unkn	unkn	I	(−)	(−)	12.3/D	Died of relapse, with good SOT function, without IS for last 9 months
11	NR	NR	0	NA	(+) (2)	1.3/D	Died of VOD with SOT failure and pneumonia, without Neu or Plt regeneration
12	14	NB	0	(−)	(−)	133.2/A	Alive, in CR, with good SOT function
13	12	NB	I (Skin 1)	(−)	(−)	90.6/A	Alive, in CR with good SOT function, on prednisolon and MMF
14	37	44 to Plt>50	0	(−)	(−)	6.4/D	Died of relapse with HSC graft loss and MOF. On day +100 was without IS, with kidney function moderately impaired
15	10	NB	I (Skin 1)	(−)	(−)	156.4/A	Alive after relapse, with good SOT function
Liver transplantation							
16	10	unkn	I	(−)	(−)	14.9/A	Alive with good SOT function, without IS
17	13	unkn	I	(−)	(−)	17.2/A	Alive with good SOT function, relapse was treated with DLI and 2nd alloSCT after 18 months from alloSCT. Good SOT function at that time
17 2nd SCT	12	14	I (Skin 2)	(+), Limited	(−)	9.2/D	Died of infection and MOF with good SOT function, in CR
18	34	23	0	(−)	(−)	48.7/A	Alive, experienced transient pancytopenia treated with GM-CSF, good SOT function, on CSA
19	14	10	0	(+), Limited	(−)	15/A	Alive with good SOT function (transient SOT anastomotic stenosis and gallstones) on CSA, in CR with well controlled cGvHD
20	9	12	1 (Skin)	(−)	(−)	4.3/A	Alive with good SOT function in CR, on tacrolimus
21	NR	NR	0	NA	(+) (4)	0.8/D	Died (SOT and kidney failure in the course of sepsis, did not reach engraftment)
22	NR	unkn	III	NA	(+), Rejection (8)	1.8/D	Died of ADV infection, aGvHD and SOT failure (described as rejection), 1 week without IS
23	17	12	III (Gut 3)	(−)	(−)	3.6/D	Died of sepsis, in CR, 1 week without IS, with good SOT function
24	12	unkn	0	(−)	(−)	191.1/A	Alive with good SOT function, in CR
25	15	15	II (Gut 2)	(−)	(−)	14/A	Alive with good SOT function, in CR
26	NB	NB	0	(−)	(−)	15.1/A	Alive, but HSC graft rejection and relapse of sclerosing cholangitis in transplanted liver. 2nd alloSCT
26 2nd SCT	13	32 to PLT>50	0	(+), Extensive	(+) (8)	30.6/A	Alive after relapse of sclerosing cholangitis, second liver SOT 44 days after 2nd alloSCT, good function on last follow-up
27	9	89	III (Skin 2, liver 2, gut 1)	(+), Extensive	(−)	6.7/D	Died of MOF, in CR without previous loss of SOT function
28	17	18	0	(−)	(−)	7.7/A	Alive with good SOT function, on tacrolimus

Neu>0.5, neutrophil regeneration to >0.5 × 10e9/L; Plt>20, platelet regeneration to >20 × 10e9/L; NR, not reached; NB, never below; unkn, unknown; SCT, stem cell transplantation; SOT, solid organ transplantation; MOF, multi-organ failure; histpat, histopathologic examination; CR, complete remission; VOD, venoocclusive disease; GvHD, graft-versus host disease; GI, gastrointestinal; IS, immune suppression; ADV, adenovirus.

