

1. Introduction

This is the fourth report of the Adult Alternative Donor Stem Cell Transplantation Service. We have completed our second year in the new transplant unit in the Beatson West of Scotland Cancer Centre. During the past year we have increased our unrelated donor transplant activity. There were 36 VUD transplants carried out on 35 patients in financial year 2009-10. 17 patients were male, 18 female, with a second transplant being performed in one of the female patients. The median age was 45.5 years (range 18–65 years). 5 patients received umbilical cord as their stem cell source. 4 patients received bone marrow and 27 patients received peripheral blood stem cells. Of the 31 patients receiving marrow or peripheral blood stem cells, 24 patients were transplanted with 10/10 matched donors at the HLA A, B, C, DRB1 and DQ loci, 7 were matched for 9/10 loci. 3/33 patients assessable have died before day 100, giving a day 100 TRM of 9.1%. To date, 2 additional patients have died beyond day 100. The Unit has applied for JACIE accreditation (Joint Accreditation Committee of ISHAGE and EBMT) and we are anticipating an inspection in July 2010. In the past year, the tissue typing laboratory has undergone successful EFI (European Federation of Immunogenetics) accreditation and the stem cell processing laboratory HTA (Human Tissue Authority) accreditation.

Abbreviations

BMT	Bone marrow transplant
CR	Complete remission
GvHD	Graft versus Host Disease
PBSCT	Peripheral blood stem cell transplant
PR	Partial response
RIC	Reduced intensity conditioning
TRM	Transplant Related Mortality
VUD	Volunteer unrelated donor

2. Activity

The activity continues to increase year on year as more patients are referred for transplant due to

- Broadening of indications,
- Improving general health of population,
- Reduction in availability of matched sibling donors,
- Raising of upper age limit for transplant
- Availability of alternative donors eg cord

An increase was predicted in the initial application for recognition of the service with an expectation that there would be a requirement for 30+ patients by 5 years. The rate of increase has been faster than predicted and demand continues to rise.

Table 1. Statement of Activity

	Actual	Planned
Unrelated Donor Searches Performed By Tissue Typing	103	N/A
Patients Having Donor Samples Requested	85	N/A
Formal Assessments	59	N/A
BMT Procedures Performed	36	25-30
Patients not proceeding to transplant who were formally assessed	23	N/A
Patients not proceeding to transplant who were not formally assessed	11	
Follow-up Appts for patients transplanted 2008-2009	720	N/A
Follow-up Appts for patients transplanted pre 2008-2009	415	N/A

In total 34 patients came off the transplant list in 2009-2010 without being transplanted. The Board of origin is shown in Table 2. Reasons for coming off the list are documented below

Patient choice	4/34 (12%)
Progressive disease/death	12/34 (35%)
Alternative therapy	15/34 (44%)
No donor identified	3/34 (9%)

Table 2. NHS Boards of Residence

Board	Transplanted	Considered but not Transplanted
Greater Glasgow & Clyde	9 1	6 2
Lothian	7	3
Grampian	2	7
Tayside	1	4
Lanarkshire	3	3
Ayrshire + Arran	2	4
Dumfries + Galloway	5	0
Fife	3	1
Highlands + Islands	1	2
Borders	0	1
Forth Valley	2	1

Table 3. Indications for VUD Transplant 2009-10

Diagnosis/Stage	Number	Comments
Acute Myeloid Leukaemia		
CR1	9	Includes 2 patients receiving cord transplants, one of whom required rescue with a VUD PB SCT for failed engraftment
CR2	7	Includes 2 cord transplants
Acute Lymphoblastic Leukaemia		
CR1	4	Includes 1 cord transplant
Hodgkin Lymphoma		
PR2	1	
PR3	1	Cord transplant
Non-Hodgkin Lymphoma		
Diffuse Large B Cell CR2	1	
Follicular NHL PR2	1	
PR4	1	Previous autograft
Mantle Cell Lymphoma PR2	1	Previous autograft
Multiple Myeloma		
PR1	1	
Myelofibrosis	2	1 patient relapsed after previous VUD transplant
Chronic Lymphocytic Leukaemia		
PR 2	1	
PR 3	1	
PR5	1	
Chronic Myeloid Leukaemia	2	1 patient relapsed after previous sibling donor transplant
Aplastic Anaemia	1	
EBV Driven Haemophagocytic Syndrome	1	

