Bone Marrow Transplantation (2019) 54:190–203
https://doi.org/10.1038/s41409-018-0255-9

REVIEW ARTICLE

Solid organ transplantation following allogeneic haematopoietic cell transplantation: experience from a referral organ transplantation center and systematic review of literature

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Received: 21 April 2018 / Accepted: 20 May 2018 / Published online: 6 August 2018

Abstract

Solid organ transplantation (SOT) following haematopoietic cell transplantation (HCT) is a rare event. Uncertainty exists whether such recipients are at higher risk of relapse of underlying haematological disease or at increased risk of developing infectious or immunological complications and malignancies following SOT. The experience at our referral organ transplantation center and the present literature of SOT ($n = 198$) in recipients following previous HCT was systematically reviewed. Outcome analysis of 206 SOT recipients following HCT challenges the validity of the frequently stated comparable outcome with recipients without prior HCT. SOT recipients after HCT are younger and have a higher mortality and morbidity in comparison with "standard" recipients. Rejection rates for SOT recipients following HCT appear to be lower for all organs, except for liver transplantation. In the setting of liver transplantation following HCT, mortality for recipients of deceased donor grafts appears to be exceptionally high, although experience with grafts of living donors are favourable. Morbidity was mostly associated with infectious and malignant complications. Of note some SOT recipients who received solid organ donation from the same HCT donor were able to achieve successful withdrawal of immune suppression. Despite limited follow-up, recipients with prior HCT show a different course after SOT, necessitating attention and closer follow-up.

Introduction

Allogeneic hematopoietic cell transplantation (HCT) is the only cure for numerous malignant and non-malignant diseases of the lympho-hematopoietic system with otherwise fatal prognosis. Morbidity and mortality associated with treatment-related organ toxicity is limiting its success. Organ failure can be secondary to pre-transplant treatment exposures, and organ injury because of conditioning regimen toxicity, graft-versus-host disease (GVHD) and/or infections. Conservative therapeutic strategies are only partially effective resulting in mortality. During recent decades, solid organ transplantation (SOT) has occasionally been used for treatment of terminal organ failure in HCT recipients. SOT included kidney, liver, lung and heart grafts for a variety of HCT-related complications.

Although, SOT following HCT has been performed for more than 25 years, comprehensive information regarding its benefit in terms of overall survival and continuative organ function is limited and only provided by case reports or case series. Limited compilation of reported cases may

Electronic supplementary material The online version of this article (https://doi.org/10.1038/s41409-018-0255-9) contains supplementary material, which is available to authorised users.

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Table 1 Performance and outcome for kidney transplantation following HSCT

Author[ref] (year)	*n*	Mean age at SOT in y (range)	SOT donor (time from HCT to SOT)	Follow-up in m mean (range)	% Patient survival	% Graft survival	Rejection in %	Complications/remarks
Sayegh [7] (1991)	2	14 30	Same as HCT Same as HCT	12 24	100	100	0	1 GVHD 1 Patient off IS
Jacobsen [8] (1994)	1		Same as HCT	18	100	100	0	Off IS at 1 year
Helg [9] (1994)	1		Same as HCT	na	100	100	0	Off IS
Sorof [10] (1995)	1		Same as HCT	na	100	100	0	Off IS at 1 year
Butcher [11] (1999)	6	34–49	3/6 Same 3/6 Different	15 (3–30)	83	83 2	0	1 Death due to metatstatic vaginal SCC
Hawami [12] (2003)	10	9–55	6/10 Same 4/10 Different	34 (2–105)	60	60	0	Interstitial pneumonitis Pneumococcal sepsis Aspergillus infection Myocardial infarction
Thomas [13] (2004)	3	8–14	All different	41 (7–72)	100	100	0	n.a.
Beitinjaneh [14] (2010)	7	11–65	All different	44 (6–108)	57	100	0	1 Cardiac death at 9 years 1 Death to tongue cancer
Koenecke [1] (2010)	13(15)	3–59	4/13 Same 9/13 Different	86 (0–280)	100	85	38 5	4 Rejections, 2 graft losses due to rejection, 2 severe UTIs reported
Bunin [37] (2010)	3	3–4.5	1/3 Same (32) 2/3 Different (26, 28)	30 (18–51)	100	100	0	
Fangmann [38] (2011)	1	18	Same	66	100	100	0	No IS
Younge [24] (2015)	1		Same	120	100	100	0	No IS
Schwarz [39] (2016)	1	22	Same	12	100	100	0	Steroid only
KFSH&RC, Riyadh	3	15 8 33*	Different (94 65 216)	13 15 16	100	100	33	Nil BK Virus nephropathy
Total	53	18.4 (3–65)	22 Same 30 Different	47.4 (0–280)	84.6	80.8	13.5	

*Including one SPK

IS immunosuppression

provoke misinformation, since an undetermined number of unsuccessful cases may not have been reported. Best published evidence for SOT following HCT so far came from the Chronic Leukaemia Working Party of the European Group of Blood and Marrow Transplantation (EBMT) carrying out a questionnaire-based survey within EBMT centres identifying 52 SOTs after allogeneic HCT [1].

