

CLINICAL PRACTICE RESEARCH

Outcomes from the first five years of allogeneic haemopoietic progenitor cell transplantation at Fiona Stanley Hospital

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ABSTRACT

Background Allogeneic haemopoietic progenitor cell transplantation (alloHPCT, previously known as ‘stem cell transplantation’) is the only curative procedure for many haematological malignancies (for example, acute leukaemia), and non-malignant conditions such as bone marrow failure and myelodysplasia. Fiona Stanley Hospital (FSH), a new tertiary metropolitan hospital in Perth Western Australia opened in 2015. A Blood and Marrow Transplant Programme (BMTP) was established and replaced the previous State service at Royal Perth Hospital. We describe here the patient demographics and outcomes of alloHPCT at FSH BMTP since its establishment in 2015.

Methods One hundred and ninety-three consecutive adult patients who had alloHPCT were identified retrospectively from 1 February 2015 to 31 December 2019. Pre-transplant, transplant and clinical outcome characteristics were analysed.

Results Acute myeloid leukaemia (AML) was the most common indication for transplant (n = 82, 42.5%) followed by myelodysplasia (16.1%). The median time from diagnosis to alloHPCT in patients with AML in first complete remission was 5.7 m (range, 2.4 – 28.4). The cumulative incidence of grade III-IV aGVHD at 6 months was 10.4% (95% CI 6.5 – 15.4%) and the cumulative incidence of severe cGVHD at 2 years was 10.2% (95% CI 5.7 – 16.3%). The median follow-up was 24.3 m (range, 5.9 – 62.1). Overall survival at 1 and 2 years was 73.7% (95% CI 70.1 – 77.3%) and 65.0% (95% CI 61.2 – 68.8%) respectively. Progression-free survival at 2-years was 62.9% (95% CI 59.6 – 66.2%). The cumulative risk of transplant-related mortality at 2-years was 17.8% (95% CI 12.6 – 23.7%), and disease relapse at 2-years was 19.3% (95% CI 13.8 – 25.6%).

Conclusions Clinical outcomes of allogeneic transplantation at the FSH BMTP appear acceptable and are comparable to those reported elsewhere within Australia and overseas. This information is valuable for transplant physicians, referrers and patients in Western Australia and will inform future practice improvement activities in this high risk and complex medical procedure.

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INTRODUCTION

Allogeneic haemopoietic progenitor cell transplantation (alloHPCT) involves the infusion of third party-derived haemopoietic precursor cells into a recipient who has

undergone sufficient chemotherapy or radiotherapy conditioning treatment to allow engraftment of these cells and eventually full haemopoietic and immunological reconstitution. The treatment is

effective as replacement of haemopoiesis in bone marrow failure syndromes, and allows high doses of chemotherapy as well as life-long immunological surveillance against relapse to treat malignant conditions. Donors are preferentially siblings who are human leukocyte antigen (HLA) matched at both class I and II loci, HLA-matched unrelated donors, or alternative donors such as partially matched unrelated adult, related adult or cryopreserved umbilical cord blood products. In usual circumstances, donor cells are infused 'fresh', immediately after collection, into a recipient who has just received conditioning therapy. Risks to recipients include toxicity of chemotherapy or radiotherapy, infection during aplasia or immunological reconstitution, relapse and graft-versus-host disease.

Western Australia (WA) has a population of 2.7 million (December 2019) and more than 80 hospitals spread across 2.5 million square kilometers (1, 2). The wide catchment area poses a challenge in providing timely and equitable healthcare to the population. A new flagship tertiary metropolitan hospital (Fiona Stanley Hospital (FSH)) with 783 beds was opened in February 2015(3). The Bone Marrow Transplantation Programme (BMTP) at FSH provides a central state-wide service for all adult alloHPCT in WA. Transitioning the service from pre-existing tertiary hospitals and creating a new centre to cater for increasing demands can be challenging. This study aimed to assess the service delivery and outcomes of patients undergoing alloHPCT at FSH since the opening.