- *Myeloablative Conditioning Regimens (excluding cords)*

11 patients received a myeloablative regimen, 6 Cyclophosphamide 120 mg/kg, total body irradiation (TBI) 1440 cGy, alemtuzumab, and 5 treosulphan, cyclophosphamide and alemtuzumab. 2 patients received a transplant from a mismatched donor. Only 1 patient developed acute GvHD (grade 2). 3 patients died before day 100 - 2 of transplant related causes (18%), 1 of relapsed disease. No patient has died beyond day 100 of transplant related causes.

- *Reduced Intensity Conditioning Regimens (excluding cords)*

19 patients received a reduced intensity conditioning regimen. 12 patients received conditioning with Fludarabine/Melphalan/ Alemtuzumab and 7 received Fludarabine/Busulphan/ Alemtuzumab. 5 patients received mismatched transplants. Acute GvHD occurred in 7 patients in the RIC group (grade I in 1 patient, grade II in 6 patients. 1/16 assessable patient died before day 100 giving a D100 TRM of 6%. 2 patients have died of transplant related causes beyond day 100.

- *Umbilical Cord Transplant*

5 further patients have undergone cord transplantation. 2 patients received myeloablative conditioning with fludarabine 75mg/m², Cyclophosphamide 120 mg/kg, total body irradiation (TBI) 1440 cGy. 3 patients underwent reduced intensity conditioning cord transplantation using fludarabine/melphalan/TBI 200cGy . 1 patient failed to engraft and subsequently underwent a reduced intensity PBSCT but died before day 100 (see above). No other patient has died of transplant related causes. 1 patient developed grade II GVHD. No patient has relapsed and no patient has died beyond day 100.

Length of Stay. The overall mean length of stay for the transplant admission was 36.5 days (range 23 - 91 days).

Readmissions (Table 4)

Prior to day 100 there were 18 readmission episodes, totalling 291 bed days. Beyond day 100 there were 24 readmission episodes totalling 497 bed days. Readmissions by Health Board are shown in Table 4.

Table 4. Readmissions per Health Board

Board	No of Pre Day 100 Readmissions (duration in days)	No of Post Day 100 Readmissions (duration in days)
GG	8 (1, 3, 7, 10, 12, 14, 20, 20)	8 (1, 3, 3, 4, 5, 11, 33, 104)
+Clyde	0	3 (2, 40, 41)
Lothian	0	0
Grampian	1 (15)	2 (5, 10)
Tayside	1 (50)	0
Lanarkshire	1 (42)	7 (2, 5, 6, 13, 13, 23, 24)
A+A	0	0
D+G	4 (11, 11, 14, 33)	3 (2, 10, 33)
Fife	1 (11)	0
Highlands	0	0
Borders	0	0
Forth Valley	2 (2, 15)	1 (104)

Table 5. The Source of Donor Stem Cells

Donor Registries		Cord Banks	
UK (Anthony Nolan, BBMR, WBMR)	16	UK	3
Germany	8	Germany	1
US	3	Barcelona	1
Australia	2	New York	4
Canada	1	Australia	1
France	1		

3. Waiting Times

Waiting times are assessed from the time of 1st appointment until admission for transplant. The median wait is 67 days (range 12-348 days). The median wait for first appointment from receipt of a formal referral is 51 days (range 16-125 days).

Factors influencing waiting times

Tissue typing. Please see below. There may be significant delays in obtaining an appropriate donor, particularly if the patient has an unusual tissue type.

Patient clinical status. Transplant can only be performed once the patient has completed their induction therapy at their base hospital, which can take 4 months or more.

Donor Availability. A donor may not be available at the desired time because of personal preference or personal circumstances. It normally takes a minimum of 6 weeks to schedule a transplant once an appropriate donor has been identified.

4. Quality of Care

There were no formal complaints during this time. The Quality management programme, audit and outcomes are discussed in detail in section 7.

