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Contents

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Contents

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REVIEW

Solid pancreas transplant: Pushing forward

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Abstract

Pancreas transplant has evolved significantly in recent years. It has now become a viable treatment option on type 1 diabetic patients with poorly controlled diabetes on conventional treatment, insulin intolerance, hypoglycaemia unawareness, brittle diabetes and/ or end-stage kidney disease. The purpose of this review is to provide an overview of pancreas transplant historical origins and current barriers to broader utilization of pancreata for transplant, with a focus on areas for future improvement to better pancreas transplant care. Donor pancreata remain underutilized; pancreatic allograft discard rates remain close to 30% in the United States. Donations after cardiac death (DCD) pancreata are seldom procured. Study groups from Europe and the United Kingdom showed that procurement professionalization and standardization of technique, as well as development of independent regional procurement teams might increase organ procurement efficiency, decrease discards and increase pancreatic allograft utilization. Pancreas transplant programs should consider exploring pancreas procurement opportunities on DCD and obese donors. Selected type 2 diabetics should be considered for pancreas transplant. Longer follow-up studies need to be performed in order to ascertain the long-term cardiovascular and quality of life benefits following pancreas transplant; the outcomes of which might eventually spearhead advocacy towards broader application of pancreas transplant among diabetics.

Key words: Pancreas transplant; Whole pancreas transplant; Donations after cardiac death pancreas transplant; Obese pancreas donors; Pancreas transplant for type 2 diabetes

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Core tip: Pancreas transplant has become a viable treatment option on type 1 diabetics. The purpose of this review is to describe current barriers to broader pancreatic allograft utilization, and focus on areas for future improvement. Donor pancreata, especially Donations after cardiac death (DCD), remain underutilized. Procurement professionalization might decrease discards and increase pancreatic allograft utilization.

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Pancreas procurements should be extended to DCDs and suitable obese donors. C-peptide positive non-obese brittle diabetics may be suitable transplant candidates. Longer studies on pancreas transplant cardiovascular benefits are needed; this might eventually drive pancreas transplant advocacy among diabetics.

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BACKGROUND

In 1894, Williams[1] reported the implantation of minced sheep's pancreas to a 15-year-old diabetic boy for the treatment of his ketoacidosis. In 1922, Banting *et al*[2] reported the use of pancreatic extract to treat diabetes mellitus (DM) in human, seemingly heralding the end of this scourge for all time. The discovery of insulin detracted from pancreatic transplant until 1966, at which time Kelly and Lillehei performed the first simultaneous human kidney-pancreas allotransplant from a deceased donor into a 28-year-old woman at the University of Minnesota, 3 years after the first reported kidney allotransplant[3]. The first living donor pancreas transplant was performed at the University of Minnesota, in 1979[4].

Other early efforts included islet cell transplant. Ballinger and Lacy demonstrated islet of Langerhans' isolation and subsequent *in vivo* post-transplant function in rats in 1972[5]. Najarian and Sutherland performed the first clinical islet transplant in 1974[6]. Further subsequent efforts culminated in the introduction of the Edmonton Protocol for islet cell transplant by Shapiro *et al*[7] in 2000.

According to the United Network for Organ Sharing (UNOS) and the International Pancreas Transplant Registry (IPTR), as of end of 2014, over 48000 pancreas transplants were reported internationally, with approximately 29000 transplants performed in the United States alone[8]. Nonetheless, pancreas transplant rates have declined in the United States by 33% from 2004 (approximately 1500) to 2014 (approximately 1000)[9]. Similar trends were identified in the Organ Donation and Transplant (ODT) report in the United Kingdom[10]: during 2015-2016, the total number of pancreas and kidney/pancreas transplants decreased by 37.9% and 3.5% respectively.

Paradoxically, this pancreas transplant decline has occurred despite of reported improvements in graft and patient survival outcomes. According to the Organ Procurement and Transplant Network (OPTN)/ Scientific Registry of Transplant Recipients (SRTR) 2014 Annual Data Report, graft and patient survival improved[8]. These positive outcomes were attributed to improvements in recipient and organ selection, introduction of T-cell depleting agents for immunosuppression induction, and combined use of tacrolimus and mycophenolate mofetil for maintenance immunosuppression[11].

In an era of an increasingly aggressive approach in other solid organ transplant categories, the transplant community seems to have remained conservative with pancreas allograft utilisation, at least within the United States territory[9]. This is presumed to be multifactorial[12].

Aim of this review is to outline the current pancreas transplant status, address barriers in pancreas donation and transplant, and describe ways to optimise pancreatic allograft utilisation and transplant of previously considered as unconventional pancreas transplant candidates.

Indications and types of pancreas transplant

Pancreas transplant has become an accepted treatment modality for both uremic and non-uremic patients with type 1 diabetes mellitus (T1DM). Pancreas transplant restores glucose homeostasis, relieving the patient from the need of ongoing glucose monitoring, insulin injections and the risk of life-threatening diabetic hypoglycemia or ketoacidosis. Nonetheless, considering the transplant-related morbidity and mortality plus the lifetime need for immunosuppression, not all T1DM patients should be considered for pancreas transplant.

Pancreas transplant has also become a viable option on T1DM patients with poorly controlled diabetes despite conventional treatment, insulin intolerance,

hypoglycaemia unawareness, brittle diabetes or end-stage kidney disease. There are currently 7 types of pancreas transplant: (1) simultaneous pancreas and kidney transplant (SPK). As per UNOS guidelines, SPK is indicated for T1DM patients or those with detectable C-peptide levels [as a surrogate indicator of type 2 diabetes mellitus (T2DM)], who are insulin dependent, have a body mass index (BMI) < 30 kg/m^2, and end stage renal disease, who are currently on dialysis or expected to require dialysis within 6 mo[13]; (2) pancreas transplant alone (PTA), indicated primarily for T1DM with hypoglycaemia unawareness, non-compliance with insulin treatment and/or impaired quality of life and adequate glomerular filtration rate to render the need of kidney transplant unlikely[14,15]; (3) pancreas-after-kidney transplant (PAK), indicated for patients who would qualify for a PTA and already have a viable renal allograft[16,17]; (4) simultaneous deceased donor pancreas and live donor kidney transplant, indicated for patients who would qualify for SPK. This approach is expected to result in reduced waiting times, lower delayed graft function (DGF) rates and better outcomes[18]; (5) total pancreatectomy and islet cell autotransplant (TPIAT). According to the PancreasFest consensus, TPIAT is indicated in selected patients with intractable pain related to chronic pancreatitis despite other appropriate treatment modalities, and no psychosocial or medical contraindications[19]. In the United States, TPIAT is subject only to regulation of human cells and tissues (the tissue rules). The centers performing it should be registered with the Federal Drug Administration (FDA) and follow the Current Good Tissue Practices, without being required to submit FDA drug application[20]; (6) laparoscopic donor distal pancreatectomy for living donor solid pancreas or isl*et al*lotransplant and pancreas-kidney transplant[21,22]; and (7) isl*et al*lotransplant. The implantation of deceased donor islets of Langerhans is a promising treatment for T1DM with labile diabetes, recurrent hypoglycaemia and hypoglycaemia unawareness[19]. In the United States, islet cell allotransplant is currently investigational and subject to both the FDA published guidelines on the tissue rules and the biologic and drug provisions.

SPK is by far the commonest pancreas transplant type. According to the SRTR data (United States), in 2014, 77% of pancreas transplants were SPKs, while PAK and PTA accounted for 13.6% and 9% of the transplants performed, respectively[8].

Outcomes

According to IPTR, in 2007, PTA, SPK and PAK 1-year unadjusted patient survival was 95%-97%; the 5-year survival was 91%, 87% and 83%, respectively. PTA recipients were by definition non-uremic. These findings raised the question whether T1DM patients benefit from a pancreas transplant over a kidney transplant alone. Gruessner *et al*[23] assessed mortality of pancreas transplant recipients over those on the waiting list (WL). Transplant recipients had elevated hazard ratios in the immediate post-transplant period up to 3 mo post-transplant[23]. However, 4 years' follow-up showed SPK patient survival benefit compared to WL (90% *vs* 59%). PAK and PTA survival benefits were indeterminate in 4 years, possibly because WL mortality in these cohorts was lower due to their non-uremic status and younger age (PTA)[23].

On their mortality assessment, Gruessner *et al*[23] reported that, kidney allograft failure after SPK/PAK increases patient death risk by eleven-fold. The pertinent question remains whether these patients benefit from a functioning pancreas allograft. Most studies provided conflicting reports, partly due to insufficient follow-up and dependence on registry data[24-30]. Morath *et al*[31,32] (Heidelberg University, Germany) performed a very long term follow-up analysis based on the International Collaborative Transplant Study and observed that SPK graft and patient survival allograft outcomes were equivalent to living donor kidney transplant (LDKT) outcomes at 10 years; and, most importantly, that very long term survival (18-20 years) was superior among the SPK over the kidney transplant alone (on both LDKT and deceased donor kidney transplant recipients). The authors also noted decreased long-term cardiovascular events among the SPK patients[31,32]. These findings should trigger extension of follow-up analysis across more pancreas transplant centers.

It remains unclear if re-establishment of long-standing euglycemia can halt or reverse end-organ diabetic complications. Fioretto *et al*[33] estimated that a period of 10 years of euglycemia is a necessary interval to reverse diabetic nephropathy features.

DONOR PANCREATA

Current status

Across the United States, transplant surgeons often appear reluctant to consider pancreas allografts from donors considered as marginal for pancreas donation. As marginal are characterized older (> 50 years of age), obese, and donation after cardiac

death (DCD) donors. According to OPTN/UNOS, between 2003 to 2014, there has been a decrease in donors aged over 50, with 83% of donors aged less than 35 years[8]; among the organs recovered, there were more recorded pancreatic discards from donors 50 years or older[8]. During the same period, obese pancreas donors decreased from 56.3% to 34.6%[8]. These findings may indicate diminished intent to use pancreata from marginal donors[8].

Expanding the pancreas donor pool

According to the OPTN/ SRTR 2016 Annual Data Report, since implementation of the new pancreas allocation system in October 2014, there has been an increase in the number of pancreas transplants for the first time over a decade[34]. At the same period, total active listings have also decreased, reaching a historic low[34]. Despite the above, the average WL times have remained largely unchanged, with 34.2% of patients waiting between 1 and 3 years[34]. Even though WL mortality has improved marginally over the recent years, there is still remarkable geographical variation across the United States, ranging from 0 to 15%[34]. At the same time, pancreas transplant programs have become more liberal with their candidates' selection, as indicated by an increased proportion of T2DM patients (9.9% in 2016), of recipients aged over 50 years, and of candidates with higher BMI[34]. Unless the pancreas donor pool is expanded, this more aggressive approach is expected to attract increasing numbers of transplant candidates and stretch the WL times further. In order to restrain WL times, decrease WL mortality and eliminate regional disparities in pancreas transplant access, it is necessary to expand the pancreas donor pool and increase pancreas transplant rates.

Utilization of pancreatic allografts from obese donors: Steatosis is a primary concern in evaluating pancreas allograft quality[35]. The effect of steatosis on the pancreas allograft is presumably twofold: first, macrovesicular pancreatic steatosis may result in microvascular occlusion and thrombosis; second, adiponecrosis can potentially trigger inflammation and post-reperfusion graft pancreatitis[35,36]. Donor obesity, the latter defined as donors with BMI of 30 kg/m^2 or greater, is a surrogate indicator of pancreatic steatosis; as such, obesity has been associated with poor pancreas transplant outcomes. For this reason, transplant centers commonly decline pancreatic allografts from obese donors. An OPTN database analysis of 9916 SPKs performed during period 2000-2013 compared the effect of donor BMI on graft outcome. The donors were categorized into 4 BMI groups: 20-25, 25-30, 30-35, and > 35 kg/m^2. BMI 20-25 kg/m^2 donor outcomes were compared to the rest of the groups. Only BMI > 35 kg/m^2 was associated with inferior kidney and pancreas allograft survival. BMI 30-35 kg/m^2 did not affect 3 mo, 1-, 5-, and 10-year kidney and pancreas graft survival. The authors concluded that pancreata from donors with BMI 30-35 kg/m^2 might be used safely for transplant[37]. Certainly, this retrospective analysis is skewed due to potential discards upon visual of organs with significant interacinar fat infiltration or evidence of acute or chronic inflammation.

DCD pancreas utilization: DCD allografts have been used successfully in liver and kidney transplant. The concept of DCD pancreas transplant is not new; it has become an increasingly common practice in several European countries and the United Kingdom[38,39]. In the latter, DCD pancreas transplant accounts for up to 19.5% of transplanted pancreatic allografts[38]. However, in the United States, DCD pancreatic donation has remained out of favor, accounting for as low as 1.5 % of transplanted pancreata over period 1996 to 2014[40].