MATERIAL AND METHODS

Patient selection and characteristics

We retrospectively analysed consecutive 193 adult patients having alloHPCT under the BMTP at FSH, from 1 February 2015 to 31 December 2019. Exclusion criteria included syngeneic transplants ($n = 1$) and patients who underwent a second alloHPCT during the study period ($n = 1$). The total number of alloHPCT per year in Western Australia since 2007 was also recorded. Ethics approval for data collection was granted by FSH Department of Safety, Quality and Risk, and all patients signed informed consent for the collection of their data for research purposes.

Patient characteristics collected included age of recipient at the time of transplantation, sex, Karnofsky performance status, and pre-transplant disease characteristics (diagnosis type, date of diagnosis and disease status). Transplant characteristics included

number of previous alloHPCT, type of conditioning, graft source and donor match, use of anti-thymocyte globulin (ATG) and GVHD prophylaxis. The Haemopoietic Comorbidity Index (HCT-CI), which incorporates pre-transplant clinical history, pulmonary function, liver and renal function results to determine risk of transplant-related mortality, and the revised Disease Risk Indices (DRI), which groups haematological malignancies according to relapse risk, were calculated according to published sources (4, 5).

Acute graft-versus-host disease (aGVHD) was graded according to published consensus criteria, and chronic graft-versus-host disease (cGVHD) as classified according to revised 2014 NIH criteria (6, 7). The cumulative incidence of aGVHD grade II to grade IV at 6 months and aGVHD grade III to IV at 6 months were analysed. For cGVHD, only patients who survived more than 100 days were included in the analysis. Patients who had alloHPCT from 1 July 2019 were excluded to allow for sufficient clinical data being available for at least 6 months follow up. The cumulative incidence of cGVHD of any severity, moderate or severe, and of severe only after 2 years of follow-up, were analysed. Immunosuppression was defined as at least 5mg prednisolone or equivalent, or other systemic immunosuppressive agent at any dose.

Neutrophil engraftment was defined as the first day of absolute neutrophil count $\geq 0.5 \times 10^9/L$ for at least 3 consecutive days. Platelet engraftment was defined as the first day of platelet count $\geq 20 \times 10^9/L$ for at least 7 days without platelet transfusions.

Statistical analysis

The median and range was calculated for continuous variables. The probabilities of overall survival (OS) and progression-free survival (PFS) were calculated using the Kaplan-Meier method. Probabilities of aGVHD, cGVHD, transplant-related mortality (TRM) and relapse were calculated using cumulative incidence analysis to accommodate competing risks (8). Death without aGVHD or cGVHD was the competing risk for its respective cumulative incidence. Relapse was used as competing risk for TRM and death without disease relapse as the competing risk for relapse. Ninety-five percent confidence intervals for probabilities were derived from point-wise estimates and were calculated using standard techniques. Statistical analyses were performed using SPSS® statistical software (version 23; Chicago, IL).

Characteristics	n = 193
Median age at BMT, years (range)	51 (16 - 67)
Gender, n (%)	
Male	116 (60.1)
Female	77 (39.9)
Diagnosis, n (%)	
AML	82 (42.5)
MDS	31 (16.1)
ALL	27 (14.0)
NHL	22 (11.4)
Myelofibrosis	13 (6.7)
Aplastic anaemia	6 (3.1)
HD	5 (2.6)
CLL	3 (1.6)
Multiple myeloma	2 (1.0)
CML	2 (1.0)
Median time from diagnosis to BMT, months (range)	9.4 (2.0 - 301.2)
AML in CR1	5.7 (2.4 - 28.4)
ALL in CR1	8.6 (4.6 - 12.6)
Prior BMT, n (%)	
0	189 (97.9)
1	4 (2.1)
Donor, n (%)	
HLA-identical Sibling	62 (32.1)
Unrelated Donor	124 (64.2)
Mismatched Related	7 (3.6)
Graft source, n (%)	
Bone Marrow	14 (7.3)
Peripheral Blood	175 (90.7)
Umbilical Cord Blood	4 (2.1)
Conditioning, n (%)	
RIC	96 (49.7)
MAC	97 (50.3)
Anti-thymocyte globulin use, n (%)	29 (15)
GVHD prophylaxis, n (%)	
CsA	1 (0.5)
CsA + MTX	180 (93.3)
CsA + MMF	6 (3.1)
CsA or tacrolimus + MMF + post-transplant cyclophosphamide	6 (3.1)
Karnofsky performance status, n (%)	
≥ 90%	148 (76.7)
< 90%	34 (17.6)
Unknown	11 (5.7)
Haemopoietic comorbidity index (HCT-CI), n (%)	
0	54 (28)
1-2	28 (14.5)
3 or higher	34 (17.6)
Unknown	77 (39.9)
Refined disease risk indices (DRI), n (%)	
Low	17 (8.8)
Intermediate	124 (64.2)
High	38 (19.7)
Very high	8 (4.1)
Unclassifiable	6 (3.1)