5. Tissue Typing

103 unrelated donor searches were performed. 587 donor samples were requested for 85 patients. Samples from 410 prospective donors were received and typed. On average 5 donors were requested per patient. For the cord blood transplants, typing was performed on 18 cords in total. The increase in activity is summarised in Table 6.

Table 6. Tissue Type and Transplant Activity

	2006-7	2007-8	2008-9	2009-10
Unrelated Donor Searches	77	85	80	103
Donor Samples requested	352	402	584	587
Donor samples received and typed	266	298	330	410
Cord samples typed	0	2	6	18
Unrelated Donor Transplants	0	32	32	36

6. Stem Cell Processing Laboratory

In addition to the stem cell products processed for the transplants undertaken, 4 peripheral blood stem cell collections were cryopreserved for future use as excess cells were obtained at initial collection. In addition, 11 donor lymphocyte collections were cryopreserved compared with 5 last year.

7. Clinical Audit and Outcomes

7.1. Quality Programme. The transplant unit has a well established quality programme with a full time Quality Manager in post. This includes 6 weekly meetings with reporting of engraftment, mortality, relapse and fungal infections. In addition, there is critical incident and variance reporting. We also have an on-going programme of audit. The audit timetable is outlined in Appendix 1

7.2. Engraftment. All patients engrafted though 1 patient then lost their graft in association with post-transplant complications.

Table 7. Engraftment Post Transplant

	Median days to Neutrophils >0.5 (x10 ⁹ /l)	Median days to Neutrophils >1.0 (x10 ⁹ /l)	Median days to Platelets >20 (x10 ⁹ /l)	Median days to Platelets >50 (x10 ⁹ /l)
All Unrelated Donor Transplants	14(6-31)	16(7-31)	13(9-35)	15(12-NYA)
Myeloablative Transplants	19.5(12-31)	21(13-31)	15.5(11-35)	26(12-NYA)
Reduced Intensity Conditioning Transplants	12(6-22)	14(7-25)	13(9-28)	15(12-NYA)

NYA – Not Yet Achieved

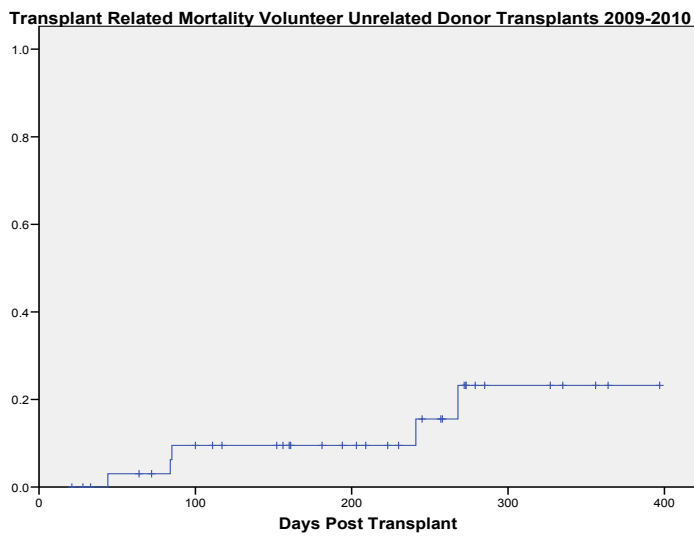
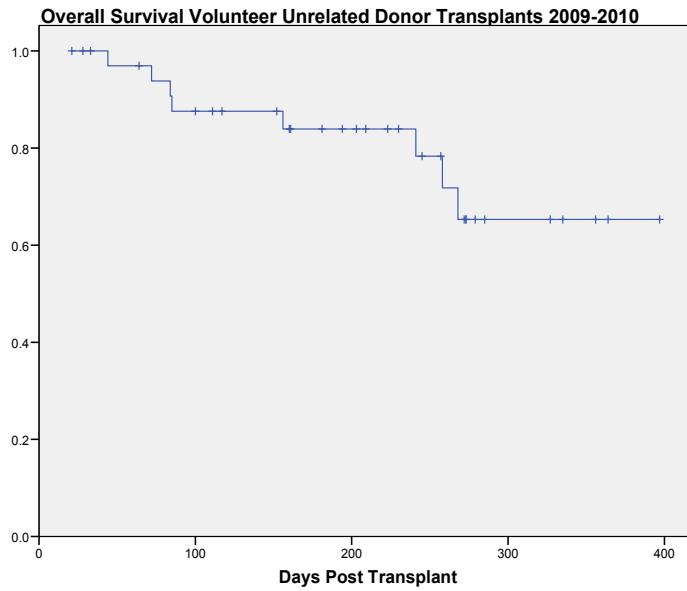
7.3. Transplant Related Mortality. 3 patients died within 100 days (2 received a myeloablative transplant and 1 received a reduced intensity transplant).