Various studies have compared DCD *vs* DBD pancreas transplant outcomes (Table 1). The University of Wisconsin has been pioneering DCD pancreas utilization in the United States, reporting no difference in graft survival, function, complication or rejection rates between DBD and DCD pancreata; even though it did report longer renal DGF in the DCD cohort[41-43]. Similarly, an OPTN/UNOS registry analysis by Salvalaggio *et al*[44] reported comparable outcomes, even though DCD SPK recipients had longer hospital stay and, not unexpectedly, more protracted renal allograft DGF. The Oxford group performed a United Kingdom registry analysis which reported equivalent patient and graft survivals among 134 and 875 pancreas transplants performed between 2006 and 2010[45]. A systematic review and meta-analysis published by Shahrestani *et al*[46] in 2017 reported no difference in 10-year survival among the DCD and DBD cohorts. Kopp *et al*[39] (Leiden University Medical Center, Netherlands) recently published a single-center cohort study, which indicated comparable outcomes among DCD and DBD pancreas transplants. The DCD donors were younger. The authors concluded that donor age was the most significant allograft survival prognosticator; therefore, younger DCD grafts might be a better option than DBD grafts from older donors[39].

Table 1 Studies comparing pancreas transplant outcomes between donations after cardiac death *vs* donation after brain death pancreas allograft recipients

First author/ yr	Country	Type of study	No. transplants	Mean donor age (yr)	Donor BMI [Median, IQR]	Warm ischemia time (min)	Cold ischemia time (hours)	Follow-up (yr)	Comments/conclusions
D'Alessandro *et al*[41], 2004	United States	Cohort	31 DCD; 455 DBD	Unclear	ns	15.3 (SD ns)	15.9 (SD ns)	5	No difference in 5-yr graft survival in SPKs
Fernandez *et al*[43], 2005	United States	Cohort	37 DCD; 539 DBD	31	ns	17.5 (SD = 9.9)	15.8 (SD = 3.4)	5	Indistinguishable patient and graft 5-yr survival in SPKs. Elevated DGF rate on DCD kidneys, with no significant long-term impact.
Salvalaggio *et al*[44], 2006	United States	Cohort; OPTN/UNOS Registry	57 DCD; 3948 DBD	DCD= 30.1; DBD = 29	ns	ns	15.7	5	For SPK recipients, the wait for DCD organs was shorter. DCD SPK recipients had longer hospital stay. Renal DGF was higher with DCD organs. Higher thrombosis rates (12.8% *vs* 6.1%)
Bellingham *et al*[42], 2011	United States	Cohort	72 DCD; 903 DBD	DCD= 30	ns	20.8 (SD = 9.4)	ns	10	No difference in surgical complications, rejection or hemoglobin A1c levels.
Muthusamy *et al*[45], 2012	United Kingdom	Cohort	134 DCD; 875 DBD	DBD = 32; DCD= 28	23	12	12.5	1	Similar patient and graft survival, with improved DCD pancreas graft survival if performed as an SPK. Early graft loss in the DCD cohort was mainly due to thrombosis (8% *vs* 4%)

Shahrestani *et al*[46], 2017	Australia	Systematic review and meta-analysis	762 DCD; 23609 DBD (included 10 cohort studies and 8 case reports)	DBD = 37 ns	21-25 ns	ns	ns	0.3-15	No significant difference in 10-yr graft or patient survival. Higher graft thrombosis risk with DCDs [95%CI: 1.04-2.67; P = 0.006]. Thrombosis risk not higher when DCD donors were given ante-mortem heparin (P = 0.62)
Kopp *et al*[39], 2018	The Netherlands	Cohort	21 DCD; 83 DBD	[a]	[a]	31 (median)	11 (median)	5	Without the DCD factor, PDRI from DCD donors was lower. Donor age was the only donor-related risk factor associated with graft survival. Post-op bleeding and renal DGF were more common with DCDs. Graft survivals were comparable. DCD pancreata had lower thrombosis incidence. DCD donors yield similar outcomes for low PDRI. Most DCD donors were younger. DCD grafts may be a better option rather than older DBD donors.

[a]Range not significantly different between DCD *vs* DBD donors. BMI: Body mass index; SD: Standard deviation; ns: Not stated in the study; DCD: Donation after cardiac death; DBD: Donation after brain death; SPK: Simultaneous kidney-pancreas transplant; DGF: Delayed graft function; PDRI: Pancreas donor risk index.

Graft thrombosis has been the DCD pancreas transplant Achilles heel. DCD pancreatic allografts appear to be more vulnerable to ischemia-reperfusion injury due to sustained peri-procurement ischemic insult, which may predispose them to higher risk of graft thrombotic events, even though its impact on overall graft survival has not been demonstrated yet[39]. OPTN/UNOS registry analysis published in 2006 did demonstrate higher thrombosis risk in the DCD cohort (12.8 *vs* 6.1%)[43]. Shahrestani *et al*[46] meta-analysis has estimated that the odds of graft thrombosis were 1.67 times higher in DCD organs; however, that thrombosis risk was not significant if the donors had been given ante-mortem heparin[45]. Interestingly, Kopp *et al*[39] reported lower DCD graft thrombotic risk.

Professionalization and standardization of the pancreas procurement process:

According to SRTR, 27.7% of pancreata were discarded after recovery[47], often due to pancreatic trauma occurring at the time of procurement. Ausania *et al*[48] performed a retrospective ODT Registry analysis, and demonstrated that pancreatic allografts are indeed more vulnerable to procurement damage. More than 50% of recovered allografts had at least one reported injury, most commonly a short portal vein[48]. Arterial and parenchymal damage were associated with higher graft loss risk[48]. DCD status was not related to graft damage; increased BMI, aberrant hepatic artery anatomy, concurrent liver donation, and non-pancreas transplant procurement team increased the risk of pancreatic injury[48]. The Dutch Transplant Foundation (DTF) developed a digital scoring system for abdominal organs donated and accepted in the Netherlands. According to DTF, pancreatic injury was reported in 25% of the recovered organs, of which only 2% led to organ discard[49]. The authors identified higher donor BMI and DCD status as risk factors associated with organ discard due to procurement-related injury (Table 2)[49].

The same research group (Leiden University Medical Center, Netherlands) also reported that organ recovery from surgeons accredited on standardized abdominal organ procurement methods, who also performed pancreas transplants in high-volume centers, was associated with more frequent recovery of the pancreas from DCD donors, less discards due to organ damage, and higher overall pancreatic allograft utilization[50]. They developed a course named "Multi Organ Donor Procurement Surgery", which has since been assimilated by the European Society for Organ Transplant[50]. Aim of this course is to standardize abdominal organ procurement surgery training, including a step-by-step e-learning module and hands-on training, with documented completion of a set number of procurements under supervision and examination before certification[50]. A same approach has been recently introduced and endorsed by the ODT in the United Kingdom.

The Netherlands is divided in 5 fully independent regional organ procurement teams, which procure all abdominal organs at their respective regions. Each of these teams consists of at least one certified surgeon, an assistant, two procurement scrub nurses and anesthesia team, and carries all necessary instruments to the donor hospital[49]. Similarly, procurements in the UK are performed by regional independent organ procurement teams, each manned by at least one certified procurement surgeon, procurement scrub nurses/perfusionists, carrying their own surgical equipment to the site of donation. This procurement model results in standardization of the procurement technique and eliminates the donor hospital-related hazards (such as lack of appropriate equipment or non-acquaintance of the local scrub team to the demands of a multi-organ, especially a DCD, procurement). It further mitigates the inter-surgeon variation on the procurement technique and therefore procurement quality, degree of organ damage, and derivation of organ description to the receiving transplant surgeons. It also results in better team coordination and time management and, therefore, more efficient execution of the procurement surgery, both of which are critical factors for a successful rapid DCD organ procurement[49,51]. Finally, this procurement model may lead to more experienced surgeons, and therefore, higher procurement quality and potentially less discards[49-51].

The outcomes of the Dutch (DTF) and United Kingdom (ODT) procurement models indicate that pancreatic allograft utilization may be optimized and pancreatic discards minimized with standardization of the procurement technique and development of independent organ procurement teams, which should be organ procurement organization rather than transplant center-based. In the United States, standardization of the procurement technique and formal credentialing of procurement surgeons may be achieved *via* institutional initiatives and through the American Society of Transplant Surgeons; based on the European and United Kingdom experience, this may result in higher procurement quality, less discard rates, and increased procurement and utilization of DCD pancreatic allografts for the purpose of whole organ or islet transplant (Table 2)[49-51].

Pancreas transplant centralization: A study published in 2017 by Kopp *et al*[52] on the outcomes of 1276 pancreas transplants in the Eurotransplant region, demonstrated that patient and graft survival after pancreas transplant are superior in higher volume centers; the outcomes remain superior even after using organs with the higher Pancreas Donor Risk Index (PDRI). An OPTN/ UNOS study published in the same year, indicated better pancreas survival rates at high-volume centers across all PDRI categories (Table 2)[53]. PDRI is a predictive model described by Axelrod *et al*[54] in 2010, that may be used at the time of organ offering, in order to better assess which allografts would be associated with good survival. Identified risk factors were increased donor age, DCD and black race[54]. In the United Kingdom, PDRI has been validated as a tool to predict survival in SPK transplant, but not in PTA or PAK transplant[55].

Table 2 Studies on the effect of pancreas procurement professionalization and center volume on pancreas transplant outcomes

First author, yr	Study aim	Region, country	Study period	No. cases	Results/comments
Boer *et al*[49], 2017	Analysis of abdominal organ procurement quality and clinical impact.	Eurotransplant, The Netherlands	2012-2013	591 procurements	13% surgical injuries on procured pancreata, leading to 3% pancreas discards. Higher BMI, DCD donation in liver procurement were risk factors for discard due to injury. High procurement volume centers were associated with less pancreatic injury.
Lam *et al*[50], 2017	Analysis on the effect of the abdominal recovery team professionalization on the pancreatic procurement injury and acceptance for transplant.	Eurotransplant, The Netherlands	2002-2015	264 procurements	31.8% pancreatic surgical injuries. 85.6% of procured pancreata were eventually transplanted. Surgeons certified in abdominal organ procurements recovered more grafts from older donors, DCDs, and had less surgical injuries. Predictors to proceed with pancreas transplant were: certified procurement surgeons; surgeons from a pancreas transplant center; DBD donation; and lower donor BMI. Procurement certification results in less surgical damage and more pancreata transplanted.
Kopp *et al*[52], 2017	Analysis of the effect of the transplant center volume on pancreas transplant outcomes.	Eurotransplant, The Netherlands	2008-2013	1276 pancreas transplants	Centers were classified into: low (< 5 transplants/yr); medium (5-13/yr); high volume (≥ 13/yr). Patient and graft survival were superior in higher volume centers. High center volumes were protective for graft failure, even though they transplanted organs with higher PDRI.
Alhamad *et al*[53], 2017	Analysis of the effect of the transplant center volume on the pancreas allograft failure risk.	UNOS, United States	2000-2013	11568 SPKs and 4308 solitary pancreas transplants	Centers were categorized into low, medium, and high tertiles. Low volume centers were associated with higher pancreatic failure risk. High volume centers had better graft survival rates irrespective of PDRI.

BMI: Body mass index; DCD: Donation after cardiac death; DBD: Donation after brain death; PDRI: Pancreas donor risk index; SPKs: Simultaneous kidney-pancreas transplants.

Living donor segmental pancreas transplant: SPK candidates are often advised to pursue LDKT, followed by PAK[56]. Inevitably, this exposes the recipient to two operations. The SPK option from a living kidney-pancreas donor has also been advocated[56-59]. This offers a pre-emptive kidney transplant, thus abolishing dialysis-related morbidity and mortality; allows the recipient to forego a second transplant operation (PAK); decreases the historically high early rejection risk-since the recipient

will be exposed to a single donor rather than two.

Living donor pancreatectomy was the first extrarenal organ to be successfully transplanted[59]. The first living donor pancreas transplant was performed at the University of Minnesota, in 1979[4]. According to Kirchner *et al*[59] between 1994-2013, 46 living donor segmental pancreas transplants have been performed, with 0% mortality. 15% of donors developed post-donation DM requiring oral hypoglycemics, and 11% developed insulin-dependent DM. A risk stratification model for post-donation DM using 3 pre-donation risk factors (oral glucose tolerance, basal insulin and fasting glucose) and 1 post-donation risk factor (ΔBMI > 15) predicted 100% of donors who developed post-donation DM[59]. In conclusion, living donor segmental pancreas transplant is a viable option, after appropriate donor selection.

PANCREAS TRANSPLANT CANDIDATES

Conventionally, pancreas transplant is intended to restore function of the endocrine portion of the pancreas, in effect restoring normoglycemia in diabetic patients devoid of insulin producing capacity, *i.e.*, T1DM patients, especially those with labile or brittle diabetes, poor response or low compliance to insulin therapy, hypoglycemia unawareness, and/or renal failure. According to the SRTR, in 2014, 9.2% of these transplants were performed on T2DM patients, increased from 7% in 2010[60]. In 2016, T2DM pancreas recipients increased further to 9.9%[34].

On this latter part of this review we will endeavor to explore the potential of pancreas transplant application to previously considered "unconventional" pancreas transplant candidates, such as T2DM ("C-peptide positive") patients, overweight and mildly obese T1DM patients, and patients with chronic pancreatitis.