This systematic review analyses all reported cases of SOT following HCT with respect to type of transplant (deceased versus living donor), associated complications and mortality. Additionally, our local experience of three lung, two kidney, one simultaneous pancreas and kidney (SPK) and one heart transplantation (HTX) is presented. The objective of this review is to determine whether

i. SOT recipients with prior HCT might require different immunosuppression,
ii. SOT recipients post-HCT are at higher risk for infections, rejections or GVHD and
iii. is SOT following HCT justifiable?

Material and methods

Own data, as well as published reports were systemically reviewed. A comprehensive MEDLINE search was carried out in order to identify published articles on SOT following HSCT. Search terms were 'bone marrow transplant,' 'hematopoietic stem cell transplant,' 'solid organ transplant,' 'renal transplant,' 'kidney transplant', 'liver transplant,' 'lung

Table 2 Performance and outcome for liver transplantation following HSCT

Author[ref] (year)	*n*	Age at LTX in years	Cause of liver failure (time post HSCT- TX type)	SOT mean follow-up in months	% Patient survival	% Graft survival	Rejection in %	Complications/cause of death
Rappaport [40] (1990)	1	34	VOD (34 days–OLT)	1	0	0	100	Death rejection
Nimer [41] (1990)	1	34	VOD (40 days–OLT)	16	100	100	0	Recurrent VOD
Rhodes [42] (1990)	1	19	GVHD (3 years–OLT)	24	100	100	0	Nil
Marks [43](1992)	1	21	GVHD (104 days–OLT)	6	100	100	0	Nil
Schlitt [44] (1995)	1	38	VOD (23 days–OLT)	39	100	100	0	Liver GVHD
Dowlati [45] (1995)	2	4 43	VOD (107 days–OLT) VOD (22 days–OLT 40 days–2ndOLT)	4 3 3	0	0	100 100 100	Death TTP Death ARDS TTP
Rosen [46] (1996)	2	32 35	GVHD (11 months–OLT) VOD (43 days–OLT)	29 9	100 100	100 100	0 0	Nil
Bunin [30] (1996)	1	<1	VOD (33 days –LR-LL)	9	100	100	0	Nil
Figuera [31] (1996)	1	31	GVHD (109 days–OLT)	6	0	0	0	Death aspergillosis, varicella
Hägglund [32] (1996)	3	32 31 32	VOD (39 days–OLT) VOD (25 days–OLT) VOD (33 days–OLT)	2 8 1	0 0 0	0 0 0	0 0 0	Liver failure Cerebral edema Pneumonia
Norris [47] (1997)	1	25	VOD (32 days–OLT)	6	0	0	0	Death PCP
Salat [48] (1997)	2	39 47	VOD (70 days–OLT) VOD (14 days–OLT)	4 3	0 0	0 0	0 0	Death due to aspergillosis Death renal failure, Pancytopenia, HCTre-Transplant, liver failure
Dey [26](1998)	1	na	Reactivated Hep B (90 days-OLT)	1	0	0	0	Septic shock
Urban [49] (2002)	1	5	GVHD (4 years–OLT)	74	100	100	0	Full withdrawal of IS at 71 months post SOT
Kim [50] (2002)	1	<1	VOD (42 days –LR-LLL)	17	100	100	100	
Andreoni [29] (2004)	1	42	HCVcir (27 years–LR-RL)	24	100	100	0	Full withdrawal of IS at 12 months post SOT
MacQuillan [51] (2004)	1	49	VOD (43 days–OLT)	1	0	0		Persistent MOF
Orlando [52](2005)	1	24	GVHD (39 months)					
IBTL (8 months)	128 120	100	0 100	100	ITBL recurrence in 1st liver graft			
Barshes [53] (2005)	1	15	GVHD (10 months–OLT)	36	100	100	0	Pancreatitis, patient well on FK monotherapy
Shimizu [34] (2006)	1	7	GVHD (3 years–LRLL)	8	100	100	0	Low dose ST and FK to prevent recurrent GVHD