7.4. Relapses. Up until April 2009, 8 patients have relapsed, 4 patients with AML, 2 multiply relapsed follicular NHLs, 1 CLL and 1 patient with myelofibrosis.

7.5. Outcomes 2009-2010

Overall Survival and Transplant Related Mortality for patients transplanted in 2009-2010 are illustrated in the following Kaplan Meier curves.

Figure 1



7.6 Outcomes 2002-2010

The following graphs represent outcome from the 203 VUD transplants performed in Glasgow from 2002-2010

Figure 2 Overall Survival and Transplant Related Mortality 2002-2010

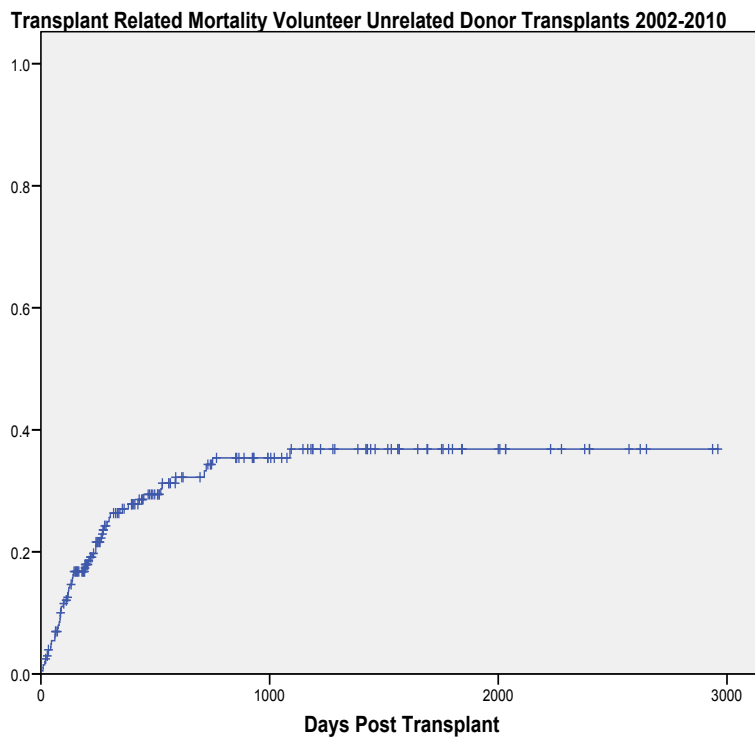
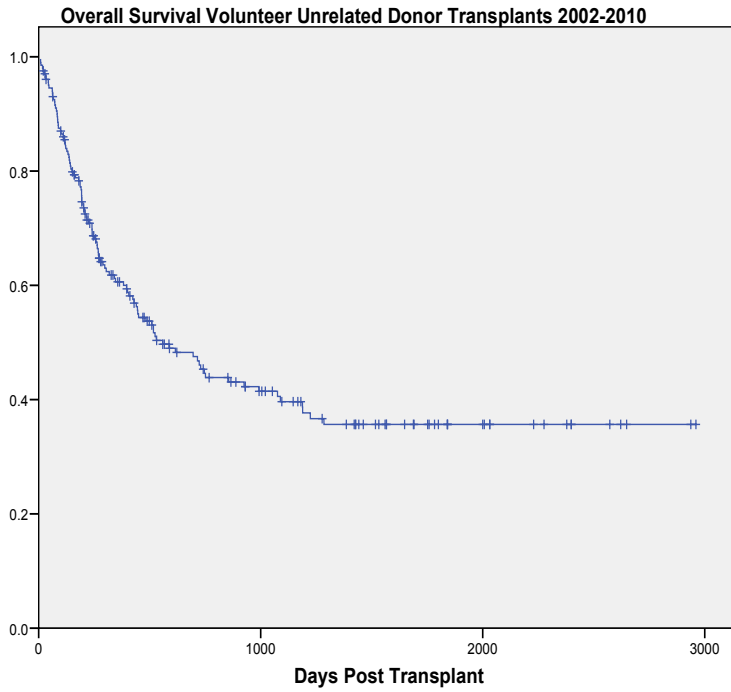