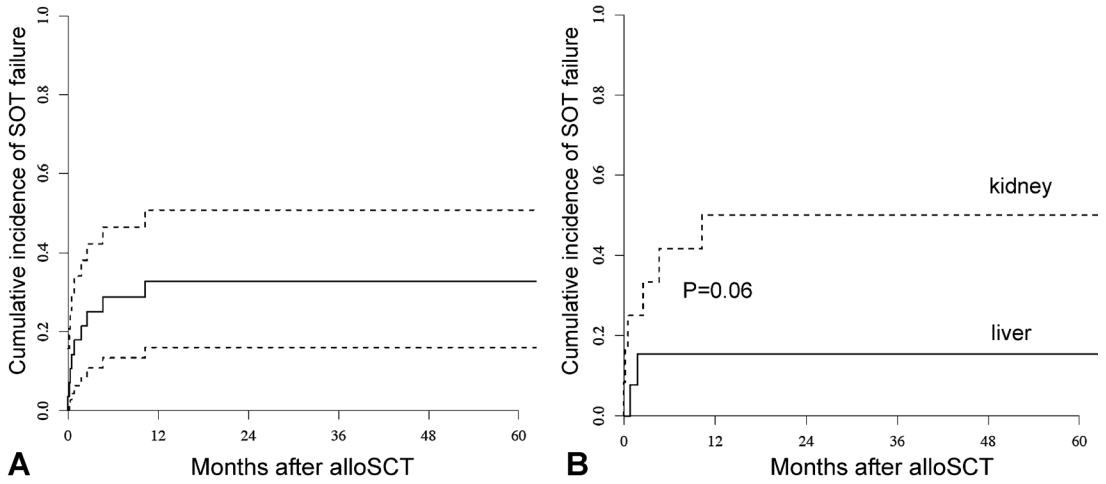

Figure 1: Incidence of terminal solid organ graft failure after the first allogeneic stem cell transplantation in all patients (95% confidence intervals were showed as dashed lines) (A) and in recipients of liver (solid line) and kidney (dashed line) grafts (B).

outcome of alloSCT (26); however, none was significantly associated with survival in this study. The analysis of potential factors influencing graft failure did not reveal significance of age, diagnosis, year of alloSCT, intensity of conditioning and donor HLA match, while the proportion of solid organ failures seemed to be higher in patients transplanted with BM (5/9, 55%) than with PB (3/20, 15%; $p = 0.061$).

Discussion

In this paper, we summarized the European experience of alloSCT performed in solid organ transplant recipients. To date, a small number of case reports have been published that reveal the feasibility of this approach. We found that it is relatively widely used at EBMT centers: at least 18% of responding centers had performed such procedures, and it is likely that additional procedures have been performed in nonresponding centers. We identified the largest series of patients published to date ($n = 28$), allowing basic statistical analysis for the first time. We showed that alloSCT after SOT has been performed in diverse settings: after different grafts (liver, kidney, heart), for different indications, after MAC or RIC, using either matched related donor (MRD) or matched unrelated donor (MUD), and also using mismatched donors, including haploidentical donors. This is probably because these transplants were performed over a

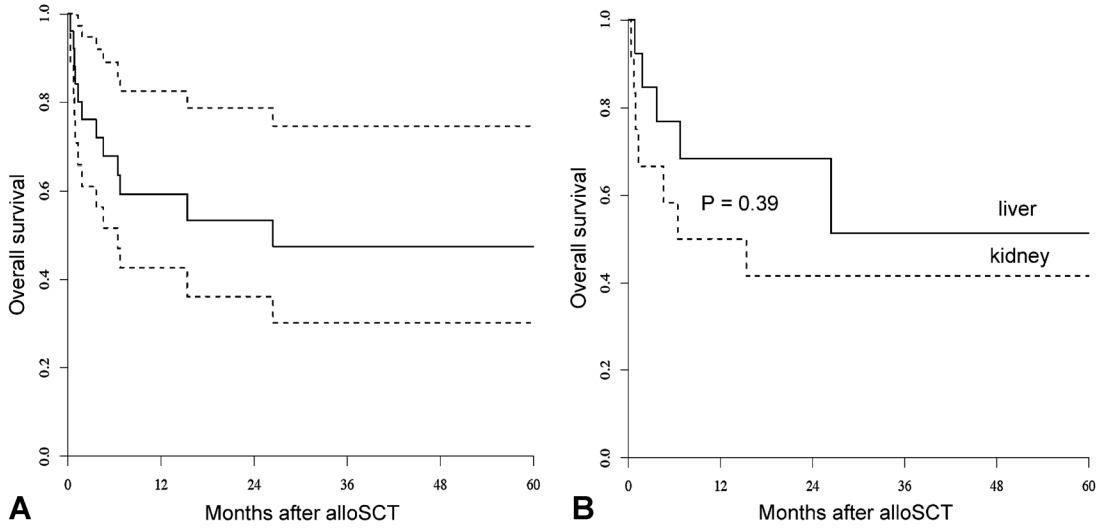

Figure 2: Overall survival of patients with solid organ transplants after the first allogeneic stem cell transplantation in all patients (95% confidence intervals were showed as dashed lines) (A) and in recipients of liver (solid line) and kidney (dashed line) grafts (B).

long period, and the increasing choice of procedures mirrors developments in the field. The limitation of this study is, however, the low response rate of EBMT centers to the survey (18%, but 25% among centers performing alloSCT), and low number of cases, which may constitute an important bias making the definite conclusions difficult.