Table 1. Patient and transplant-related characteristics. BMT = bone marrow transplantation; AML = acute myeloid leukaemia; MDS = myelodysplastic syndrome; ALL = acute lymphoblastic leukaemia; NHL = non-Hodgkin's lymphoma; HD = Hodgkin's lymphoma; CLL = chronic lymphocytic leukaemia; CML = chronic myeloid leukaemia; CR1 = first complete remission; RIC = reduced intensity conditioning; MAC = myeloablative conditioning; GVHD = graft-versus-host disease; CsA = cyclosporin; MTX = methotrexate; MMF = mycophenolate

USA), GraphPad Prism (version 8.4.3; La Jolla, CA, USA) and R (version 4.0.2; cran.r-project.org) on the RStudio platform (version 1.3.1056; Boston, MA, USA).

RESULTS

The total annual number of patients undergoing alloHPCT in WA has been increasing progressively since 2007 (Fig. 1), and reached 54 patients in 2019.

Patient, disease, and transplant-related characteristics

The characteristics of patients who had alloHPCT are summarised in Table 1. Median age at transplant was 51 y (range, 16 – 67 y) and 60.1% were males. Acute myeloid leukaemia was the most common indication (42.5%), followed by myelodysplastic syndromes (16.1%). Median time from diagnosis to alloHPCT (all patients) was 9.4 months (range, 2.0 – 301.2 [one patient was diagnosed in 1992]). In patients with AML who were in their first complete remission the median time from diagnosis to alloHPCT was 5.7 m (range, 2.4 – 28.4 m). The corresponding datum for patients with acute lymphoblastic leukaemia (ALL) in CR1 was 8.6 m (range, 4.6 – 12.6 m).

Referrals for AML in the most recent two years of the study period were analysed to reveal patterns of referral and transplantation. Of 41 referrals, 27 (65.9%) received alloHSCT, 26.8% were deemed not suitable or declined transplant, and 7.3% died before transplant. Median time from referral to review in transplant clinic was 26 days (range 7-105 days) and did not differ according to referring centre ($p = 0.534$).

The majority of patients (64.2%) received transplants from unrelated donors. Peripheral blood was the most common graft source (90.7%). Reduced intensity conditioning (RIC) was used in 49.7% of all recipients. A minority ($n = 29$, 15%) received anti-thymocyte globulin. Cyclosporin combined with methotrexate was the most frequently used prophylaxis for graft-versus-host disease (93.3%).

The baseline Karnofsky performance status of the cohort at time of transplant was $\geq 90\%$ in 76.7% of patients. Eleven patients did not have performance status recorded. The pre-transplant HCT-CI score was 0 in 28% of patients, 1-2 in 14.5%, and 3 or higher in 17.6% of patients. HCT-CI was not recorded in 39.9% of patients, and was more likely to be missing for patients undergoing transplant during the early years of the programme (30 in 2016 vs. 0 in 2019). The pre-transplant refined DRI score was ‘Low’ in 8.8%,

‘Intermediate’ in 64.2%, ‘High’ in 19.7% and ‘Very High’ in 4.1% of the cohort. Six patients were unclassifiable as their pre-transplant disease was aplastic anaemia.