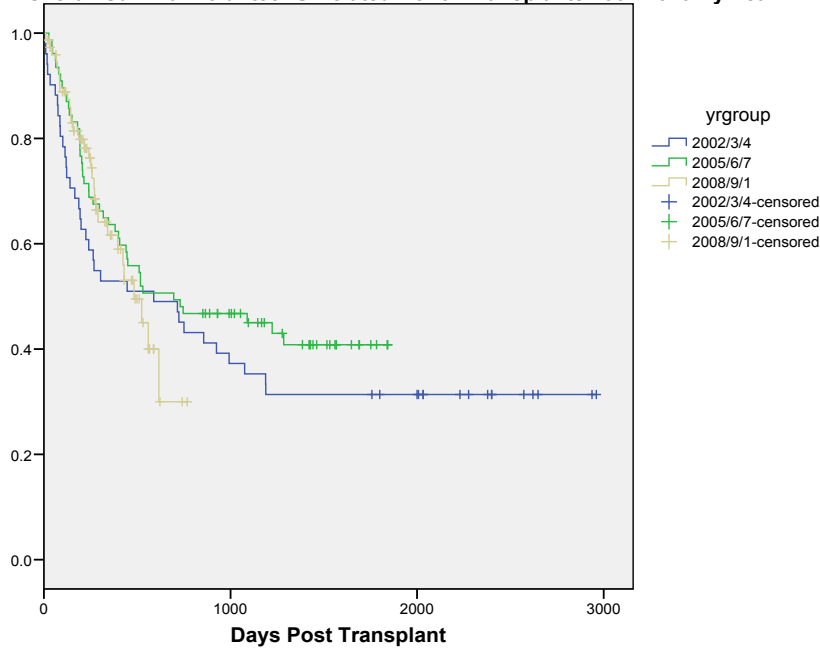
Figure 3. Increasing Age of Transplanted Patients and Outcomes by Years of



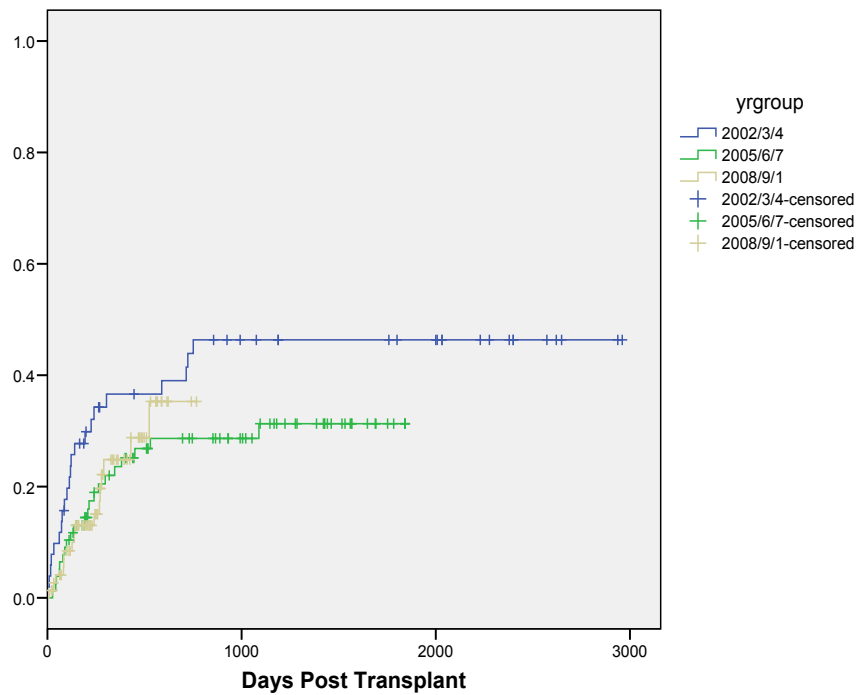
Transplant

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Overall Survival Volunteer Unrelated Donor Transplants 2002-2010 By Year