Table 2 (continued)

Author[ref] (year)	*n*	Age at LTX in years	Cause of liver failure (time post HSCT- TX type)	SOT mean follow-up in months	% Patient survival	% Graft survival	Rejection in %	Complications/cause of death
Koenecke [54] (2006)	1	55	VOD (42 days–OLT)	0.3	0	0		MOF, thrombocytopenia
Membreno [55] (2008)	1	25	GVHD (60 days–OLT)	3	0	0	0	Sepsis
Beitinjaneh [14] (2010)	2	12 8	HBVfh (10 years–OLT) cGVHD (7 years–OLT)	18 1	100 0	100 0	0	Uneventful Systemic aspergillosis
Bunin [37] (2010)	3	1.5 4.6 0.5	VOD (1 month–LR-LL) Liver failure (7 m–DD) VOD (2 weeks–LD 4 weeks-DD)	15 0.5 1.5	100 100 0	100 100 0	0	Not on IS On Tac MMF Died due to HAT and SMA Thrombosis
Koenecke [1] (2010)	14(15)	na	9 Unrelated deceased 2 LR and 1 HCTdonor GVHD 6 VOD 4 Viral hepatitis 2 Underlying disease 2 Graft failure 34 months (1-37)	49 (1–169)	71	n.a.		
Mahansaria [56] (2015)	1	34	HPS (9 years–LR-LL)	22	100	100	0	
Total	47	24.4 (.5-55)	21.7 months (range 0.5-324) 0.5 20% living donors 80 % deceased donors	28.3	55.3	53.1 death censored 96%	16.7	

HBVfh hepatitis B virus fulminant hepatitis, *HCVc* hepatitis C virus cirrhosis, *MOF* multiorgan failure, *VOD* veno-occlusive disease, *LR-RL* living related right lobe, *cGVHD* chronic graft versus host disease, *LR-LL* living related left lobe, *LR-LLL* living related left lateral lobe

transplant', 'pancreatic transplant', 'heart transplant,' 'intestinal transplant', 'small bowel transplant' and 'cardiac transplant'. The references of all relevant papers were manually reviewed for studies not found via MEDLINE. A total of 253 reports were identified and reviewed for repeat publication, and in case excluded. Only SOT following HCT were considered for analysis, autologous HCT before and HCT after SOT were excluded. Seven HCT recipients receiving eight SOT at King Faisal Specialist Hospital and Research Center (KFSH&RC) were extensively reviewed and included in the systemic analysis.

Review for outcomes included SOT survival, death-censored graft survival and patient survival. Definitions for organ failure were death due to impaired organ function, organ replacement, re-transplantation in lung and liver transplant recipients. In renal transplant recipients, graft loss was determined by re-transplantation or return to dialysis. Need for insulin post pancreas transplant and heart failure and need for re-transplantation were considered graft failure in the setting of pancreas and heart SOT post HCT. The cumulative incidences of relapse and SOT graft failure were calculated using competing events statistics. Non-relapse mortality was considered as competing event for relapse incidence. All-cause mortality, except for failure of the transplanted organ was considered as competing event for organ-specific failure rates.

Results

Kidney transplantation (KTX) after HSCT

An estimated 18–66% of allogeneic HCT survivors develop chronic renal insufficiency [2–5]. Renal failure post HCT can be attributed to a number of aetiologies, including radiation, cytotoxic therapy, nephrotoxic agents, chronic GVHD or transplant associated thrombotic microangiopathy. Among patients who progress to end stage renal disease (ESRD) and are in need for haemodialysis, mortality approaches 90% and renal transplant may be the only therapy that may offer a chance for long-term survival [6]. Although experience in HCT survivors is limited to a total number of 53 kidney transplants (Table 1) published outcomes conclude that it is feasible in selected patients [7–14].

Main reason for ESRD in HCT recipients is drug nephrotoxicity secondary to immunosuppressive or antifungal drug exposure ($n = 7$). One KTX was performed due to long-term toxicity of immunosuppressive medication for a heart transplant following HCT. Other single causes for ESRD are Wiskott–Aldrich syndrome, diabetes mellitus type I and one kidney failure was considered secondary to conditioning radiation therapy. All patients undergoing KTX after HCT were dialysis dependent. One patient had kidney failure for unknown reason, two required second KTX for rejection. Twenty-two out of 53 kidney recipients received the kidney from their HCT donor. The absence of third party alloreactivity may potentially enable weaning off immunosuppression. This was achieved in a total of six cases (27%). One additional case was reported to be only on corticosteroid maintenance. On the other hand, subjecting a recipient with a second encounter of identical donor lymphocytes might potentially increase the risk of graft versus host disease (GVHD) which is reported in one out of 22 cases (5%), and passenger lymphocyte syndrome, which was not observed.