The C-peptide positive recipient

Pancreas transplant on T2DM contradicts traditional wisdom. T2DM has been attributed to insulin resistance rather than low or nil insulin production; in the presence of insulin resistance, pancreas transplant will arguably confer little or no benefit upon the recipient. There is also the potential to harm: pancreas transplant carries a high complication risk in a population with a multitude of inherent comorbidities; and, it places the transplant recipient under obligatory lifetime immunosuppression. Lastly, pancreas transplant on a T2DM may result in the waste of a precious commodity and the opportunity cost of its use on a T1DM patient.

Multiple studies have attempted to explore the effect of C-peptide presence on SPK outcomes (Table 3)[61,62,64-66]. Stratta *et al*[62], performed a single center retrospective analysis of 162 SPK patients, including 30 (18.5%) of C-peptide positive (C-peptide levels ≥ 2.0 ng/mL) *vs* 132 C-peptide negative patients. In a mean follow-up period of 6.5 years, there were no differences between the two groups in terms of patient, pancreas and kidney graft survival, acute rejection, HbA1c, serum creatinine levels or estimated glomerular filtration rate. However, C-peptide positive patients had higher post-transplant C-peptide levels and T2DM phenotype (overweight or obese, hyperlipidemia, family history of diabetes, progressive insulin resistance)[63]. The authors concluded that positive C-peptide "should not be used exclusively to determine candidacy for SPK transplant"[62].

Light *et al*[64] performed a retrospective analysis of 173 SPK recipients, of whom 66.5% had negligible C-peptide ("C-peptide negative", < 0.8 ng/mL). The elevated C-peptide group ("C-peptide positive", ≥ 0.8 ng/mL) tended to have T2DM phenotype and C-peptide levels > 5 ng/mL. In long-term follow-up (up to 20 years), "C-peptide negative" patients had significantly improved survival (P = 0.019); "C-peptide positive" recipients showed a trend to better survival (P = 0.069). Similar to Stratta *et al*[62], this study indicates that "C-peptide positive" (T2DM phenotype) patients can have favorable outcomes post SPK transplant[64]. A more recent by Shin *et al*[65] compared 5-year outcomes among 151 T1DM and 42 T2DM pancreas transplant recipients. There was no difference in hemoglobin A1c levels, fasting insulin levels, homeostasis model assessment of insulin resistance or the insulinogenic index between the groups. Notably, insulin resistance decreased between both groups, even though T2DM recipients kept significantly higher C-peptide levels[65].

The overweight and obese T1DM recipient

C-peptide positive or not, overweight (BMI 25-30 kg/m^2) and obese (BMI > 30 kg/m^2) pancreas transplant candidates are becoming increasingly common[34]; possibly reflecting the global obesity epidemic[66]. T1DM patients may be overweight or obese and still benefit from pancreas transplant. That being said, such patients are not immune to the general obesity-linked surgical risk[68,71]. On a large scale SRTR analysis of 21000 pancreas transplant recipients, Bedat *et al*[72] showed that overweight and

Table 3 Studies on Simultaneous pancreas and kidney transplant outcomes of C-peptide positive *vs* C-peptide negative recipients

First author, yr	Country	No. patients	Study period	C-peptide positive (%)	BMI (kg/m²) Mean (SD)	Follow-up (yr)	Outcomes	Conclusion
Chakkera *et al*[61], 2010	United States	80	2003-2008	[a]15	T1DM 24.8 (4.2); T2DM 27 (3)	1	No difference in graft (kidney and pancreas) or patient survival.	SPK should be considered in selected patients with T2DM and ESRD. C-peptide measurements for ESRD patients can be misleading.
Light *et al*[64], 2013	United States	173	1989-2008	[c]33.5	T2DM 26.1 (ns)[d]; T1DM 22.5 (ns)[d] (P < 0.0001)	20	T2DM were older at diabetes diagnosis, older at transplant, and heavier pre- and post-transplant, and had better graft survival. T1DM had better patient survival	There was a difference in patient but not graft survival in 20 yr follow-up.
Stratta *et al*[62], 2015	United States	162	2001-2013	[b]18.5	T2DM 26.1 (3.3); T1DM 24.4 (3.2)	5.6 (median)	No difference in patient and graft survival or surgical complications, rejections, serum creatinine, HbA1c, eGFR, C-peptide and weight gain were higher in the C-peptide positive group.	C-peptide "positive" patients appear to have a T2DM phenotype. Outcomes were similar between the two groups, suggesting that C-peptide should not be used exclusively when assessing for SPK transplant candidacy.
Shin *et al*[65], 2017	Republic of Korea	217	2004-2015	[e]ns	T2DM 38 (9); T1DM 18 (7)	5	Similar post-operative HbA1c (< 6%), fasting insulin, HOMA of insulin resistance, and insulinogenic index. Higher post-transplant C-peptide in T2DM recipients.	No significant difference in insulin resistance or β-cell function in 5 yr.

[a]T2DM definition: C-peptide presence, negative glutamic acid decarboxylase antibody, no diabetic ketoacidosis, use of oral hypoglycemics;
[b]C-peptide "positive" (T2DM) = C-peptide ≥ 2.0 ng/mL; C-peptide "negative" = C-peptide < 2.0 ng/mL;
[c]Patients with undetectable C-peptide (< 0.8 ng/mL) were considered T1DM; patients with detectable C-peptide (> 0.8 ng/mL) were considered T2DM;
[d]SD not stated;
[e]Patients were classified as T1DM and T2DM, based upon the American Diabetes Association and the World Health Organization definitions of T2DM. As such, there were 151 T1DM [C-peptide 0.92 (SD = 0.58) ng/mL] and 42 T2DM [C-peptide 3.49 (SD = 3.95) ng/mL] patients. T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; ESRD: End-stage renal disease; eGFR: Estimated glomerular filtration rate; HbA1c: Glycosylated hemoglobin A1; SPK: Simultaneous kidney-pancreas transplant; ns: Not stated; HOMA: Homeostasis model assessment.

obesity are independent predictors of increased early mortality and graft loss, and obesity is associated with inferior long-term graft survival. In an earlier series, Sampaio *et al*[73] reached similar conclusions.

Is there a role for bariatric surgery?

Bariatric and metabolic surgery is an established method of treatment of T2DM and metabolic syndrome[74-76]. It is yet to be clarified whether a metabolic procedure, may it

be sleeve gastrectomy or a more complex restrictive and malabsorptive procedure such as Roux-en-Y gastric bypass, would provide survival benefit on a patient with negligible insulin production.

T2DM patients with BMI ≥ 32 kg/m^2, currently non-eligible for pancreas transplant in most United States centers, should be considered for metabolic surgery[74-76] ; if their post-bariatric surgery BMI drops to ≤ 30 kg/m^2 but they remain insulin-dependent, suffer from brittle diabetes, insulin intolerance and/or hypoglycemia unawareness, they may be channeled towards pancreas transplant.

T1DM patients with BMI > 28 kg/m^2, who are currently considered poor pancreas transplant candidates, may be reconsidered for transplant after adequate weight loss. Excess weight loss prior to pancreas transplant may improve pancreatic graft survival[72]; plus, it will probably temper the obesity-related cardiovascular morbidity and mortality[77]; even though its benefit on T1DM population post-pancreas transplant is yet to be described.

The chronic pancreatitis patient: Islet autotransplant after total pancreatectomy

Total pancreatectomy without pancreatic endocrine function replacement will result in brittle diabetes and life-threatening hypoglycemia due to vanished pancreatic α- and β-cell function. According to 2014 PancreasFest consensus and 2015 National Institute of Diabetes and Digestive and Kidney Diseases, TPIAT is a potential treatment option for selected patients with impaired quality of life due to severe painful chronic pancreatitis, where conservative measures have failed[19,20]. TPIAT should not be performed in patients with active alcoholism or illicit substance use, T1DM, pancreatogenic diabetes, portal vein thrombosis, portal hypertension, significant liver disease, severe cardiopulmonary disease, pancreatic cancer, untreated or uncontrolled psychiatric disorder or history of poor compliance[78]. A retrospective review of 75 children undergoing TPIAT showed sustained pain relief and improved quality of life, whereas beta-cell function was dependent on islet yield[78]. Fan *et al*[79] from Johns Hopkins University recently published a smaller series of 32 patients who underwent laparoscopic TPIAT, resulting in sustained pain relief, earlier recovery and variable insulin dependence. There is vast potential for future research in this emerging field.

DISCUSSION

Pancreas transplant is a potentially curative option for T1DM, re-establishing euglycemia and, therefore, independence from the need of external insulin administration and glucose monitoring. The Heidelberg group analysis of > 20 year outcomes based on International Collaborative Transplant Study data, demonstrated that pancreas transplant benefits become obvious after 10 years, at which time it confers survival benefit superior to LDKT among uremic T1DM patients[31,32]. The group also reported diminished death rates from cardiovascular events beyond 10 years[31,32]. Despite these obvious benefits, the transplant community maintains a rather conservative approach. Donor pancreata remain underutilized[8]; the United States pancreatic discard rates are close to 30%[47]. DCD pancreata are seldom procured[40]; steatotic pancreatic allografts are commonly discarded; and obese donors are commonly considered poor pancreatic donation candidates[35,36]. European study groups showed that procurement professionalization is associated with increased pancreatic allograft utilization, and that high-volume pancreas transplant centers are associated with superior outcomes (Table 2)[49-53]. United Kingdom and OPTN registry analyses demonstrated that DCD and DBD SPKs could have indistinguishable outcomes (Table 1)[41,43-46]. OPTN registry analysis indicated that heavier donor (BMI 30-35 kg/m^2) pancreata might provide comparable outcomes[37]. On the recipient end, pancreas transplant has been shown to be beneficial to selected C-peptide positive patients (Table 3)[64-66].

This study has several limitations. It is a narrative review; as such, it has strong vulnerability to article selection bias; and databases have not been searched in a systemic way. There is limited number of studies exploring the various topics discussed, with series of publications often reported by the same institutions. Another inherent limitation is that most studies included were prospective or retrospective OPTN/UNOS, United Kingdom or DTF cohort reports or case series, which were founded on skewed datasets, since surgeons had already balanced donor-recipient risk at the time of organ/recipient selection and transplant.

CONCLUSION

Pancreas donors remain underutilized. DCD and obese donors should be considered for pancreas donation; the pancreas procurement process should be audited, standardized and optimized. Selected T2DM patients should be considered for pancreas transplant.

More very long-term follow-up studies should be performed in order to delineate the long-term cardiovascular and quality-of-life benefits of pancreas transplant; the results of which might eventually ascertain the pancreas transplant role in the armamentarium of definitive diabetes treatment.