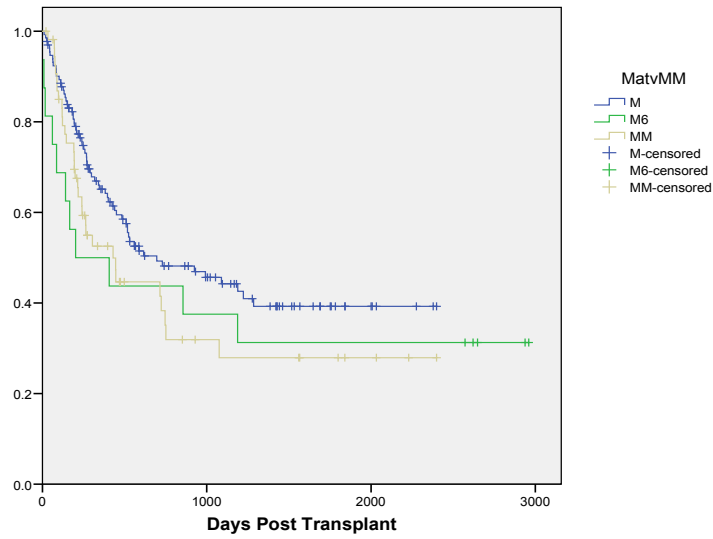
Transplant Related Mortality Post Volunteer Unrelated Donor Transplant By Years



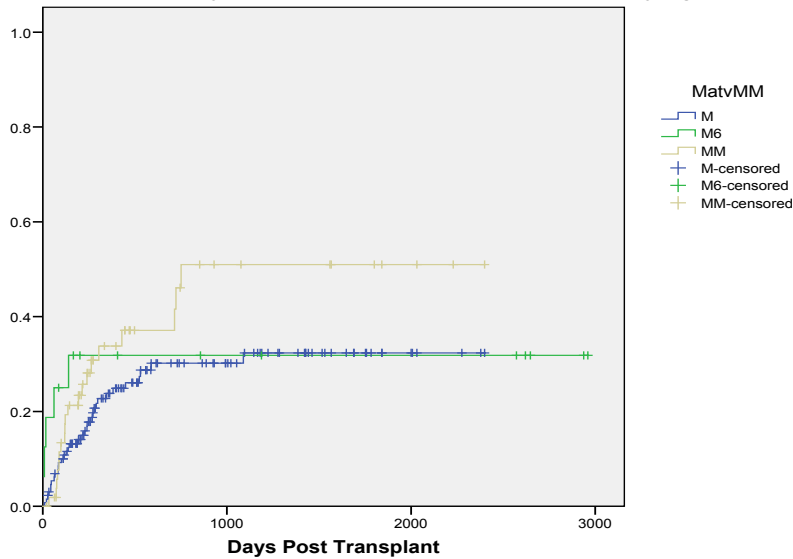
These graphs demonstrate that the median age of patients being transplanted continues to increase. Despite this, the overall outcome and in particular the transplant related mortality is maintained.

Figure 4 The Beneficial Effect of Matching on Outcome

Overall Survival of Volunteer Unrelated Donor Transplants 2002-2010 By Degree of Matching



Transplant Related Mortality Volunteer Unrelated Donor Transplants 2002-2010 By Degree of Matching