Outcome analysis of 53 kidney recipients following HCT reveals an actuarial patient survival of 85 percent, death censored graft survival of 81 percent at a mean follow-up of around four years. Recipient mean age of 18.4 years (range 3–64) at time of SOT is significantly lower compared to non-HCT kidney recipients. The twelve percent rejection incidence is lower compared to non-HCT renal recipients. Seven recipients died (15 %) because of infectious complications ($n = 3$; 6%), malignancies ($n = 2$; 4%) and myocardial infarction ($n = 1$; 2%), respectively. Metastatic squamous cell carcinoma of the tongue caused death at 2.2 years following kidney transplantation in one patient 7.4 years out of non-Hodgkin lymphoma at an age of 43 years. Two cardiac mortalities were reported nine years post kidney transplantation. Low rejection incidence and high rate of fatal infections and malignancies suggests that kidney transplant recipients following HCT are over immunosuppressed or reflect long term exposure to immunosuppressive agents.

Liver transplantation (LTX) after HSCT

Liver failure in HCT survivors is related to infectious hepatitis, veno-occlusive disease (VOD), GVHD, sepsis, drugs, or haemosiderosis. Similar to kidney transplantation, experience with liver transplantation for end-stage liver disease among HCT survivors is limited. 47 reported cases were identified (Table 2). However, liver transplantation is consistently reported feasible in selected end-stage liver disease HCT survivors. Early LTX, i.e., within four months after HSCT, was performed for acute liver failure due to VOD in 18 patients and acute GVHD in 5 patients. Later LTX was carried out for chronic liver-GVHD, cirrhosis secondary to viral hepatitis in two patients or liver failure for chronic mycobacterial disease, Lyell´s syndrome (toxic epidermal necrolysis), congenital interferon-c receptor deficiency and post LTX intrahepatic ischemic biliary tract lesions in one patient each. Stratifying recipients receiving LTX within the first 4 months following HCT mortality was 71 percent, whereas there was no mortality observed in

Table 3 Performance and outcome for lung transplantation following HSCT

Author[ref] (year)	*n*	Age at SOT in y	Cause of lung failure (in years post HCT- TX type)	Follow-up in *m*	Survival	% Graft survival	Rejection in %	Complications/cause of death
Calhoon [57] (1992)	1	25	rLD (6–DD)	9	Yes	100	0	
Gascoigne [58] (1994)	1	27	BO (2–DD)	9	No	0	100	Rejection
Boas [59] (1994)	1	14	cGVHD (9)	15	Yes	100	0	
Svendsen [60] (1999)	1	5	PF (6–Llo)	14	Yes	100	0	
Rabitsch [61] (2001)	1	37	BO (1.3–DD)	24	Yes	100	100	Mild rejection
Heath [62] (2001)	4	16 6 3 9	RP (14–DD) BO (10–DD) BO (3–DD) BO (6–DD)	36 62 62 24	No Yes Yes No	0 100 100 100	0 0 0 0	Infection
Chiang [63] (2003)	1	8	BO (5–DD)	12	Yes	100	0	
Pechet [64] (2003) range median %	6	5-17 12.4	1 cGVHD (1.2–Llo) 5 × DD	48	67		0.2 acute rejection per patient in 1st yr	1 in hospital death for a 17 yo female recipient with Llo death following haemorrhage after lung BX, 1 death > 4 years post LTX due to BO
Sano [21] (2005)	1	29	BO (5– Llo)	36	Yes	100	0	
Okumura [22] (2007)	1	17	BO (6–Llo)	24	Yes	100	0	
Shiraishi [65] (2007)	1	4.8	BO (3.5–Llo)	1.5	Yes	100	0	Allograft volume reduction post ventilation
Yamane [66] (2008)	7	29 45 24 6 23 13 27	cGVHD (4.5 bLlo cGVHD (3.3 bLlo cGVHD (1.3 bLio cGVHD (0.7 RsLlo cGVHD (5.5 bLlo cGVHD (3.7 RsLlo cGVHD (8.5 bLlo	100.7 69.2 55.5 2 10.5 20.3 10.4	Yes Yes Yes No No Yes Yes	100 100 100 0 0 100 100	1.1 rejection per patient per year	1 death due to aspergillus infection in the native lung on day 61 1 patient died due to CMV encephalitis at 10 Months
Matsuzaki [67] (2008)	1	5	BO (3–iLlo)	15	Yes	Yes		Complete IS tapering at 10 months
Oshima [68] (2009)	1	13	cGVHD (4.6–iLlo)	18	Yes	Yes		Minmimal IS for non-pulmonary cGVHD
Koenecke [1] (2010)	12		BO/cGVHD 12, rejection1	0-123 23	66.6	66.6	33.3	5 infections 1 death due to rejection