As expected, the commonest indication for alloSCT was acute leukemia. In most patients (9/14), leukemia was of an advanced stage (more than first complete remission) at the time of alloSCT. All four patients with CML underwent alloSCT before the era of tyrosine kinase inhibitors (TKIs; the most recent alloSCT was in 2001): such patients would now be treated with TKIs and not proceed to transplantation unless they had resistant disease. BM failure, frequently diagnosed as SAA, is a known complication of viral hepatitis that leads to liver failure, and can occur after liver transplantation for cirrhosis of the liver. Accordingly, SAA/BM failure was the indication for alloSCT in four recipients of liver grafts. PTLD was an uncommon indication for alloSCT (occurring only two patients). In 8/28 patients, the hematologic disease existed before SOT. For most of these patients, precise information on why SOT was performed was lacking. Recently, a report on cases of SOT after alloSCT was published by our group (27), which showed an encouraging 78% OS rate 5 years after SOT. However, in the present particular situation, it is likely that the symptoms of the hematologic disorder worsened after SOT, necessitating alloSCT.

Our study clearly showed that performing alloSCT in SOT patients may lead to long-term survival without loss of function of the solid organ graft. However, the estimated probability of survival 5 years after alloSCT is only 40%, which is mostly due to mortality within 1 year of alloSCT. Importantly, the decrease in OS was not caused by the relapse of malignancy, despite the large proportion of alloSCTs performed to treat resistant, relapsed disease. Therefore, transplant-related mortality was the most significant cause of failure. Our analysis revealed infection to be the most common cause of death. This was consistent with our expectations, because most patients continued to receive immunosuppressive therapy as recipients of SOT. The second most common cause of death was terminal loss of transplant function. The cumulative incidence of solid organ graft failure was 25% at 3 months, and it remained stable at 33% 12 months after the first alloSCT. This finding, together with a median terminal transplant failure time of 1.8 months after alloSCT, clearly indicates that the first year following HSC transplantation is crucial for transplant function. Terminal loss of function was more frequently observed in recipients of kidney grafts than liver grafts, although this did not influence OS significantly (possibly because of differences in transplant period, conditioning regimen, and TBI use between the two groups). Only three of nine patients survived transplant failure: two kidney transplant recipients received dialysis (with subsequent successful kidney retransplantation in one) and one recipient of a liver graft underwent a second liver transplantation.

We can only speculate about the mechanism of graft rejection. An immune response could have been directed against mismatched HLA molecules, because the hematopoietic graft was HLA-matched with the recipient rather than the solid organ. However, recent studies (28) suggested that alloSCT can have a tolerogenic effect, allowing maintenance of a solid organ graft without immune suppression. Conditioning prior to alloSCT and infection may increase the immunogenicity of transplants by enhancing antigen presentation, increasing costimulatory signals, changing the properties of the vascular endothelium, and suppressing regulatory T cell function. Whereas the majority of solid organ grafts are matched with the recipient based on blood group, this is not required for HSC donors. Thus, the majority of transplants are probably not matched with the hematopoietic graft, and this could affect graft survival. Moreover, in most patients, the immunosuppressive regimen was changed after alloSCT from a regimen typical for SOT to an alloSCT-specific regimen, which could be suboptimal in this situation.

The choice of stem cell donor (MRD vs. MUD) did not influence OS after alloSCT. All but one haploidentical transplantation were unsuccessful; a single patient (Patient 16), who received haploidentical stem cells from the same donor as the liver transplant, was reportedly alive almost 15 months after alloSCT, with good transplant function and without immune suppression. None of the standard prognostic factors for survival postHSC transplantation were significantly associated with survival in this study, probably because of the low number of patients. Therefore, we can make no recommendations to guide the choice of conditioning, stem cell source or donor in patients after SOT.

In conclusion, alloSCT is a useful therapeutic strategy for selected patients after SOT, where the risk of this procedure is exceeded by the expected consequences of not performing stem cell transplantation. Long-term survival is in line with the results for high-risk patients; however, the procedure is associated with the risk of loss of transplant function, including rejection. End-stage impairment of the transplanted organ seemed more frequent in kidney than liver recipients, but this did not contribute significantly to OS.

Centers Reporting Cases

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Table S1: Description of cases of solid organ transplant failure.