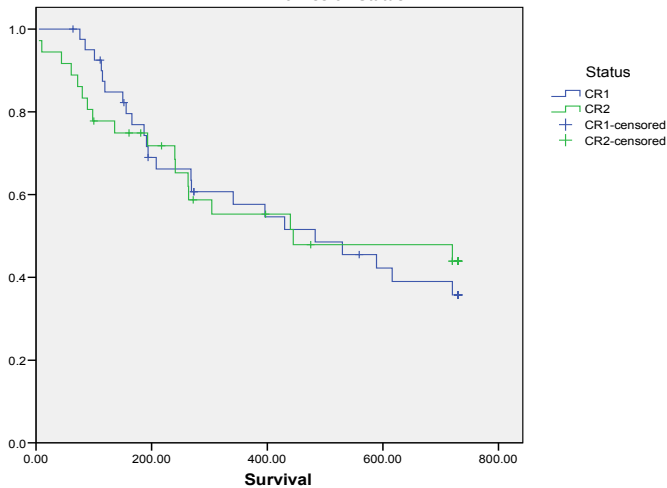


Patients who had a 10/10 molecular match (M) had the best outcome compared with patients who were a 6/6 match when this was the standard for matching (M6). Those who had transplants from a mismatched donor have the poorest outcome (MM).

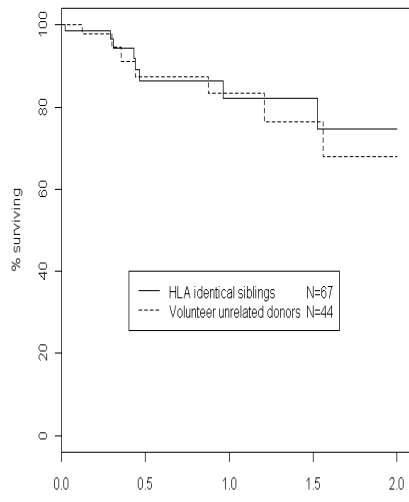
Figure 5 Acute Leukaemia Outcomes

To benchmark our outcomes we have attempted to compare our outcomes for AML and ALL patients with those produced by BSBMT (British Society of Blood and Marrow Transplantation). The BSBMT curves represent patients transplanted in 1 calendar year (2008). We have produced curves censored at 2 years for patients transplanted between 2002 and 2010 to ensure there are enough patients on our curve. The 2 groups CR1 and CR2 represent remission status at the time of transplant. Clearly the groups are not directly comparable, and this will always be the case comparing registry data with our own – there will always be differences in the type of patients transplanted and other factors such as co-morbidity which are not taken account of here and this will always be an unsophisticated comparison.

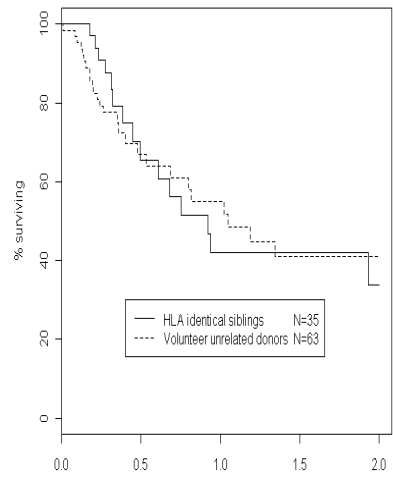
2 Year Survival for AML Patients Receiving Unrelated Donor Transplants Depending on Remission Status



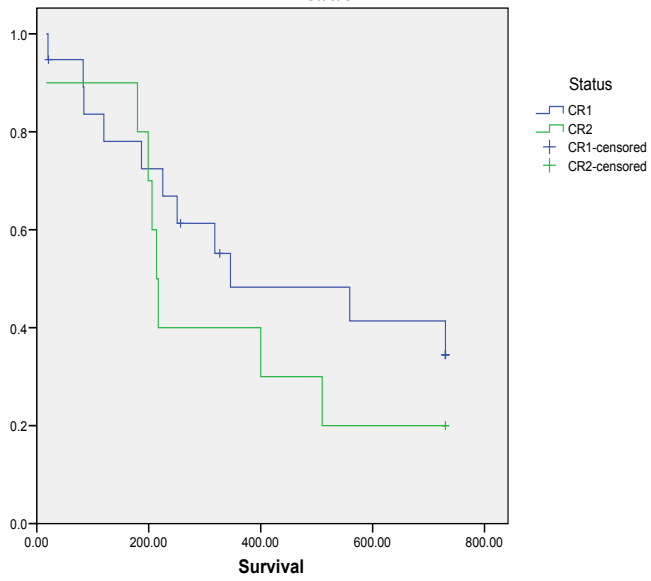
Allogeneic first transplants in 2006: AML in 1st CR
Overall survival by donor type