Table 3 (continued)

Author[ref] (year)	*n*	Age at SOT in y	Cause of lung failure (in years post HCT- TX type)	Follow-up in *m*	Survival	% Graft survival	Rejection in %	Complications/cause of death
range median			7-196 69 10DD, 1 iLlo, 1Llo					1 death > 10 years post iLlo 1 death MDS recurrence
Redel-Montreo [69](2010)	3	28 36 34	BO (20 years–DD) BO (9 years–DD) BO (11 years–DD)	96 48 9	Yes Yes Yes	Yes Yes Yes	Yes No yes	BO recurrence after 4 years No complication Steroid sensitive
Beitinjaneh [14] (2014)	3	16 20 27	BO (1year Llo) BO (10 years–DD) PF (7 years–DD)	1 1.5 60	No Yes Yes	No Yes Yes		PTLD (HSV, VV, EBV) Pneumonia Sepsis, MOF
Bunin [37] (2010)	2	5 13	BO (31 months–DD) BO (89 months–DD)	168 34	100 100	100 100		
Whitson [70] (2012)	4	40 20 30 59	PF (30 years–rlo) GVHD, PF(14 years–bllo) PF (10 years–bllo)	108 52 15 19	100	100		3 Out of 4 recipients developed diabetes High CMV rate
Kim [71] (2012)	1	23	BO (21 years–DD bl)	10	100	100	no	Stable chimerism, FK, MMF, Steroids
Holm [72] (2013)	13	37 37 21 24 34 17 15 52 46 34 18 22 55	BO 8 BO 13 BO 21 BO 32 BO 37 BO 41 BO 99 BO 107 BO 111 BO 120 BO 124 BO 174 BO 198	24 12 10 24 24 60 60 60 60 8 7 120 60	No No	BO Re LuTX BO BO	0 (24%) 1 0 0 1 4 0 0 0 0 0 q 0	
Yousef [73] (2013)	11	8.5 15 12 8 7 16 10 6 11 6 15	BO 18 BO 38 BO 109 GVHD 44 GVHD 61 GVHD 123 PF 24 BO 61 PF 115 PF 31 BO 89	84 72 120 48 156 60 180 72 60 216 72	4 (36%)		0 0 0 0 0 0 0 0 0 0 0	Higher infection rate and doubling of early mortality when compared to paediatric LuTX without HSCT
	9	37						

Table 3 (continued)

Author[ref] (year)	*n*	Age at SOT in y	Cause of lung failure (in years post HCT- TX type)	Follow-up in *m*	Survival	% Graft survival	Rejection in %	Complications/cause of death
Vogl [74] (2013)			BO in all after a median of 18.2 months (range 6–120)	26 months (range 1 month–16 years)	3 (43%) 1 Immediate death respiratory failure 1 Respiratory failure of unknown cause and (TTP)/haemolytic uremic syndrome (HUS) at 86 days 1 Death due to secondary malignancy (myxofibrosarcoma) at 24 months 1 Death due to chronic rejection and recurring infections at 63 months			2 Patients CMV infection 1 Patient Pneumocystis jirovecii pneumonia 1 Patient pulmonary fungal infections (Aspergillus, Candida) 1 Patient w acute heart failure ischemic heart disease 5 months after LuTX9
Soubani [15] (2014)	2	39 66	cGVHD (8 years–DD) cGVHD (6.5 years–DD)	104 30	No No	0	0	Myoepithelial jaw bone cancer Oesophageal cancer
Cheng [23] (2014)	9	25 17 40 24 44 41 37 34 32	600,1 13 PF 35 single IF 66 single BO 292 bl BO 174 bl IF 123 single PPH 113 single PF 326 bl PF 204 bl IF 25 bl	62 54 42 25 0.5 87 61 30 > 36	No No No No No No No No Yes	62 54 42 25 0.5 87 61 30 > 36		Chronic rejection/CMV pneumonitis Respiratory failure/progressive pneumonia Chronic graft rejection Brain damage due to cardiac/ respiratory arrest Immediate post-LT; Respiratory failure/viral pneumonia i Septic shock, pulmonary fungal infection Chronic graft rejection Na
KFSH and RC	3	22 32 56	BO 4 years GVHD 10 years BO 14 years	51 6 6	100 100 100	100 100 100	0 0 0	CMV reactivation Perioperative bleeding Perioperative acute kidney failure, fungal pneumonia
Total	101	24.8 (range 3-66)	8.4 years (range 8 months to 30 years)	50.5 (range 0.5-216)	65.2	64.2	19 (18.8%)	