Characteristic	Number (% or CI)*
aGVHD, n (%)	
None	92 (47.7)
Grade I	36 (18.7)
Grade II	46 (23.8)
Grade III	13 (6.7)
Grade IV	6 (3.1)
Cumulative incidence of grade II-IV aGVHD at 6 months, % (95% C.I)	35.4 (28.4 - 42.4)
Cumulative incidence of grade III-IV aGVHD at 6 months, % (95% C.I)	10.4 (6.5 - 15.4)
Cumulative incidence of cGVHD, % (95% C.I)	
Any cGVHD at 2 years	67.0 (58.3 – 74.3)
Moderate and severe at 2 y	29.6 (21.9- 37.7)
Severe at 2 years	10.2 (5.7 - 16.3)
Immunosuppression, n (% of patients alive at timepoint)	
12 months	81 (68.1)
24 months	41 (50.0)

Table 2. Graft-versus-host disease and immunosuppression

GVHD incidence

The graft-versus-host disease outcomes are summarised in Table 2. Overall, 101 patients were diagnosed with aGVHD of any grade and 92 patients had no aGVHD. The cumulative incidence probabilities are outlined on Fig. 2. The cumulative incidence of grade II to IV aGVHD at 6 months was 35.4% (95% CI 28.4 – 42.4%) (Fig. 2a). The cumulative incidence of grade III or IV aGVHD at 6 m was 10.4% (95% CI 6.5 – 15.4%) (Fig. 2b).

In patients who survived >100 days after alloHPCT and had transplant between 1 February 2015 to 30 June 2019 ($n = 147$), the cumulative incidence of cGVHD of any severity at 2 years was 67.0% (95% CI 58.3 – 74.3%). The cumulative incidence of moderate or severe cGVHD at 2 years was 29.6% (95% CI 21.9 – 37.7%) (Fig. 2c). The cumulative incidence of severe cGVHD at 2 years was 10.2% (95% CI 5.7 – 16.3%) (Fig. 2d).

In survivors twelve and 24 m after alloHPCT, 68.1% and 50.0% of patients remained on immunosuppression.

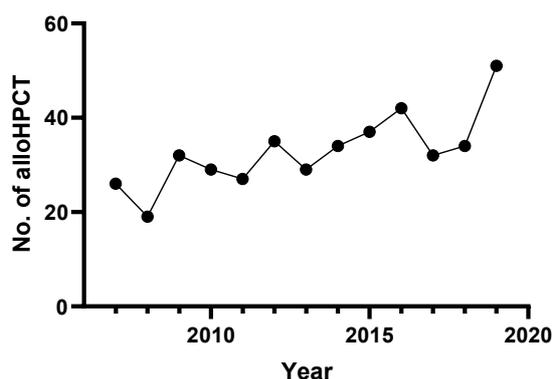


Fig. 1: Total number of allogeneic haematopoietic progenitor cell transplantations per year in Western Australia. The Fiona Stanley Hospital BMTP replaced the Royal Perth Hospital programme in February 2015.

Outcome	N or % (range)
Median follow-up, months (range)	24.3 (5.9 - 62.1)
Neutrophil recovery, n (%)	183 (94.8)
Median time to neutrophil engraftment, days (range)	16 (6 - 36)
Platelet recovery, n (%)	171 (88.6)
Median time to platelet engraftment, days (range)	18 (6 - 136)
OS % (95% C.I.)	
1-year	73.7 (70.1 - 87.3)
2-year	65.0 (61.2 - 68.8)
OS by disease, 2-year, % (95% C.I.)	
AML	62.3 (50.9 - 73.7)
ALL	64.8 (46.0 - 83.6)
Lymphoma	64.3 (42.7 - 85.9)
MDS	65.7 (48.3 - 83.1)
Myelofibrosis	92.3 (77.8 - 106.8)
PFS, % (95% C.I.)	
1-year	67.4 (64.1 - 70.7)
2-years	62.9 (59.6 - 66.2)
TRM, % (95% C.I.)	
3-months	10.4 (6.6 - 15.2)
1-year	16.9 (11.9 - 22.6)
2-year	17.8 (12.6 - 23.7)
Relapse, % (95% C.I.)	
3-months	5.2 (2.6 - 9.0)
1-year	15.7 (9.3 - 19.1)
2-year	19.3 (13.8 - 25.6)

Table 3. Engraftment and survival outcomes. For abbreviations, see text.

Engraftment and survival outcomes

Clinical outcomes and survival end-points are described on Table 3. Median follow-up was 24.3 m (range, 5.9 – 62.1 m). The median time to neutrophil engraftment was 16 days (range, 6 – 36 days) and 94.8% of patients achieved neutrophil recovery. Median time to platelet engraftment was 18 days (range, 6 – 136 days) and 88.6% achieved platelet recovery.