REFERENCES

1 **Williams PW**. Notes on diabetes treated with extract and by grafts of sheep's pancreas. *Br Med J* 1894; 1303-1304 Available from: URL: https://ci.nii.ac.jp/naid/10005565713
2 **Banting FG**, Best CH, Collip JB, Campbell WR, Fletcher AA. Pancreatic extracts in the treatment of diabetes mellitus: preliminary report. 1922. *CMAJ* 1991; **145**: 1281-1286 [PMID: 1933711]
3 **Kelly WD**, Lillehei RC, Merkel FK, Idezuki Y, Goetz FC. Allotransplantation of the pancreas and duodenum along with the kidney in diabetic nephropathy. *Surgery* 1967; **61**: 827-837 [PMID: 5338113]
4 **Sutherland DE**, Goetz FC, Najarian JS. Living-related donor segmental pancreatectomy for transplantation. *Transplant Proc* 1980; **12**: 19-25 [PMID: 6784307]
5 **Ballinger WF**, Lacy PE. Transplantation of intact pancreatic islets in rats. *Surgery* 1972; **72**: 175-186 [PMID: 4262169]
6 **Najarian JS**, Sutherland DE, Matas AJ, Steffes MW, Simmons RL, Goetz FC. Human islet transplantation: a preliminary report. *Transplant Proc* 1977; **9**: 233-236 [PMID: 405770]
7 **Shapiro AM**, Lakey JR, Ryan EA, Korbutt GS, Toth E, Warnock GL, Kneteman NM, Rajotte RV. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *N Engl J Med* 2000; **343**: 230-238 [PMID: 10911004 DOI: 10.1056/NEJM200007273430401]
8 **Hart A**, Smith JM, Skeans MA, Gustafson SK, Stewart DE, Cherikh WS, Wainright JL, Boyle G, Snyder JJ, Kasiske BL. Kidney. *Am J Transplant* 2016; **16** Suppl 2: 11-46 [PMID: 26755262 DOI: 10.1111/ajt.13666]
9 **Gruessner AC**, Gruessner RW. Declining numbers of pancreas transplantations but significant improvements in outcome. *Transplant Proc* 2014; **46**: 1936-1937 [PMID: 25131075 DOI: 10.1016/j.transproceed.2014.06.045]
10 NHS Blood and Transplant, in collaboration with NHS England. Organ specific reports. Interim report on pancreas and islet transplant [cited 2018 September 12]. Available from: URL: https://www.odt.nhs.uk/statistics-and-reports/organ-specific-reports/
11 **Gruessner AC**, Gruessner RW. Pancreas transplant outcomes for United States and non United States cases as reported to the United Network for Organ Sharing and the International Pancreas Transplant Registry as of December 2011. *Clin Transpl* 2012; 23-40 [PMID: 23721008]
12 **Stratta RJ**, Gruessner AC, Odorico JS, Fridell JA, Gruessner RW. Pancreas Transplantation: An Alarming Crisis in Confidence. *Am J Transplant* 2016; **16**: 2556-2562 [PMID: 27232750 DOI: 10.1111/ajt.13890]
13 **Rayhill SC**, D'Alessandro AM, Odorico JS, Knechtle SJ, Pirsch JD, Heisey DM, Kirk AD, Van der Werf W, Sollinger HW. Simultaneous pancreas-kidney transplantation and living related donor renal transplantation in patients with diabetes: is there a difference in survival? *Ann Surg* 2000; **231**: 417-423 [PMID: 10714635 DOI: 10.1097/00000658-200003000-00015]
14 **Odorico JS**, Voss B, Munoz Del Rio A, Leverson G, Becker YT, Pirsch JD, Hoffman RM, Sollinger HW. Kidney function after solitary pancreas transplantation. *Transplant Proc* 2008; **40**: 513-515 [PMID: 18374117 DOI: 10.1016/j.transproceed.2008.01.038]
15 **Scalea JR**, Butler CC, Munivenkatappa RB, Nogueira JM, Campos L, Haririan A, Barth RN, Philosophe B, Bartlett ST, Cooper M. Pancreas transplant alone as an independent risk factor for the development of renal failure: a retrospective study. *Transplantation* 2008; **86**: 1789-1794 [PMID: 19104423 DOI: 10.1097/TP.0b013e3181913fbf]
16 **Gruessner AC**, Sutherland DE, Dunn DL, Najarian JS, Humar A, Kandaswamy R, Gruessner RW. Pancreas after kidney transplants in posturemic patients with type I diabetes mellitus. *J Am Soc Nephrol* 2001; **12**: 2490-2499 [PMID: 11675427]
17 **Dholakia S**, Mittal S, Quiroga I, Gilbert J, Sharples EJ, Ploeg RJ, Friend PJ. Pancreas Transplantation: Past, Present, Future. *Am J Med* 2016; **129**: 667-673 [PMID: 26965300 DOI: 10.1016/j.amjmed.2016.02.011]
18 **Farney AC**, Cho E, Schweitzer EJ, Dunkin B, Philosophe B, Colonna J, Jacobs S, Jarrell B, Flowers JL, Bartlett ST. Simultaneous cadaver pancreas living-donor kidney transplantation: a new approach for the type 1 diabetic uremic patient. *Ann Surg* 2000; **232**: 696-703 [PMID: 11066142 DOI: 10.1097/00000658-200011000-00012]
19 **Bellin MD**, Freeman ML, Gelrud A, Slivka A, Clavel A, Humar A, Schwarzenberg SJ, Lowe ME, Rickels MR, Whitcomb DC. Total pancreatectomy and islet autotransplantation in chronic pancreatitis: recommendations from PancreasFest. *Pancreatology* 2014; **14**: 27-35 [PMID: 24555976 DOI: 10.1016/j.pan.2013.10.009]
20 **Bellin MD**, Gelrud A, Arreaza-Rubin G, Dunn TB, Humar A, Morgan KA, Naziruddin B, Rastellini C, Rickels MR, Schwarzenberg SJ. Total pancreatectomy with islet autotransplantation: summary of an NIDDK workshop. *Ann Surg* 2015; **261**: 21-29 [PMID: 25599324 DOI: 10.1097/SLA.0000000000001059]
21 **Tan M**, Kandaswamy R, Sutherland DE, Gruessner RW. Laparoscopic donor distal pancreatectomy for living donor pancreas and pancreas-kidney transplantation. *Am J Transplant* 2005; **5**: 1966-1970 [PMID: 15996246 DOI: 10.1111/j.1600-6143.2005.00950.x]
22 **Matsumoto S**, Okitsu T, Iwanaga Y, Noguchi H, Nagata H, Yonekawa Y, Yamada Y, Fukuda K, Tsukiyama K, Suzuki H. Insulin independence after living-donor distal pancreatectomy and isl*et al*lotransplantation. *Lancet* 2005; **365**: 1642-1644 [PMID: 15889479 DOI:

10.1016/S0140-6736(05)66383-0]
23 **Gruessner RW**, Sutherland DE, Gruessner AC. Mortality assessment for pancreas transplants. *Am J Transplant* 2004; **4**: 2018-2026 [PMID: 15575904 DOI: 10.1111/j.1600-6143.2004.00667.x]
24 **Jukema JW**, Smets YF, van der Pijl JW, Zwinderman AH, Vliegen HW, Ringers J, Reiber JH, Lemkes HH, van der Wall EE, de Fijter JW. Impact of simultaneous pancreas and kidney transplantation on progression of coronary atherosclerosis in patients with end-stage renal failure due to type 1 diabetes. *Diabetes Care* 2002; **25**: 906-911 [PMID: 11978689 DOI: 10.2337/diacare.25.5.906]
25 **Reddy KS**, Stablein D, Taranto S, Stratta RJ, Johnston TD, Waid TH, McKeown JW, Lucas BA, Ranjan D. Long-term survival following simultaneous kidney-pancreas transplantation versus kidney transplantation alone in patients with type 1 diabetes mellitus and renal failure. *Am J Kidney Dis* 2003; **41**: 464-470 [PMID: 12552511 DOI: 10.1053/ajkd.2003.50057]
26 **Tydén G**, Bolinder J, Solders G, Brattström C, Tibell A, Groth CG. Improved survival in patients with insulin-dependent diabetes mellitus and end-stage diabetic nephropathy 10 years after combined pancreas and kidney transplantation. *Transplantation* 1999; **67**: 645-648 [PMID: 10096516 DOI: 10.1097/00007890-199903150-00001]
27 **Ojo AO**, Meier-Kriesche HU, Hanson JA, Leichtman A, Magee JC, Cibrik D, Wolfe RA, Port FK, Agodoa L, Kaufman DB. The impact of simultaneous pancreas-kidney transplantation on long-term patient survival. *Transplantation* 2001; **71**: 82-90 [PMID: 11211201 DOI: 10.1097/00007890-200101150-00014]
28 **Smets YF**, Westendorp RG, van der Pijl JW, de Charro FT, Ringers J, de Fijter JW, Lemkes HH. Effect of simultaneous pancreas-kidney transplantation on mortality of patients with type-1 diabetes mellitus and end-stage renal failure. *Lancet* 1999; **353**: 1915-1919 [PMID: 10371569 DOI: 10.1016/S0140-6736(98)07513-8]
29 **Young BY**, Gill J, Huang E, Takemoto SK, Anastasi B, Shah T, Bunnapradist S. Living donor kidney versus simultaneous pancreas-kidney transplant in type I diabetics: an analysis of the OPTN/UNOS database. *Clin J Am Soc Nephrol* 2009; **4**: 845-852 [PMID: 19201918 DOI: 10.2215/CJN.02250508]
30 **Weiss AS**, Smits G, Wiseman AC. Twelve-month pancreas graft function significantly influences survival following simultaneous pancreas-kidney transplantation. *Clin J Am Soc Nephrol* 2009; **4**: 988-995 [PMID: 19406961 DOI: 10.2215/CJN.04940908]
31 **Morath C**, Zeier M, Döhler B, Schmidt J, Nawroth PP, Schwenger V, Opelz G. Transplantation of the type 1 diabetic patient: the long-term benefit of a functioning pancreas allograft. *Clin J Am Soc Nephrol* 2010; **5**: 549-552 [PMID: 20093348 DOI: 10.2215/CJN.03720609]
32 **Morath C**, Zeier M, Döhler B, Schmidt J, Nawroth PP, Opelz G. Metabolic control improves long-term renal allograft and patient survival in type 1 diabetes. *J Am Soc Nephrol* 2008; **19**: 1557-1563 [PMID: 18495965 DOI: 10.1681/ASN.2007070804]
33 **Fioretto P**, Steffes MW, Sutherland DE, Goetz FC, Mauer M. Reversal of lesions of diabetic nephropathy after pancreas transplantation. *N Engl J Med* 1998; **339**: 69-75 [PMID: 9654536 DOI: 10.1056/NEJM199807093390202]
34 **Kandaswamy R**, Stock PG, Gustafson SK, Skeans MA, Curry MA, Prentice MA, Fox A, Israni AK, Snyder JJ, Kasiske BL. OPTN/SRTR 2016 Annual Data Report: Pancreas. *Am J Transplant* 2018; **18** Suppl 1: 114-171 [PMID: 29292605 DOI: 10.1111/ajt.14558]
35 **Dholakia S**, Sharples EJ, Ploeg RJ, Friend PJ. Significance of steatosis in pancreatic transplantation. *Transplant Rev (Orlando)* 2017; **31**: 225-231 [PMID: 28855081 DOI: 10.1016/j.trre.2017.08.001]
36 **Verma AR**, Papalois V. Evaluating steatosis in pancreatic transplant. *Exp Clin Transplant* 2011; **9**: 159-164 [PMID: 21649562]
37 **Alhamad T**, Malone AF, Lentine KL, Brennan DC, Wellen J, Chang SH, Chakkera HA. Selected Mildly Obese Donors Can Be Used Safely in Simultaneous Pancreas and Kidney Transplantation. *Transplantation* 2017; **101**: 1159-1166 [PMID: 27428713 DOI: 10.1097/TP.0000000000001303]
38 **Mittal S**, Gilbert J, Friend PJ. Donors after circulatory death pancreas transplantation. *Curr Opin Organ Transplant* 2017; **22**: 372-376 [PMID: 28678058 DOI: 10.1097/MOT.0000000000000437]
39 **Kopp WH**, Lam HD, Schaapherder AFM, Huurman VAL, van der Boog PJM, de Koning EJP, de Fijter JW, Baranski AG, Braat AE. Pancreas Transplantation With Grafts From Donors Deceased After Circulatory Death: 5 Years Single-Center Experience. *Transplantation* 2018; **102**: 333-339 [PMID: 28885491 DOI: 10.1097/TP.0000000000001940]
40 **Siskind E**, Akerman M, Maloney C, Huntoon K, Alex A, Siskind T, Bhaskeran M, Ali N, Basu A, Molmenti E. Pancreas transplantation from donors after cardiac death: an update of the UNOS database. *Pancreas* 2014; **43**: 544-547 [PMID: 24632550 DOI: 10.1097/MPA.0000000000000084]
41 **D'Alessandro AM**, Fernandez LA, Chin LT, Shames BD, Turgeon NA, Scott DL, Di Carlo A, Becker YT, Odorico JS, Knechtle SJ. Donation after cardiac death: the University of Wisconsin experience. *Ann Transplant* 2004; **9**: 68-71 [PMID: 15478896]
42 **Bellingham JM**, Santhanakrishnan C, Neidlinger N, Wai P, Kim J, Niederhaus S, Leverson GE, Fernandez LA, Foley DP, Mezrich JD. Donation after cardiac death: a 29-year experience. *Surgery* 2011; **150**: 692-702 [PMID: 22000181 DOI: 10.1016/j.surg.2011.07.057]
43 **Fernandez LA**, Di Carlo A, Odorico JS, Leverson GE, Shames BD, Becker YT, Chin LT, Pirsch JD, Knechtle SJ, Foley DP. Simultaneous pancreas-kidney transplantation from donation after cardiac death: successful long-term outcomes. *Ann Surg* 2005; **242**: 716-723 [PMID: 16244546 DOI: 10.1097/01.sla.0000186175.84788.50]
44 **Salvalaggio PR**, Davies DB, Fernandez LA, Kaufman DB. Outcomes of pancreas transplantation in the United States using cardiac-death donors. *Am J Transplant* 2006; **6**: 1059-1065 [PMID: 16611344 DOI: 10.1111/j.1600-6143.2006.01310.x]
45 **Muthusamy AS**, Mumford L, Hudson A, Fuggle SV, Friend PJ. Pancreas transplantation from donors after circulatory death from the United Kingdom. *Am J Transplant* 2013; **13**: 824 [PMID: 23437884 DOI: 10.1111/ajt.12037]
46 **Shahrestani S**, Webster AC, Lam VW, Yuen L, Ryan B, Pleass HC, Hawthorne WJ. Outcomes From Pancreatic Transplantation in Donation After Cardiac Death: A Systematic Review and Meta-Analysis. *Transplantation* 2017; **101**: 122-130 [PMID: 26950713 DOI: 10.1097/TP.0000000000001084]
47 **Kandaswamy R**, Skeans MA, Gustafson SK, Carrico RJ, Tyler KH, Israni AK, Snyder JJ, Kasiske