rLD restrictive lung disease, *PF* pulmonary fibrosis, *IF* interstitial fibrosis, *Llo* living lobar, *DD* deceased donor, *bl* bilobar, *BO* bronchiolitis obliterans, *cGVHD* chronic graft versus host disease, *RP* radiation pneumonitis, *RsLob* right single living lobar, *BLlo* bilateral living lobar, *iLlo* HCT identical living lobar, *CTX* chemotherapy, *RTX* radiation therapy, *PPH* primary pulmonary hypertension

patients with a liver transplant 4 months or later following HSCT.

LTX recipient age of 24.4 years (range 0.5–55) is low compared to recipients with no prior HCT. Mortality for patients undergoing deceased donor LTX was 62%, whereas mortality for living donor LTX was 14% ($n = 1$) resulting in an overall mortality of 55% at 29 months follow-up. The single mortality related to living donor LTX was for an urgent re-transplant following deceased donor LTX.

Average time to death following LTX was 3.2 months (range 0.3–8). Infection was most frequent cause for death ($n = 9$, 43%), namely multi organ failure ($n = 4$, 20%), aspergillosis ($n = 2$, 10%), pneumonia ($n = 2$, 10%) and one ARDS. Other causes were thrombocytopenic purpura ($n = 2$, 10%), and single incidences of VOD recurrence, graft failure, kidney failure, hepatic and superior mesentery artery thrombosis, pancytopenia, cerebral oedema, rejection and GVHD.

Three out of 25 patients alive following LTX (11%), were weaned off immunosuppression at one and six years. Rejection rate for LTX recipients is 13%. Death censored graft survival is 96%, re-transplantation rate is 4% with a mortality of 50%.

Lung transplantation (LuTX) following HSCT

Main complication of HCT involving the lung is Bronchiolitis obliterans (BO) with an incidence of 1.7–32% [1, 14–19]. Other non-infectious complications include interstitial pneumonitis, pulmonary fibrosis and organising pneumonia. The pathogenesis of BO following allogeneic HCT remains poorly understood clinically diagnosed via pulmonary function and radiologic testing in absence of respiratory tract infection [16, 20]. Bone Marrow Transplant Registry data suggest peripheral blood stem cell source, long duration to transplant, female donor to male recipient, history of interstitial pneumonitis in addition to acute GVHD, and busulfan-based conditioning regimen as risk factors [1, 16]. There is no standard treatment for BO. In general, management consists of immunosuppression (high dose corticosteroids, calcineurin inhibitors). Response rates are limited to improvement of lung function tests in about 20% of patients [21, 22]. Results of salvage immunosuppressive therapies like calcineurin inhibitors, mycophenolate mofetil (MMF), or sirolimus are disappointing, and no randomised clinical trials have investigated their efficacy. Patients not responding to conventional treatment reveal 2-year and 5-year survival rates of 20 and 13%, respectively [15]. Recently, other approaches such as imatinib mesylate, antithymocyte globulins, anti-tumour necrosis factor-α and extracorporeal photopheresis (ECP) have been tried with variable successes [15–18]. ECP has shown to be beneficial in patients with lung involvement by chronic GVHD. Other immunosuppressive strategies, like administration of tumour necrosis factor (TNF)-alpha blockers, rituximab or imatinib, have been used in small patient numbers and to be considered experimental. In severe therapy-refractory BO, LuTX can be a therapeutic option. In general, the donor of LuTX is different from hematopoietic stem cell donor. Therefore, there is high risk of rejection and relapse of BO. Recently, there was one report of a living-donor lobar LuTX from the same donor of bone marrow [23].

It has been reported that allogeneic HCT increases risk of rejection after LuTX because of the amount of immunocompetent leucocytes present in the donor lung. However, most LuTX recipients might not experience graft rejection because long term pre-transplant immunosuppression potentially inducing a down-regulation of alloreactivity [5, 13, 24].