The estimated OS for the entire cohort at 1 year was 73.7% (95% CI 70.1 – 77.3%) and the 2-year OS was 65.0% (95% CI 61.2 – 68.8%) (Fig. 3a). The estimated PFS at 1-year was 67.4% (95% CI 64.1 – 70.7%) and PFS at 2-years was 62.9% (95% CI 59.6 – 66.2%) (Fig. 3b). The 2-year cumulative incidence of TRM was 17.8% (95% CI 12.6 – 23.7%) following alloHPCT (Fig. 3c) and was similar for both RIC and myeloablative conditioning (MAC) recipients ($p = 0.622$). The 2-year cumulative incidence of disease relapse was 19.3% (95% CI 13.8 – 25.6%) (Fig. 3d).

DISCUSSION

We have analysed the five-year outcomes of adult patients undergoing alloHPCT in Western Australia for both non-malignant and malignant indications. The overall increase in the total number of patients undergoing alloHPCT since 2007 is likely to be a combination of reflection of demands of a growing population and also growing confidence by the authors in offering alloHPCT to older patients.

Our results compare well with other Australian centres (1-year survival, 73.7% for all donor types) compared to the survival reported by the Australian Bone Marrow Transplant Recipient Registry (63 – 70%). (9). Our study reveals a 1-year TRM of 16.9% (all donor type) compared to 19.7% in unrelated alloHPCT (9).

These comparisons, while appearing favourable, are limited by a lack of adjustment for patient and disease risk factors which may not be equal across groups. Such benchmarking practices are performed regularly by the Australian Bone Marrow Transplant Recipient Registry, but not yet for the FSH 2015-2019 cohort. A number of developments may account for the reassuring outcomes observed at FSH. First, incremental improvements in donor selection and supportive care have led to improved outcomes at other centres over recent decades, and current FSH practice has benefitted from these improvements (10, 11). Second, FSH BMTP embarked on a rigorous quality management programme from its establishment, leading to full accreditation by the National Australian Testing