BL. OPTN/SRTR 2013 Annual Data Report: pancreas. *Am J Transplant* 2015; **15** Suppl 2: 1-20 [PMID: 25626343 DOI: 10.1111/ajt.13196]
48 **Ausania F**, Drage M, Manas D, Callaghan CJ. A registry analysis of damage to the deceased donor pancreas during procurement. *Am J Transplant* 2015; **15**: 2955-2962 [PMID: 26484838 DOI: 10.1111/ajt.13419]
49 **de Boer JD**, Kopp WH, Ooms K, Haase-Kromwijk BJ, Krikke C, de Jonge J, van Heurn LW, Baranski AG, van der Vliet JA, Braat AE. Abdominal organ procurement in the Netherlands - an analysis of quality and clinical impact. *Transpl Int* 2017; **30**: 288-294 [PMID: 27992973 DOI: 10.1111/tri.12906]
50 **Lam HD**, Schaapherder AF, Kopp WH, Putter H, Braat AE, Baranski AG. Professionalization of surgical abdominal organ recovery leading to an increase in pancreatic allografts accepted for transplantation in the Netherlands: a serial analysis. *Transpl Int* 2017; **30**: 117-123 [PMID: 27874968 DOI: 10.1111/tri.12893]
51 **Andres A**, Assalino M, Oldani G, Toso C, Berney T. Procurement professionalization: a mandatory step to improve the availability and quality of whole pancreas grafts. *Transpl Int* 2017; **30**: 115-116 [PMID: 27987369 DOI: 10.1111/tri.12904]
52 **Kopp W**, van Meel M, Putter H, Samuel U, Arbogast H, Schareck W, Ringers J, Braat A. Center Volume Is Associated With Outcome After Pancreas Transplantation Within the Eurotransplant Region. *Transplantation* 2017; **101**: 1247-1253 [PMID: 27379557 DOI: 10.1097/TP.0000000000001308]
53 **Alhamad T**, Malone AF, Brennan DC, Stratta RJ, Chang SH, Wellen JR, Horwedel TA, Lentine KL. Transplant Center Volume and the Risk of Pancreas Allograft Failure. *Transplantation* 2017; **101**: 2757-2764 [PMID: 28099402 DOI: 10.1097/TP.0000000000001628]
54 **Axelrod DA**, Sung RS, Meyer KH, Wolfe RA, Kaufman DB. Systematic evaluation of pancreas allograft quality, outcomes and geographic variation in utilization. *Am J Transplant* 2010; **10**: 837-845 [PMID: 20121753 DOI: 10.1111/j.1600-6143.2009.02996.x]
55 **Mittal S**, Lee FJ, Bradbury L, Collett D, Reddy S, Sinha S, Sharples E, Ploeg RJ, Friend PJ, Vaidya A. Validation of the Pancreas Donor Risk Index for use in a UK population. *Transpl Int* 2015; **28**: 1028-1033 [PMID: 25789920 DOI: 10.1111/tri.12563]
56 **Gruessner RWG**, Sutherland D. Living Donor Pancreas Transplant. *Transplant Rev-orlan* 2002; **16**: 108-119 [DOI: 10.1053/trre.2002.123264]
57 **Gruessner RW**, Sutherland DE. Simultaneous kidney and segmental pancreas transplants from living related donors - the first two successful cases. *Transplantation* 1996; **61**: 1265-1268 [PMID: 8610429 DOI: 10.1097/00007890-199604270-00025]
58 **Benedetti E**, Dunn T, Massad MG, Raofi V, Bartholomew A, Gruessner RW, Brecklin C. Successful living related simultaneous pancreas-kidney transplant between identical twins. *Transplantation* 1999; **67**: 915-918 [PMID: 10199743 DOI: 10.1097/00007890-199903270-00021]
59 **Kirchner VA**, Finger EB, Bellin MD, Dunn TB, Gruessner RW, Hering BJ, Humar A, Kukla AK, Matas AJ, Pruett TL. Long-term Outcomes for Living Pancreas Donors in the Modern Era. *Transplantation* 2016; **100**: 1322-1328 [PMID: 27203593 DOI: 10.1097/TP.0000000000001250]
60 **Gruessner AC**. 2011 update on pancreas transplantation: comprehensive trend analysis of 25,000 cases followed up over the course of twenty-four years at the International Pancreas Transplant Registry (IPTR). *Rev Diabet Stud* 2011; **8**: 6-16 [PMID: 21720668 DOI: 10.1900/RDS.2011.8.6]
61 **Chakkera HA**, Bodner JK, Heilman RL, Mulligan DC, Moss AA, Mekeel KL, Mazur MJ, Hamawi K, Ray RM, Beck GL. Outcomes after simultaneous pancreas and kidney transplantation and the discriminative ability of the C-peptide measurement pretransplant among type 1 and type 2 diabetes mellitus. *Transplant Proc* 2010; **42**: 2650-2652 [PMID: 20832562 DOI: 10.1016/j.transproceed.2010.04.065]
62 **Stratta RJ**, Rogers J, Farney AC, Orlando G, El-Hennawy H, Gautreaux MD, Reeves-Daniel A, Palanisamy A, Iskandar SS, Bodner JK. Pancreas transplantation in C-peptide positive patients: does "type" of diabetes really matter? *J Am Coll Surg* 2015; **220**: 716-727 [PMID: 25667140 DOI: 10.1016/j.jamcollsurg.2014.12.020]
63 American Diabetes Association. 2. Classification and Diagnosis of Diabetes. *Diabetes Care* 2016; **39** Suppl 1: S13-S22 [PMID: 26696675 DOI: 10.2337/dc16-S005]
64 **Light J**, Tucker M. Simultaneous pancreas kidney transplants in diabetic patients with end-stage renal disease: the 20-yr experience. *Clin Transplant* 2013; **27**: E256-E263 [PMID: 23480129 DOI: 10.1111/ctr.12100]
65 **Shin S**, Jung CH, Choi JY, Kwon HW, Jung JH, Kim YH, Han DJ. Long-term Metabolic Outcomes of Functioning Pancreas Transplants in Type 2 Diabetic Recipients. *Transplantation* 2017; **101**: 1254-1260 [PMID: 27336397 DOI: 10.1097/TP.0000000000001269]
66 **Lo DJ**, Sayed BA, Turgeon NA. Pancreas transplantation in unconventional recipients. *Curr Opin Organ Transplant* 2016; **21**: 393-398 [PMID: 27328037 DOI: 10.1097/MOT.0000000000000334]
67 World Health Organization. Prevalence of obesity, ages 18+, 2010-2014. Geneva, Switzerland. [Accessed June 5 2016.]. Available from: URL: http://www.who.int/gho/ncd/risk_factors/overweight_obesity/obesity_adults/en/
68 **Nair S**, Verma S, Thuluvath PJ. Obesity and its effect on survival in patients undergoing orthotopic liver transplantation in the United States. *Hepatology* 2002; **35**: 105-109 [PMID: 11786965 DOI: 10.1053/jhep.2002.30318]
69 **Hakeem AR**, Cockbain AJ, Raza SS, Pollard SG, Toogood GJ, Attia MA, Ahmad N, Hidalgo EL, Prasad KR, Menon KV. Increased morbidity in overweight and obese liver transplant recipients: a single-center experience of 1325 patients from the United Kingdom. *Liver Transpl* 2013; **19**: 551-562 [PMID: 23408499 DOI: 10.1002/lt.23618]
70 **Hillingsø JG**, Wettergren A, Hyoudo M, Kirkegaard P. Obesity increases mortality in liver transplantation--the Danish experience. *Transpl Int* 2005; **18**: 1231-1235 [PMID: 16221152 DOI: 10.1111/j.1432-2277.2005.00206.x]
71 **Flancbaum L**, Choban PS. Surgical implications of obesity. *Annu Rev Med* 1998; **49**: 215-234 [PMID: 9509260 DOI: 10.1146/annurev.med.49.1.215]
72 **Bédat B**, Niclauss N, Jannot AS, Andres A, Toso C, Morel P, Berney T. Impact of recipient body mass index on short-term and long-term survival of pancreatic grafts. *Transplantation* 2015; **99**: 94-99 [PMID: 24914570 DOI: 10.1097/TP.0000000000000226]
73 **Sampaio MS**, Reddy PN, Kuo HT, Poommipanit N, Cho YW, Shah T, Bunnapradist S. Obesity

was associated with inferior outcomes in simultaneous pancreas kidney transplant. *Transplantation* 2010; **89**: 1117-1125 [PMID: 20164819 DOI: 10.1097/TP.0b013e3181d2bfb2]

74 **Schauer PR**, Nor Hanipah Z, Rubino F. Metabolic surgery for treating type 2 diabetes mellitus: Now supported by the world's leading diabetes organizations. *Cleve Clin J Med* 2017; **84**: S47-S56 [PMID: 28708482 DOI: 10.3949/ccjm.84.s1.06]

75 **Rubino F**, Nathan DM, Eckel RH, Schauer PR, Alberti KG, Zimmet PZ, Del Prato S, Ji L, Sadikot SM, Herman WH. Metabolic Surgery in the Treatment Algorithm for Type 2 Diabetes: a Joint Statement by International Diabetes Organizations. *Obes Surg* 2017; **27**: 2-21 [PMID: 27957699 DOI: 10.1007/s11695-016-2457-9]

76 **Rubino F**, Panagiotopoulos S. Surgery: Metabolic surgery: the cutting edge of diabetes care. *Nat Rev Gastroenterol Hepatol* 2017; **14**: 389-390 [PMID: 28428637 DOI: 10.1038/nrgastro.2017.45]

77 **Abdelaal M**, le Roux CW, Docherty NG. Morbidity and mortality associated with obesity. *Ann Transl Med* 2017; **5**: 161 [PMID: 28480197 DOI: 10.21037/atm.2017.03.107]

78 **Chinnakotla S**, Bellin MD, Schwarzenberg SJ, Radosevich DM, Cook M, Dunn TB, Beilman GJ, Freeman ML, Balamurugan AN, Wilhelm J. Total pancreatectomy and islet autotransplantation in children for chronic pancreatitis: indication, surgical techniques, postoperative management, and long-term outcomes. *Ann Surg* 2014; **260**: 56-64 [PMID: 24509206 DOI: 10.1097/SLA.0000000000000569]

79 **Fan CJ**, Hirose K, Walsh CM, Quartuccio M, Desai NM, Singh VK, Kalyani RR, Warren DS, Sun Z, Hanna MN. Laparoscopic Total Pancreatectomy With Islet Autotransplantation and Intraoperative Islet Separation as a Treatment for Patients With Chronic Pancreatitis. *JAMA Surg* 2017; **152**: 550-556 [PMID: 28241234 DOI: 10.1001/jamasurg.2016.5707]

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ORIGINAL ARTICLE

Retrospective Cohort Study

Graft *vs* host disease impacts overall survival post allogeneic hematopoietic stem cell transplantation for acute lymphoblastic leukemia/lymphoma

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Author contributions: Damlaj M designed the study and analyzed data; Damlaj M, Ghazi S and Snnallah M collected data; all authors provided patients, wrote and reviewed the manuscript, and approved final version of the manuscript.

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Abstract

AIM

To examine the outcome and prognostic factors for high risk patients with acute lymphoblastic leukemia/lymphoma (ALL/LBL) who underwent allogeneic hematopoietic stem cell transplantation (HCT) at our center during the period of 2010-2017

METHODS

After due institutional review board approval, patients with high risk ALL/LBL post HCT were identified and included. All records were retrospectively collected. Time to event analysis was calculated from the date of HCT until event of interest or last follow up with Kaplan-Meir means. Cox regression model was used for multivariable analysis calculation.

RESULTS

A total of 69 patients were enrolled and examined with a median age of 21 (14-61). After a median follow up of 15 mo (2-87.3), the 2-year cumulative incidence of relapse, cumulative incidence of non-relapse mortality, progression free survival and overall survival (OS) were 34.1%, 10.9%, 54.9% and 62.8%, respectively. In a multivariable analysis for OS; acute graft *vs* host disease (GVHD) and chronic GVHD were significant with corresponding hazard ratio 4.9 (1.99-12; $P = 0.0007$) and 0.29 (0.1-0.67; $P = 0.0044$), respectively.

CONCLUSION

Allogeneic-HCT for high risk ALL/LBL resulted in promising remissions particularly for patients with cGVHD.

Key words: Acute lymphoblastic leukemia; Allogeneic hematopoietic stem cell

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Core tip: Allogeneic hematopoietic stem cell transplantation (HCT) is a potentially curative therapy for acute lymphoblastic leukemia/lymphoma (ALL/LBL) patients. We examined the outcome and prognostic factors of HCT for high risk ALL/LBL at our center. After due institutional review board approval, 69 patients were enrolled. After a median follow up of 15 mo (2-87.3), the 2-year overall survival (OS) was 62.8%. In a multivariable analysis; acute graft *vs* host disease (GVHD) and chronic GVHD predicted OS. In conclusion, allogeneic-HCT for ALL/LBL results in promising remissions in high risk disease and early referral for HCT to be considered for young and fit patients.