In 101 lung transplants (Table 3) following HCT average recipient age is 24.8 years (range 3-66). Mean time from HCT to lung transplantation was 8.4 years (range: 0.7–30 years). At follow-up of 50.5 months patient survival is 65.2 percent. One recipient required lung re-transplantation translating to a graft survival of 61.2 percent. Mortality is due to infectious complications in seven patients (7%-aspergillosis 2×, CMV encephalitis, PJP pneumonitis, 2 unspecified) and because of rejection in six cases (6%). Recurrence of BO and relapse of disease were fatal in two patients. Post-transplant lymphoproliferative disorders (PTLD), myxofibrosarcoma and cardiac arrest were singular causes for death. Rejections were observed in 19% percent. In one patient immunosuppression was completely tapered ten months post SOT, while in another patient it was reduced for ongoing GVHD.

Heart transplant (HTX) following HCT

Severe cardiac toxicity after HCT occurs in 5–10% of patients receiving cyclophosphamide, proteasome inhibitors, particularly bortezomib, or radiation containing conditioning regimens and is characterised by loss of electrocardiographic voltage, progressive cardiac failure, or pericarditis with or without tamponade occurring within several weeks of cyclophosphamide administration [25]. On post-mortem examination, patients with fatal cardiac toxicity have haemorrhagic myocardial necrosis [26]. Although fatal haemorrhagic myocardial necrosis has been well described in patients receiving >240 mg/kg or more cyclophosphamide, cardiac toxicity can occur after doses <200 mg/kg. Anthracyclines used for remission induction and consolidation therapy of acute leukaemias are known to cause dose-dependent cardiomyopathy [27] progressing to congestive heart failure.

The four HTX recipients post HCT (Table 4) all had pre-terminal heart failure, as a consequence of preceding

Table 4 Heart TX following HSCT

Author[ref] (year)	*n*	Age at SOT in y	Cause of heart failure (in months post HCT- TX type)	Follow-up in m	Survival	% Graft survival	Rejection in %	Complications/ cause of death
Dey [75] (1998)	2	na	HF DCM (12)	12 6	Yes Yes	100	0	
Koenecke [1] (2010)	1	15	HF (138)	12	Yes	100	0	Subsequent kidney transplant
KFSH and RC	1	17	HF DCM	105	no	0	100	Non-adherence, heavy smoking
Toatl	4			34	75%	75%	33%	

HF heart failure, *DCM* dilative cardiomyopathyl

treatments. One recipient developed ESRD due to immunosuppressive therapy and received subsequent kidney transplantation [28]. Follow-up did not exceed more than 12 months. The recipients were reported to have excellent performance status at 12 months post SOT of the heart.

Discussion

SOT following HCT is a rare event but its prevalence is increasing. While only 21 cases were reported by 1998 [26], today the number has increased by 10-fold. Considering that more than 100,000 allogeneic HCTs were performed within the last 30 years and currently 30,000 allogenic HCT ´s are being performed anually, isolated solid organ failure within this treatment regimen occurs in up to 8%.[29–32] The number of reported SOT appears relatively low in only 0.02 % of HCT recipients suggesting that SOT represents a highly selected treatment modality.

Results might be influenced as physicians are more likely to publish only favourable outcomes. Notably, SOT following HCT recipients show higher incidence of benign underlying diseases. 30% of SOT patients received allogeneic HCT for non-malignant disease compared to less than 5% of patients in the EBMT registry [1] selection bias. In patients with history of malignant disease live-long immunosuppression post SOT could increase the risk of relapse. Seven percent of patients with malignant diseases as indication for HCT showed relapse after SOT, this is a fear most likely being overestimated. However, majority of SOTs have been performed late after HCT, when hazard of relapse is low compared to relapse rates within the first two years following HSCT. Two patients had a relapse of the underlying malignant disease after SOT at 10 and 85 months after SOT with a fatal outcome for both.

Despite potential publication bias, actual transplant mortality rates are higher compared to non HCT SOT recipients. Average recipient age of 23.2 years is well below overall and median age of patients who usually receive SOT [29].

Reported survival rates at 5 years post-transplantation for the general population is 91%, 71% and 49% for KTX, LTX and LuTX recipients, respectively [30–32]. At median follow-up of 44 months overall survival after SOT after HCT was 66.2 %. Stratified for the different types of SOT overall survival is 85% for kidney, 55% for liver (2 year follow-up) and 65 for lung recipients (3 year follow-up), respectively (Table 5). Three out of four patients following HTX, as well as the SPK recipient were alive at 16 months. 2-year-incidence of graft failure in kidney, liver and lung recipients is 20%. Including re-transplantations the actual 2-year incidence of overall SOT failure in survivors is 26%. Fatal complications after SOT that led to patients' death were graft failure, lethal infections and malignancies.