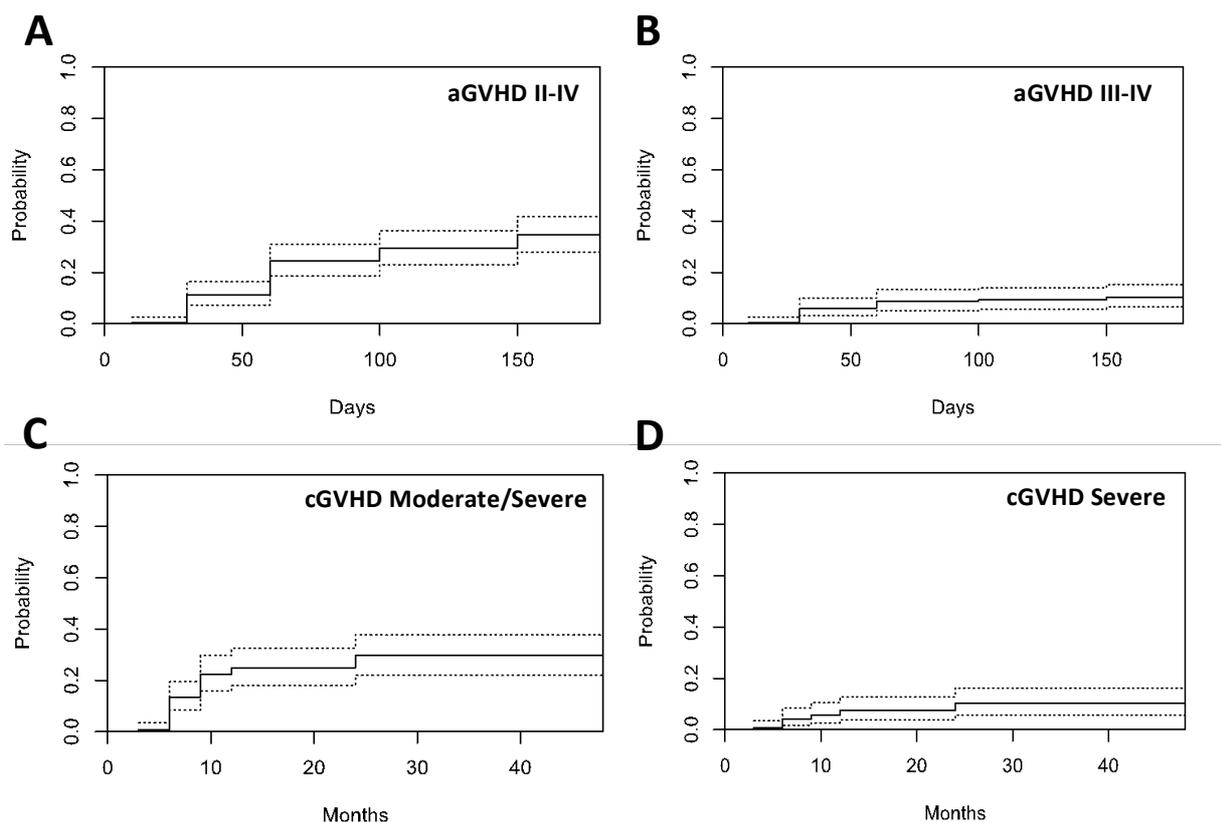


Figure 2. Cumulative incidence of acute graft-versus-host disease grade II-IV (A), grade III-IV (B), chronic graft-versus-host disease severity of moderate or severe (C) and severe (D) after allogeneic haematopoietic progenitor cell transplantation

Authority (NATA) in 2016 and the Foundation for the Accreditation of Cellular Therapy (FACT) in 2019. These achievements reflect the development of policies and procedures for audit, reporting of adverse events and near-misses, practice improvement, outcome reporting and clinical practice, as well as the development of a close multi-disciplinary quality management team. Indeed, in 2016, the FSH BMTP created 38 new clinical standard operating procedures alone. Such quality management procedures have been shown to improve patient outcomes after transplantation at other centres (12-14). Finally, FSH BMTP has benefitted from increasing involvement in clinical trials in cellular therapy. In 2015, only one interventional clinical trial was available to alloHPCT recipients at FSH, and even then only for the minority who developed grade II-IV aGVHD. By contrast, five prospective interventional clinical trials were available for the vast majority of patients undergoing allogeneic transplantation in 2019.

The most common indication for alloHPCT was AML. The median wait time from diagnosis to transplant (5.7

months) in those being transplanted in first remission appears relatively long, given that the decision to proceed to transplant is usually made within the first 21 days after diagnosis, and it is known that further delay after achieving remission risks either relapse or toxicity from ongoing consolidation chemotherapy. Efforts to shorten the delay until alloHPCT appear warranted, to be achieved via increased early communication with referring centres, optimising donor search and streamlining clinical review and workup prior to transplant.

Interestingly, nearly two thirds (64.2%) of recipients in Western Australia received HPCT from an unrelated donor, a marked reversal of early transplantation practice where almost all donors were matched siblings. This likely reflects both smaller family sizes, resulting in lower likelihood of identifying a matched related donor, and the increased size of the unrelated donor registry, now numbering nearly 37 million donors worldwide, most of whom reside in Europe or the United States of America (15). This reliance on unrelated donors has created significant challenges