Damlaj M, Snnallah M, Alhejazi A, Ghazi S, Alahmari B, Alaskar A, Al-Zahrani M. Graft *vs* host disease impacts overall survival post allogeneic hematopoietic stem cell transplantation for acute lymphoblastic leukemia/lymphoma. *World J Transplantation* 2018; 8(7): 252-261
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INTRODUCTION

Acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) constitute around 5% of all adult lymphoid malignancies and is typically diagnosed in the second to third decade of life. Complete morphologic remission, evident by presence of less than 5% clonal blasts in the bone marrow, following induction therapy can be achieved in the majority of patients. Incidence of relapse (IR) remains high; therefore, optimization of post remission therapy is vital. Furthermore, outcome of patients post relapse is dismal[1].

The role of allogeneic hematopoietic stem cell transplantation (HCT) in adult ALL/LBL in first complete remission (CR1) is debated. This is in part due to conflicting evidence with regards to the utility of this therapy due to on-going developments in the field. Typically accepted indications for allogeneic HCT in CR1 include elevated white blood count (WBC) > 30 × 10^9/L in B-cell disease and > 100 × 10^9/L in T-cell disease, age > 35 years, CD20 expression in B-cell disease, high risk cytogenetics including Philadelphia chromosome (Ph +ve), among others[2,3].

A number of prospective studies have examined the role of allogeneic HCT in CR1 spanning an enrolment period of almost two decades (1986-2005). The French Leucemie Aigue Lymphobalstique del'Adulte (LALA) group reported outcomes on over 400 patients from two studies (LAL-87 and LALA-94) and found that allogeneic HCT in CR1 resulted in improved survival in high risk patients[4,5]. Similar conclusions were drawn from the Groupe Ouest-Est des Leucémies Aiguës et Maladies du Sang (GOELAL02) clinical trial[6]. Conversely, the Eastern Cooperative Oncology Group/Medical Research Council (ECOG/MRC) and the Haemato-Oncology Foundation for adults in the Netherlands (HOVON) clinical trials demonstrated that this survival advantage is restricted to patients with standard risk disease[7,8]. Collectively, these results created some controversy within the transplant community on the optimal indication for all-HCT in CR1. The American Society of Blood and Marrow Transplantation recently published recommendations for the indications of various diseases for HCT, and they endorsed transplant for ALL in high risk disease in CR1 or CR2; however, these recommendations were not consistent with their European counterparts[9,10].

Out our center, we reserve allogeneic HCT for patients exhibiting conventional high risk features or evidence of minimal residual disease (MRD) at end of induction. We also perform allogeneic HCT for patients in second or subsequent CR (≥ CR2) due to its curative potential, albeit lower, in these patients and lack of better therapeutic strategies in this setting. Our aim from this analysis is to examine the prognostic factors and outcome in these high risk patients.

MATERIALS AND METHODS

Patient cohort

The project was approved by the institutional review board (IRB) prior to commencing. We identified all patients ≥ 14 years of age at our institution that underwent HCT for ALL during the time period of 2010-2017. All clinical records with regards to patient, disease, therapy and outcome were collected retrospectively from electronic medical records at our institution. The inclusion criteria were; patients who received allogeneic HCT for ALL using different conditioning intensity from matched related donor (MRD), matched unrelated donor (MUD) or haploidentical donors. The intensity of the conditioning regimen was based on the criteria suggested by the Centre of International Blood and Marrow Transplant Research (CIBMTR)[11]. Choice of regimen was based on the Hematopoietic Stem Cell Co-morbidity index (HCT-CI); patients scoring < 3 were considered for a myeloablative (MAC) regimen while the remaining patients received reduced intensity conditioning (RIC) regimen. Patients preferentially received a total body irradiation (TBI) regimen if they were candidates for a MAC regimen. We excluded patients who received a cord blood or bone marrow graft, second transplant and any patient that underwent in vivo or in vitro T-cell depletion. All records were retrospectively collected. Cytogenetics with hypodiploid karyotype, translocations at (4;11), (11q23), (9;22) and (1;19) were classified as high risk while all others were deemed standard risk.

Treatment protocol and indications for allogeneic HCT

The majority of patients received hyper-fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone with high dose methotrexate and cytarabine (HyperCVAD) given in alternating cycles (A and B) with cycle A consisting of 300 mg/m^2 of intravenous (IV) cyclophosphamide every 12 h on days 1-3 for a total of 6 doses with appropriate mesna dose for bladder protection; vincristine 1.4 mg/m^2 (maximum dose 2 mg) IV for two days (day 1 and 11); doxorubicin 50 mg/m^2 IV on day 4 followed by dexamethasone 40 mg IV on days 1-4 then 11-14. Cycle B contained of high dose methotrexate 1 g/m^2 given over 24 h on day 1 with appropriate hydration with sodium bicarbonate, leucovorin and therapeutic drug monitoring; cytarabine 3000 mg/m^2 IV over 2 h given every 12 h on days 2-3 for a total of 4 doses and methylprednisolone 50 mg IV every 12 h on days 1-3. Patients with CD20 expression were given the monoclonal antibody rituximab on days 1 and 8 at a dose of 375 mg/m^2. Ph positive ALL patients were given tyrosine kinase inhibitor (TKI) dasatinib 140 mg daily days 1-14 of each cycle of therapy and reinitiated post HCT once immunosuppression is tapered. Central nervous system prophylaxis consisted of intrathecal (IT) methotrexate 12 mg and hydrocortisone 50 mg given on day 2 of cycles A and B, and cytarabine 50 mg on day 8 of cycle A only. Patients were given at least 6 doses of IT chemotherapy prior to HCT. Patients were given 4 cycles of therapy (until 2B) prior to proceeding to HCT.

Supportive care consisted of granulocyte colony stimulating factor (GCSF) 300 mcg given starting day 5 until neutrophil recovery; ciprofloxacin 500 mg orally or IV equivalent twice daily; acyclovir 200 mg orally or IV equivalent twice daily; fluconazole 200 mg orally or IV equivalent twice daily and prednisolone 1% eye drops in each eye four times daily 1 d prior to and continued for 3 d post completion of cytarabine.

Bone marrow aspirate and trephine biopsy was done on day 28 post cycle 1A induction to assess for remission status with morphologic remission defined as < 5% blasts in the bone marrow with complete count recovery. The following high risk features were considered as indications for allogeneic HCT in first remission; presenting WBC > 30 × 10^9/L or 100 × 10^9/L in B- *vs* T-cell ALL, respectively; high risk cytogenetics as indicated above or evidence of persistent MRD post induction with HyperCVAD. Patients with relapsed disease and successfully achieved CR2 following salvage chemotherapy proceeded to HCT.

Preparative regimens and graft vs host disease prophylaxis

The MAC preparative regimen for matched related or unrelated donors (MRD or MUD) consisted of cyclophosphamide 60 mg/kg IV for a total of two days then a total of 1200 cGy of TBI divided twice daily for three days. Mesna was given for bladder protection. The MAC preparative regimen for haploidentical HCT consisted of fludarabine 25 mg/m^2 IV for 3 d and TBI 1200 cGy fractionated twice daily for 4 d as previously described[12]. For RIC regimens and MRD or MUD donors, patients received fludarabine 30 mg/m^2 IV on a daily basis for a total of 5 d with melphalan 70 mg/m^2 IV for 2 d. For those with RIC haploidentical HCT, the preparative regimen consisted of fludarabine 30 mg/m^2 IV daily for 5 d, cyclophosphamide 14.5 mg/kg IV daily for 2 d and TBI 200 cGy in a single fraction[13].

Prophylaxis for graft *vs* host disease (GVHD) contained methotrexate and cyclosporine for MRD and MUD HCT. Methotrexate was administered at 15 mg/m^2

on day +1 then at 10 mg/m^2 on days +3, +6 and +11. GVHD prophylaxis for haploidentical HCT consisted of tacrolimus 0.1 mg/kg per day orally twice daily (or IV equivalent) starting on day +6 adjusted to trough level of 10-15 ng/mL, mycophenolate mofetil (MMF) 15 mg/kg/dose three times daily starting on day +6 until +36 and cyclophosphamide 50 mg/kg IV daily on days +3 and +5 with appropriate mesna dose for bladder protection.

Definitions and transplant related outcomes

We defined overall survival (OS) as the time from transplant until the time of death of any cause or last patient encounter while progression free survival (PFS) was defined as the time from transplant until death due to any cause or relapsed disease. Cumulative incidence of relapse (CIR) was defined as the time from transplant until evidence of disease relapse or last patient encounter. While cumulative incidence of non-relapse mortality (NRM) was defined as the time from transplant until death due to any cause without evidence of relapse. Absolute neutrophil count (ANC) of 0.5 × 10^9/L or for 3 d constituted neutrophil engraftment while platelet count greater than 20 × 10^9/L for 7 d without transfusion support constituted platelet engraftment.

Statistical analysis

All baseline variables relating to patient, disease or treatment characteristics were reported in a descriptive fashion. Pearson's χ^2 and Wilcoxon/Kruskal-Wallis tests were used to analyze categorical or continuous variables, respectively. The Kaplan-Meir method with log ranks was used to estimate the probability of OS and PFS. Grey's model was used to estimate the incidence of events with competing nature, *i.e.*, CIR and cumulative incidence of NRM (CI-NRM). Cox regression model was used for univariate and multivariate analysis with outcome expressed as a hazard ratio (HR) with 95% confidence interval (CI) and P value. Variables with a $P \leq 0.05$ were inserted into the multivariate model. Analysis was performed using JMP and EZR[14].

RESULTS

Patient and transplant variables

During the study period, 69 patients were identified per our inclusion criteria and were further analyzed. The median (range) age was 21 (14-61) years with 41 (59%) being male. B-cell ALL was the most common pathology representing 50 (72%) of cases with the remaining being T-cell subtype. Ph-ALL was detected in 16/50 (32%) of B-cell ALL. LBL was seen in 17 (25%) of cases. 35 (51%) of patients had high risk cytogenetics. A total of 42 (61%) of patients received HCT in CR1 while the remaining patients were in second or subsequent CR. Indications for HCT in these patients were; 27 (64%) for high risk cytogenetics including Ph-ALL; 11 (26%) for high presenting WBC at diagnosis and 4 (10) for persistent MRD post induction. Matched sibling donor (MSD) was the most common donor type in 58 (84%) of cases and the majority of patients received MAC regimen (90%) containing TBI (87%). The baseline characteristics of the cohort are shown in Table 1.

Engraftment and GVHD

The median total of CD34 cells infused was 6 × 10^6/kg of recipient weight (range; 8.9-2) and all collected cells were infused through a Hickman catheter or a peripherally inserted central catheter (PICC). Infusion was over one day for all patients. GCSF was used in 33 (47.8%) of patients at the discretion of the treating physician. Median time to ANC engraftment, defined as ANC ≥ 0.5 × 10^6/L sustained over three days was 17 d (range; 9-28). There was no significant difference between time to ANC engraftment between patients receiving GCSF and those who did not. On the other hand, the median time to platelet engraftment was 12 (range; 0-29).

Acute GVHD (aGVHD) developed in a total of 20 patients (29%), with grades II, III or IV with 8 (40%), 8 (40%) and 4 (20%), respectively. All of them required systemic corticosteroid therapy, 5/20 (25%) required second line immune-suppressants while 2/20 (10%) required third line immune-suppressants. A high incidence of mortality was noted within these patients with 8/20 (40%) dying due to organ toxicity or infectious etiology. On the other hand, chronic GVHD (cGVHD) developed in a total of 30 patients (43.5%) with mild, moderate or severe forms in 8 (26.7%), 15 (50%) and 7 (23.3%), respectively. A total of 9 patients had overlap GVHD syndrome.

Post-transplant outcomes

Overall cohort: The median follow up was 15 mo (2-87.3), following which the 2 year CIR, CI-NRM, PFS and OS were 34.1%, 10.9%, 54.9% and 62.8%, respectively as shown in Figure 1). Stratified by remission status at the time of HCT, patients in CR1 had an

Table 1 Baseline characteristics of the cohort *n* (%)

Characteristic	Entire cohort (*n* = 69)
Patient age in years, median (range)	21 (14-61)
Recipient gender, male	41 (59%)
Cell subtype	
B-cell	50 (72)
T-cell	19 (28)
Philadelphia chromosome (B-cell)	16/50 (32)
Disease subtype	
Lymphoblastic leukemia	52 (75)
Lymphoblastic lymphoma	17 (25)
Cytogenetic status	
Standard	30 (43)
High risk	35 (51)
Missing	4 (6)
ECOG, median (range)	0 (0-2)
HCT-CI, median (range)	0 (0-5)
Gender mismatch	28 (41)
Female donor/male recipient	11 (16)
Donor type	
MSD	58 (84)
MORD	2 (3)
MUD	3 (4)
Haploidentical	6 (9)
Status at HCT	
CR1	42 (61)
≥ CR2	27 (39)
ABO matching	
Match	50 (73)
Major/bidirectional	10 (14)
Minor	9 (13)
TBI containing regimen	60 (87)
Conditioning intensity	
MAC	62 (90)
RIC/NMA	7 (10)

ECOG: Eastern Cooperative Oncology Group; HCT-CI: Hematopoietic stem cell transplant comorbidity index; MSD: Matched sibling donor; MORD: Matched other related donor; MUD: Matched unrelated donor; CR: Complete remission; TBI: Total body irradiation; MAC: Myeloablative conditioning; RIC/NMA: Reduced intensity conditioning/non-myeloablative.

improved survival compared to those in CR2 or CR3 with 2-year OS of 69.5% *vs* 46.5% *vs* 25% with a trend towards significance (P = 0.083) as shown in Figure 2A. On the other hand, when stratified by presence of cGVHD post HCT, patients with evidence of cGVHD had a significantly improved outcome with a 2-year OS of 70% *vs* 47.6% (p = 0.033) as shown in Figure 2B.