A United Network for Organ Sharing (UNOS) database review of all LTX between 1998 and 2012 identified early liver failure to be more frequent than late liver failure in recipients of allogeneic HCT [33]. Outcome of LTX <4 months post HCT is associated with high mortality. Whether this is due to the fact that most of transplants were performed with a less than ideal graft or that the recipients had active GVHD at time of LTX remains unclear. Whether or not inevitable mortality of acute severe VOD justifies a 60% mortality of deceased donor LTX is ethically questionable. In an UNOS LTX analysis for GVHD 48 out of 112 were performed following HCT. Median survival for HCT-GVHD patients was 8.5 years. 1, 3 and 5 year survival of the HCT-GVHD patients were 0.69, 0.64 and 0.59, respectively [33]. Outcome of living related LTX in the acute setting is more successful and therefore early LTX following HCT should be reserved for centres performing living related LTX only.

HLA compatibility could play a pivotal role in obtaining better results in living related donor compared to deceased donor graft origin in LTX following HCT, as a higher estimated degree of HLA matching within the setting of living related LTX is likely.

Twenty-two kidney, three liver and one lung transplant recipient received grafts from related donors. In 28 patients

Table 5 Overall outcome for SOT per Organ for SOT following HSCT

Organ	*N*	Age at SOT	FU in m	Pat survival %	Graft survival %	Rejection rate %	Infection rate %	Malignancy rate % (letal)	Freedom of IS n = (%)
Lung	101	25	51	65.2	64	19	27	3	n.a.
Kidney	53	18	47	85	81	14	13	3	6 (11)
Liver	47	25	28	55	53	17	15	0	3 (6)
Heart	4	16	34	75	75	25	0	0	n.a
Pancreas	1	34	24	100	100	0	100	0	n.a.
Total	206	23.1	45	63.1	63.3	17.3	20.5	2.9	9 (4)

receiving SOT, the organ donor was the same as the HCT donor. This was probably done cherishing hope that the recipient tolerates the SOT without additional immunosuppressive therapy [34]. Notably, six of 22 kidney recipients and three out of six liver recipients were weaned off immunosuppression after SOT completely. One KTX and one LuTX recipient were only on single-drug immunosuppressive therapy. Although of particular interest the reviewed reports did not mention incidence, degree and duration of macrochimerism most likely being causative effect for this phenomenon [35, 36].

Of concern is the high incidence of malignancy following SOT post HCT. Four percent of all analysed recipients developed lethal malignancies; PTLD in 2 and tongue cancer, oesophageal SCC, vaginal SCC, and myoepithelial jaw bone cancer in one patient each. The relatively short follow up period between SOT and onset of these malignancies, suggests that recipients were likely to be over-immunosuppressed. Many previously published articles suggested that SOT can be done safely in a selected group of patients. The selection criteria are neither mentioned nor reported within the current literature. The outcome data were assumed to be in keeping of the outcomes of non-HCT SOT recipients. Considering the young recipient average age of 23.2 years and the short overall follow-up of 44 months morbidity and mortality has to be considered higher than in SOT recipients without previous HCT.

The authors recommend for SOT recipients after HCT:

- underlying haematological disorder should effectively be treated by HCT providing reasonable prognosis. If feasible, SOT should be carried out not before 2 years after HCT.
- SOT within the first 2 years of HCT should be performed in the setting of living donation.
- In case of living donor SOT utilisation of the previous HCT donor is desireable.
- In case of successful SOT after HCT, minimising immunosuppression maintenance should be attempted if possible.

Impact of induction therapy at time of SOT could not be answered by this review. Therefore, no clear recommendations can be made. Treating physicians are encouraged to follow their standard protocols. Given the relatively high rate of infectious complications depleting antibody induction should be avoided or minimised and steroid withdrawal once feasible is recommended.

Conclusion

SOT after allogeneic HCT for terminal organ failure remains a very rare event. It may offer a valuable treatment strategy in selected HCT recipients, although associated with higher morbidity and mortality.

Of particular concern is the outcome of deceased donor LTX performed within four months following HCT. Therefore, in such settings living donor LTX is recommended providing better outcome and deceased donor graft utility. Rejection rates for all types of SOT seem to be comparable. Higher incidences of infections and malignancies in SOT after HCT makes over-immunosuppression the most likely explanation. Evaluation of recipient immunologic status might help directing post-transplant immunosuppression. Selection criteria remain individual.

Compliance with ethical standards

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

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