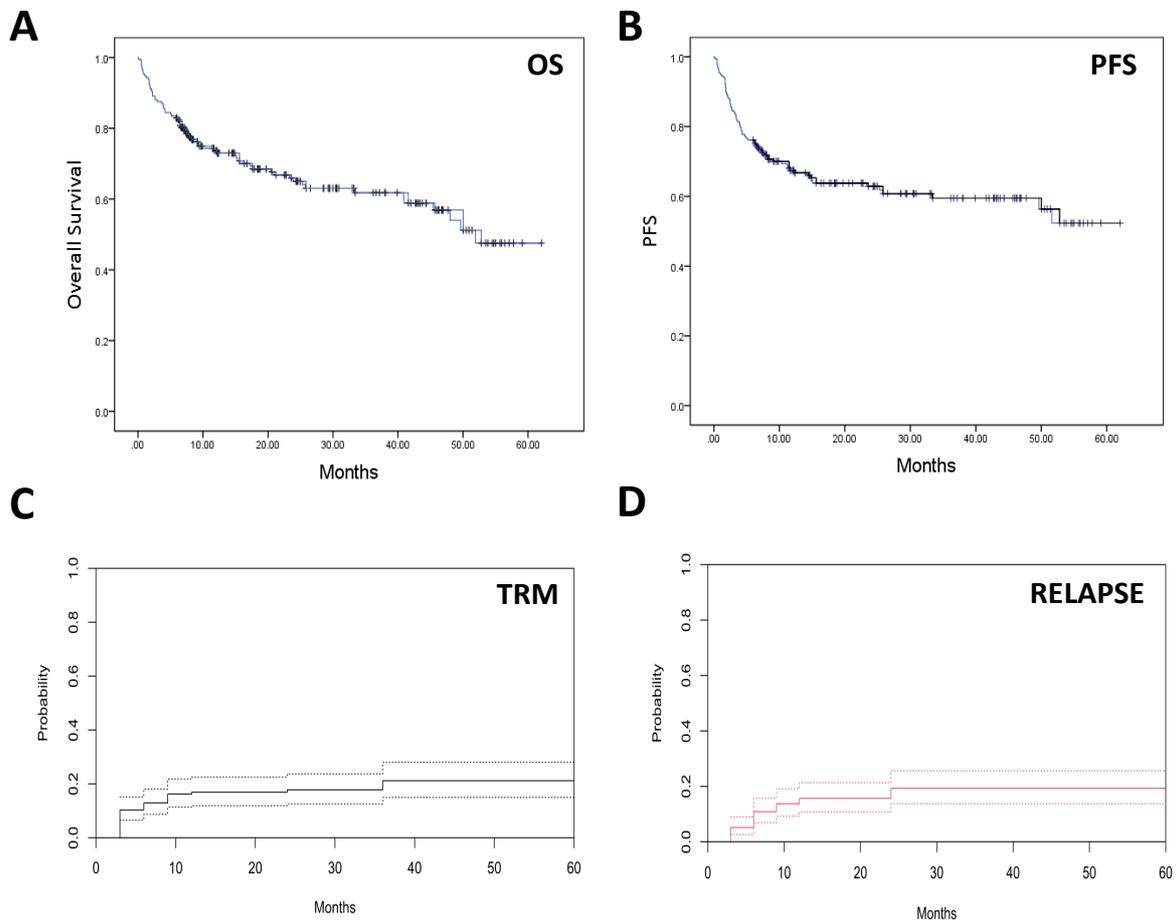


Figure 3. Kaplan-Meier curves of overall survival (A), progression-free survival (B) and cumulative incidences of transplant-related mortality (C) and disease relapse (D) after allogeneic haematopoietic progenitor cell transplantation.

during the current COVID-19 pandemic, due to reduced availability of donors and severe disruption in international travel for HPC products. Previously, such products were collected locally and shipped to FSH accompanied by a courier, to be infused immediately on arrival. This practice has become untenable and unsafe in the current environment, and all unrelated donor cells are now being cryopreserved prior to shipment, and recipient conditioning therapy is not started until the cryopreserved product has arrived at FSH and product viability is established. While these practices have enabled some unrelated donor transplants to continue, they are logistically complex and do not overcome the problem of reduced donor availability due to local hospital incapacity, donor illness or unwillingness to attend medical facilities for collection. These circumstances have led to increased alternative donor use at FSH in 2020. However, the allogeneic transplant service is still active in Western Australia compared to other interstate and international transplant centres where services had to be halted due to increasing numbers of COVID-19 cases.

In keeping with rapid haematological advance in this area, the most recent clinical standard operating procedures at BMTP includes quality processes for

delivering chimeric antigen receptor T-cell therapy (CAR-T). BMTP increasingly participates in national and international clinical trials, and in 2020 successfully delivered the first CAR-T treatment. We anticipate that BMTP will become further involved in immune effector cell therapies and therapeutic clinical trials.

This study provides details of patient disease characteristics, pre-transplant functional status, transplant characteristics and clinical outcomes in patients undergoing alloHPCT in Western Australia. These clinical details have not previously been published. The FSH BMTP has had results that are comparable to published national data.

Provenance: Externally reviewed

Ethical Approval: Granted by FSH Department of Safety, Quality and Risk.

Disclosures: None

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