Predictors of outcome: In multivariable analysis for PFS or OS as the outcome of interest, the following variables were included; age at HCT, cell subtype, ALL *vs* LBL, Ph-chromosome status, female donor to male recipient, donor gender mismatch, MSD *vs* other donor source, TBI containing regimen, MAC regimen *vs* other, CR1 *vs* other, acute or cGVHD. For PFS, aGVHD and cGVHD were significant for PFS with corresponding HR of 3.14 (1.36-7.1; P = 0.008) and HR 0.38 (0.15-0.89; P = 0.026), respectively. Whereas for OS aGVHD and cGVHD were significant at the multivariable analysis with HR 4.9 (1.99-12; P = 0.0007) and 0.29 (0.1-0.67; P = 0.0044), respectively. These results are shown in Table 2.

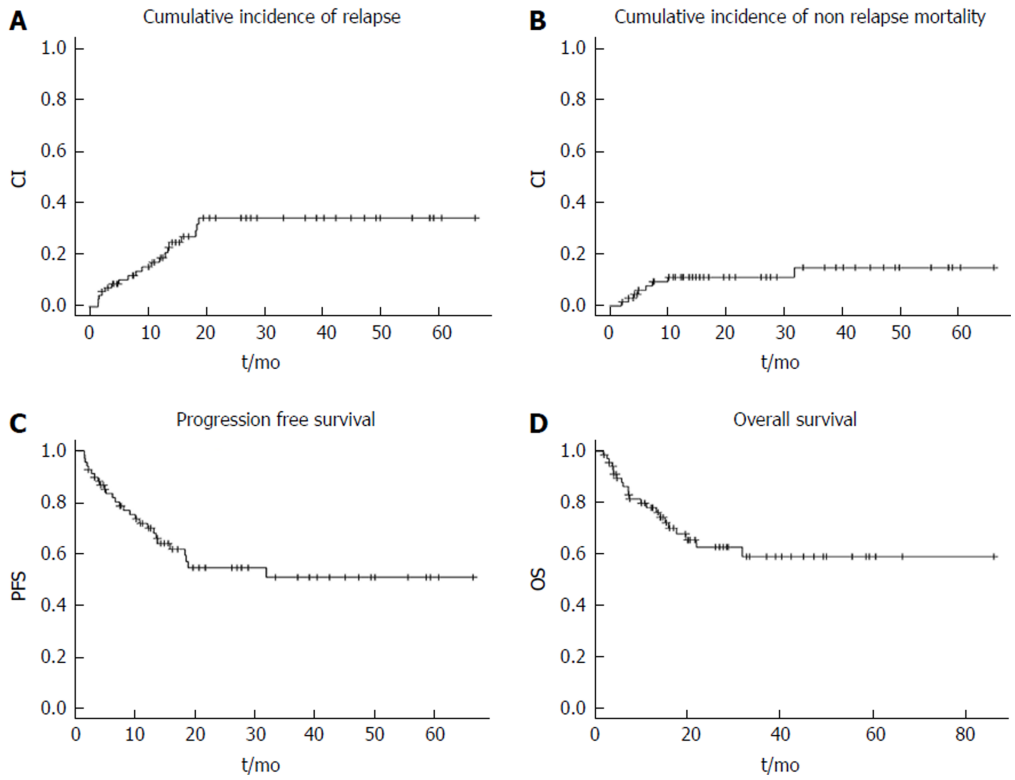

Figure 1 Outcome of post hematopoietic stem cell transplant for high risk acute lymphoblastic leukemia/lymphoma. A: Cumulative incidence of relapse; B: Cumulative incidence of non-relapse mortality; C: Progression free survival; D: Overall survival. PFS: Progression free survival; OS: Overall survival; CI: Cumulative incidence.

DISCUSSION

The optimal post remission therapy in ALL/LBL continues to be debated amongst experts given the ongoing developments in the field. On the one hand, allogeneic HCT offers good disease control relative to chemotherapy alone but the potential toxicity depending on prior therapy and hematopoietic stem cell transplant comorbidity index (HCT-CI) can be a hindering factor for some patients[15]. On the other hand, more refined methods of risk stratification specifically with the use of MRD and the utilization of a pediatric inspired regimens in eligible patients have significantly reduced relapse rates[16]. Importantly, optimal therapy should be delivered upfront as outcome of these patients post relapse are inferior. Oriol *et al*[17] reported on outcome of ALL patients with relapsed disease treated on one of four risk adapted trials by the PETHEMA study group. Only 10% of patients were alive at 5 years but more favorable outcomes were seen in younger patients and those relapsing late beyond 2 years.

A large comparative study examined 422 Ph negative ALL patients who underwent HCT in CR1 from the Center of International Blood and Marrow Transplantation Research (CIBMTR) to an age matched concurrent cohort of 108 patients treated with the Dana-Farber Consortium (DFC) Pediatric protocol found that while the relapse rate was similar among both approaches, patients fared significantly better with the DFC mainly due to a transplant related mortality (TRM) of 37%[18]. With regards to chemotherapy regimen comparison, the MD Anderson Cancer Center performed a comparative analysis between HyperCVAD, a common regimen for ALL used at their institution and the Augmented Berlin-Frankfurt-Munster (ABFM)[19]. Both regimens were associated with comparable overall outcomes, but with differing adverse event profile; ABFM resulting in higher hepatotoxicity, pancreatitis and osteonecrosis whereas HyperCVAD resulting in more bone marrow suppression related toxicity. Of note, the 5-year OS was 60% in both groups and around 10% of patients underwent HCT in CR1. Collectively, it remains unclear which treatment modality is preferred and further studies are needed to resolve this debate. The heterogeneity within the inclusion criteria among studies is the likely result in such discrepant outcomes.

Our aim with this analysis was to ascertain outcome of patients whom underwent HCT for ALL/LBL at our center. The patients presented herein were all those with high risk features, *i.e.*, conventional risk factors, positive MRD or those with relapsed

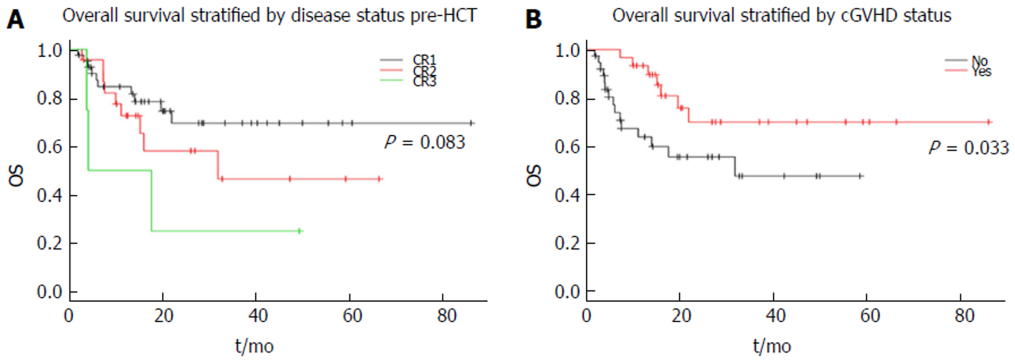

Figure 2 Overall survival of high risk acute lymphoblastic leukemia. A: Stratified by remission status prior to transplantation; B: Stratified by chronic graft *vs* host disease status HCT: Hematopoietic stem cell transplant; OS: Overall survival; cGVHD: Chronic graft *vs* host disease.

disease in second or subsequent remissions. We observed an OS of 62.8% at 2-year for the entire cohort which is quite promising. Furthermore, the CIR at 2-years was 34.1% for the entire cohort irrespective of the remission status at HCT. The majority of patients in this cohort underwent HCT utilizing MAC intensity conditioning and a MSD. Previously, the largest prospective trial in ALL, *i.e.*, the ECOG/MRC trial cohort reported a 5-year OS of 41% for high risk patients undergoing HCT in CR1[7]. Interestingly, the relapse rate observed within this trial was 37% for the high risk group and 24% within the standard risk which was comparable to our cohort. However, the incidence of NRM within the high risk cohort was 35.8% at 2-years which is substantially higher than what we observed despite having similar HCT criteria. We have two plausible observations that could have resulted in such higher NRM; first, the median age within our cohort was younger, and as such the expected complications post HCT are likely to be lower. This was reported previously where younger patients were reported to fare better than their older counterparts which was largely driven by higher incidence of NRM, whereas disease control with HCT is the same[20]. Second, the changes in supportive care over the last 1-2 decades, particularly with the use of antimicrobials for prophylaxis and management could have led to a reduction in post HCT complications[21].

Subsequently, we analyzed the cohort to ascertain factors influencing outcome at the multivariable analysis stage. We included typical patient, disease and transplant variables that may impact outcome. We observed that acute and chronic GVHD predicted for OS. There was a trend towards significance for B-cell subtype and CR1 remission status for OS and perhaps a larger sample size could have identified such variables as significant as well. Interestingly in our cohort, presence of Ph chromosome did not portend a negative prognostic marker and is likely due to the use of dasatinib as targeted TKI therapy during induction and as post HCT maintenance.

Allogeneic HCT is favored as post remission therapy due to relatively potent graft *vs* leukemia effect. Although difficult to measure or quantify, it is felt that cGVHD is a surrogate for such GVL effect[22,23]. Such effect is felt to be mediated by a number of donor factors but perhaps largely T-lymphocytes that exhibit their role by targetting any residual leukemia cells and prolonging patient's remission. However, this is a double edged sword as significant GVHD can augment the NRM effect and lead to more detrimental outcomes. Our patients experienced largely mild to moderate cGVHD, possibly due to majority of donors being MRD and we observed a favorable effect of such cGVHD on OS. aGVHD on the other hand had a detrimental impact on OS with a high case fatality ratio due to organ toxicity or infectious complications. Lastly, all B-ALL/LBL within this cohort received the monoclonal antibody rituximab, if CD20 positive, and it is possible that this has contributed to the trend of improved OS seen within our cohort. Previously, multiple studies reported on the favorable impact of rituximab on the outcome of ALL including Burkitt type ALL[24-26].

This analysis has some inherent limitations, particularly with its retrospective single center design and sample size. However, a number of important observations were noted; First, conventional high risk features of ALL/LBL can be overcome by the conditioning effect of the transplant coupled by the GVL effect. This is evident as the survival curve has plateaued indicating the curative potential of this therapy. Second, cGVHD leads to enhanced OS likely as it represents a surrogate for GVL. Third, aGVHD can be detrimental to outcome as it causes significant morbidity and mortality mainly due to infectious complications. In conclusion, allogeneic-HCT for high risk ALL/LBL results in promising remissions in high risk disease and early

Table 2 Univariable and multivariable risk factors influencing post hematopoietic stem cell transplant outcome

		Univariable HR (95%CI; *P* value)	Multivariable HR (95%CI; *P* value)
PFS	Age at HCT	1.5 (0.27-6; *P* = 0.6)	
	B-cell *vs* T-cell	0.53 (0.25-1.17; *P* = 0.11)	
	ALL *vs* LBL	0.6 (0.27-1.45; *P* = 0.24)	
	Female D → male R	0.87 (0.25-2.26; *P* = 0.79)	
	Donorgender mismatch	0.53 (0.22-1.17; *P* = 0.12)	
	MSD *vs* other	0.5 (0.22-1.28; *P* = 0.14)	
	TBI regimen	1.1 (0.41-3.67; *P* = 0.89)	
	MAC *vs* RIC/NMA	1.37 (0.41-8.5; *P* = 0.65)	
	CR1 *vs* other	0.59 (0.28-1.28; *P* = 0.18)	
	aGVHD	2.1 (0.95-4.5; *P* = 0.066)	3.14 (1.36-7.1; *P* = 0.008)
	cGVHD	0.43 (0.18-0.94; *P* = 0.033)	0.38 (0.15-0.89; *P* = 0.026)
OS	Age at HCT	1.02 (0.98-1.05; *P* = 0.28)	
	B-cell *vs* T-cell	0.57 (0.24-1.37; *P* = 0.2)	
	ALL *vs* LBL	0.44 (0.19-1.11; *P* = 0.08)	
	Female D → male R	1.15 (0.33-3.1; *P* = 0.8)	
	Donorgender mismatch	0.62 (0.23-1.48; *P* = 0.29)	
	MSD *vs* other	1.27 (0.43-5.4; *P* = 0.69)	
	TBI regimen	1.99 (0.58-12.5; *P* = 0.31)	
	MAC *vs* RIC/NMA	0.69 (0.23-2.92; *P* = 0.56)	
	CR1 *vs* other	0.5 (0.21-1.17; *P* = 0.11)	
	aGVHD	3.35 (1.42-7.9; *P* = 0.006)	4.9 (1.99-12; *P* = 0.0007)
	cGVHD	0.4 (0.15-0.97; *P* = 0.043)	0.29 (0.1-0.67; *P* = 0.0044)

HCT: Hematopoietic stem cell transplant; ALL: Acute lymphoblastic leukemia; LBL: Lymphoblastic lymphoma; Ph: Philadelphia chromosome; MSD: Matched sibling donor; TBI: Total body irradiation; CR: Complete remission; MAC: Myeloablative conditioning; RIC/NMA: Reduced intensity conditioning/no myeloablative; a/cGVHD: Acute/chronic graft *vs* host disease.

referral for HCT to be considered for young and fit patients.

ARTICLE HIGHLIGHTS

Research background

Allogeneic hematopoietic stem cell transplantation (HCT) is a potentially curative therapy for patients with high risk acute lymphoblastic leukemia (ALL). The indications for HCT have evolved over time with the introduction of pediatric inspired protocols and minimal residual disease (MRD) monitoring. Our aim from this study is to examine the outcome and prognostic factors for high risk ALL patients at our center.

Research motivation

Identifying the prognostic factors that may facilitate patient selection and select the ideal candidate for transplantation.

Research objectives

Our aim from this study is to examine the outcome and prognostic factors for high risk ALL patients.

Research methods

After due institutional review board approval, patients with high risk ALL/ lymphoblastic lymphoma (LBL) post HCT were identified and included. All records were retrospectively collected. Time to event analysis, was calculated from the date of HCT until event of interest or last follow up with KM means. Cox regression model was used for multivariable analysis calculation.

Research results

A total of 69 patients were enrolled and examined with a median age of 21 (14-61). After a median follow up of 15 mo (2-87.3), the 2-year cumulative incidence of relapse (CIR), cumulative incidence of non-relapse mortality (CI-NRM), progression free survival (PFS) and overall survival (OS) were 34.1%, 10.9%, 54.9% and 62.8%, respectively. In a multivariable analysis for OS; acute graft *vs* host disease (GVHD) and chronic GVHD were significant with corresponding

HR 4.9 (1.99-12; P = 0.0007) and 0.29 (0.1-0.67; P = 0.0044), respectively.

Research conclusions

Allogeneic-HCT for high risk ALL/LBL results in promising remissions and early referral for HCT is to be considered for young and fit patients.

Research perspectives

We identified that acute and chronic graft *vs* host diseases were prognostic for overall survival. We also observed that patients with Philadelphia positive ALL whom were given tyrosine kinase inhibitor therapy fared better than expected. Post HCT outcome of patients with ALL is expected to improve over time with the changing therapeutic landscape. We wished to examine the outcome of ALL patients treated in a contemporary era and identify prognostic factors for outcome. Our findings warrant confirmation in a larger cohort of patients.

REFERENCES

1 **Fielding AK**, Richards SM, Chopra R, Lazarus HM, Litzow MR, Buck G, Durrant IJ, Luger SM, Marks DI, Franklin IM. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. *Blood* 2007; **109**: 944-950 [PMID: 17032921 DOI: 10.1182/blood-2006-05-018192]

2 **Thomas DA**, O'Brien S, Jorgensen JL, Cortes J, Faderl S, Garcia-Manero G, Verstovsek S, Koller C, Pierce S, Huh Y. Prognostic significance of CD20 expression in adults with de novo precursor B-lineage acute lymphoblastic leukemia. *Blood* 2009; **113**: 6330-6337 [PMID: 18703706 DOI: 10.1182/blood-2008-04-151860]

3 **Rowe JM**. Prognostic factors in adult acute lymphoblastic leukaemia. *Br J Haematol* 2010; **150**: 389-405 [PMID: 20573154 DOI: 10.1111/j.1365-2141.2010.08246.x]

4 **Sebban C**, Lepage E, Vernant JP, Gluckman E, Attal M, Reiffers J, Sutton L, Racadot E, Michallet M, Maraninchi D. Allogeneic bone marrow transplantation in adult acute lymphoblastic leukemia in first complete remission: a comparative study. French Group of Therapy of Adult Acute Lymphoblastic Leukemia. *J Clin Oncol* 1994; **12**: 2580-2587 [PMID: 7989932 DOI: 10.1200/JCO.1994.12.12.2580]

5 **Thomas X**, Boiron JM, Huguet F, Dombret H, Bradstock K, Vey N, Kovacsovics T, Delannoy A, Fegueux N, Fenaux P. Outcome of treatment in adults with acute lymphoblastic leukemia: analysis of the LALA-94 trial. *J Clin Oncol* 2004; **22**: 4075-4086 [PMID: 15353542 DOI: 10.1200/JCO.2004.10.050]

6 **Hunault M**, Harousseau JL, Delain M, Truchan-Graczyk M, Cahn JY, Witz F, Lamy T, Pignon B, Jouet JP, Garidi R, Caillot D, Berthou C, Guyotat D, Sadoun A, Sotto JJ, Lioure B, Casassus P, Solal-Celigny P, Stalnikiewicz L, Audhuy B, Blanchet O, Baranger L, Béné MC, Ifrah N; GOELAMS (Groupe Ouest-Est des Leucémies Airguës et Maladies du Sang) Group. Better outcome of adult acute lymphoblastic leukemia after early genoidentical allogeneic bone marrow transplantation (BMT) than after late high-dose therapy and autologous BMT: a GOELAMS trial. *Blood* 2004; **104**: 3028-3037 [PMID: 15256423 DOI: 10.1182/blood-2003-10-3560]

7 **Goldstone AH**, Richards SM, Lazarus HM, Tallman MS, Buck G, Fielding AK, Burnett AK, Chopra R, Wiernik PH, Foroni L. In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). *Blood* 2008; **111**: 1827-1833 [PMID: 18048644 DOI: 10.1182/blood-2007-10-116582]

8 **Cornelissen JJ**, van der Holt B, Verhoef GE, van't Veer MB, van Oers MH, Schouten HC, Ossenkoppele G, Sonneveld P, Maertens J, van Marwijk Kooy M. Myeloablative allogeneic versus autologous stem cell transplantation in adult patients with acute lymphoblastic leukemia in first remission: a prospective sibling donor versus no-donor comparison. *Blood* 2009; **113**: 1375-1382 [PMID: 18988865 DOI: 10.1182/blood-2008-07-168625]

9 **Majhail NS**, Farnia SH, Carpenter PA, Champlin RE, Crawford S, Marks DI, Omel JL, Orchard PJ, Palmer J, Saber W. Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant* 2015; **21**: 1863-1869 [PMID: 26256941 DOI: 10.1016/j.bbmt.2015.07.032]

10 **Sureda A**, Bader P, Cesaro S, Dreger P, Duarte RF, Dufour C, Falkenburg JH, Farge-Bancel D, Gennery A, Kröger N. Indications for allo- and auto-SCT for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2015. *Bone Marrow Transplant* 2015; **50**: 1037-1056 [PMID: 25798672 DOI: 10.1038/bmt.2015.6]

11 **Bacigalupo A**, Ballen K, Rizzo D, Giralt S, Lazarus H, Ho V, Apperley J, Slavin S, Pasquini M, Sandmaier BM. Defining the intensity of conditioning regimens: working definitions. *Biol Blood Marrow Transplant* 2009; **15**: 1628-1633 [PMID: 19896087 DOI: 10.1016/j.bbmt.2009.07.004]

12 **Solomon SR**, Sizemore CA, Sanacore M, Zhang X, Brown S, Holland HK, Morris LE, Bashey A. Total Body Irradiation-Based Myeloablative Haploidentical Stem Cell Transplantation Is a Safe and Effective Alternative to Unrelated Donor Transplantation in Patients Without Matched Sibling Donors. *Biol Blood Marrow Transplant* 2015; **21**: 1299-1307 [PMID: 25797174 DOI: 10.1016/j.bbmt.2015.03.003]

13 **Luznik L**, O'Donnell PV, Symons HJ, Chen AR, Leffell MS, Zahurak M, Gooley TA, Piantadosi S, Kaup M, Ambinder RF. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. *Biol Blood Marrow Transplant* 2008; **14**: 641-650 [PMID: 18489989 DOI: 10.1016/j.bbmt.2008.03.005]

14 **Kanda Y**. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant* 2013; **48**: 452-458 [PMID: 23208313 DOI: 10.1038/bmt.2012.244]

Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, Storer B. Hematopoietic

15 cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood* 2005; **106**: 2912-2919 [PMID: 15994282 DOI: 10.1182/blood-2005-05-2004]

16 **Dhédin N**, Huynh A, Maury S, Tabrizi R, Beldjord K, Asnafi V, Thomas X, Chevallier P, Nguyen S, Coiteux V. Role of allogeneic stem cell transplantation in adult patients with Ph-negative acute lymphoblastic leukemia. *Blood* 2015; **125**: 2486-96; quiz 2586 [PMID: 25587040 DOI: 10.1182/blood-2014-09-599894]

17 **Oriol A**, Vives S, Hernández-Rivas JM, Tormo M, Heras I, Rivas C, Bethencourt C, Moscardó F, Bueno J, Grande C. Outcome after relapse of acute lymphoblastic leukemia in adult patients included in four consecutive risk-adapted trials by the PETHEMA Study Group. *Haematologica* 2010; **95**: 589-596 [PMID: 20145276 DOI: 10.3324/haematol.2009.014274]

18 **Seftel MD**, Neuberg D, Zhang MJ, Wang HL, Ballen KK, Bergeron J, Couban S, Freytes CO, Hamadani M, Kharfan-Dabaja MA. Pediatric-inspired therapy compared to allografting for Philadelphia chromosome-negative adult ALL in first complete remission. *Am J Hematol* 2016; **91**: 322-329 [PMID: 26701142 DOI: 10.1002/ajh.24285]

19 **Rytting ME**, Jabbour EJ, Jorgensen JL, Ravandi F, Franklin AR, Kadia TM, Pemmaraju N, Daver NG, Ferrajoli A, Garcia-Manero G. Final results of a single institution experience with a pediatric-based regimen, the augmented Berlin-Frankfurt-Münster, in adolescents and young adults with acute lymphoblastic leukemia, and comparison to the hyper-CVAD regimen. *Am J Hematol* 2016; **91**: 819-823 [PMID: 27178680 DOI: 10.1002/ajh.24419]

20 **Burke MJ**, Gossai N, Wagner JE, Smith AR, Bachanova V, Cao Q, MacMillan ML, Stefanski HS, Weisdorf DJ, Verneris MR. Survival differences between adolescents/young adults and children with B precursor acute lymphoblastic leukemia after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 2013; **19**: 138-142 [PMID: 22960388 DOI: 10.1016/j.bbmt.2012.08.020]

21 **Brissot E**, Rialland F, Cahu X, Strullu M, Corradini N, Thomas C, Blin N, Rialland X, Thebaud E, Chevallier P. Improvement of overall survival after allogeneic hematopoietic stem cell transplantation for children and adolescents: a three-decade experience of a single institution. *Bone Marrow Transplant* 2016; **51**: 267-272 [PMID: 26642337 DOI: 10.1038/bmt.2015.250]

22 **Appelbaum FR**. Graft versus leukemia (GVL) in the therapy of acute lymphoblastic leukemia (ALL). *Leukemia* 1997; **11** Suppl 4: S15-S17 [PMID: 9179275]

23 **Kolb HJ**. Graft-versus-leukemia effects of transplantation and donor lymphocytes. *Blood* 2008; **112**: 4371-4383 [PMID: 19029455 DOI: 10.1182/blood-2008-03-077974]

24 **Maury S**, Chevret S, Thomas X, Heim D, Leguay T, Huguet F, Chevallier P, Hunault M, Boissel N, Escoffre-Barbe M. Rituximab in B-Lineage Adult Acute Lymphoblastic Leukemia. *N Engl J Med* 2016; **375**: 1044-1053 [PMID: 27626518 DOI: 10.1056/NEJMoa1605085]

25 **Levato L**, Molica S. Rituximab in the management of acute lymphoblastic leukemia. *Expert Opin Biol Ther* 2018; **18**: 221-226 [PMID: 29310477 DOI: 10.1080/14712598.2018.1425389]

26 **Hoelzer D**, Walewski J, Döhner H, Viardot A, Hiddemann W, Spiekermann K, Serve H, Dührsen U, Hüttmann A, Thiel E. Improved outcome of adult Burkitt lymphoma/leukemia with rituximab and chemotherapy: report of a large prospective multicenter trial. *Blood* 2014; **124**: 3870-3879 [PMID: 25359988 DOI: 10.1182/blood-2014-03-563627]

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