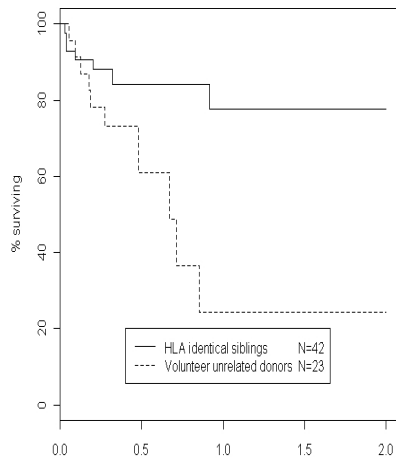
Allogeneic first transplants in 2006: AML not in 1st CR
Overall survival by donor type



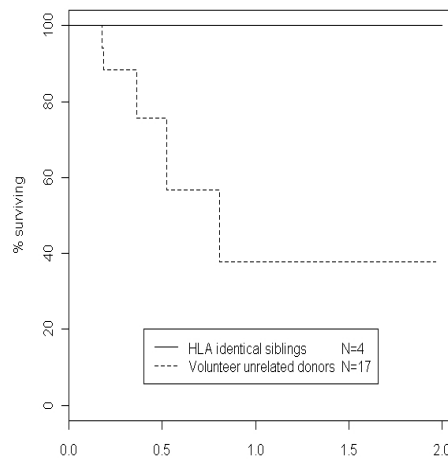
2 Year Survivals for ALL Patients Receiving Unrelated Donor Transplants By Remission Status



Allogeneic first transplants in 2006: ALL in 1st CR
Overall survival by donor type



Allogeneic first transplants in 2006: ALL not in 1st CR
Overall survival by donor type



7.7. Hospital Acquired Infections. The MRSA and Clostridium Difficile incidence is documented on a monthly basis by the infection control team – see Appendix 2.

7.8. ITU Admissions. 2 patient undergoing unrelated donor transplantation required ITU admission. Both patients died on ITU from transplant related problems

8.0 Teaching and Research Activities

The unit is actively involved in a number of National and International studies which involve transplantation from unrelated donors. Active studies involving transplantation during the past year include

1. NCRI AML16 study
2. NCRI AML 17 study
3. UKALL 2003
4. Transplantation of Umbilical Cord Blood in patients with haematological disease using a non myeloablative preparative regimen (BSBMT study)
5. TOPPS trial (a study assessing the role of prophylactic versus symptomatic treatment of thrombocytopenia in transplant patients)

Proposed New Studies for 2010

The following are currently undergoing R&D assessment prior to initiation.

1. UKALL 14 study
2. Phase II study of low intensity allogeneic transplantation in Mantle Cell Lymphoma
3. PAIReD study to assess the role of allogeneic transplantation in patients with primary refractory Hodgkin Lymphoma

The unit is an active contributor to BSBMT, EBMT and CIBMTR studies.

The unit collaborates closely with the Paul O’Gorman Leukaemia Research Centre led by Professor Holyoake and Dr Copland, Clinical Senior Lecturer at the University of Glasgow, is a member of the Transplant Consultant Team. The Paul O’Gorman Leukaemia Research Centre is part of the Division of Cancer Sciences at the University of Glasgow. The Centre opened in March 2008 is built on the Gartnavel Hospital campus and has 5 group leaders with interests in CML and leukaemia stem cell biology (Tessa Holyoake), normal and leukaemic

stem cell fate and microenvironment (Mhairi Copland), CLL biology and normal lymphopoiesis (Alison Michie), the role of signal transduction in stem cell self-renewal, haemopoiesis and angiogenesis (Helen Wheadon) and modelling of myeloid leukaemia (Kamil Kranc).. The Centre houses state-of-the-art facilities including a dedicated tissue culture suite, FACS Aria cell sorter, FACSCanto flow cytometer, Taqman quantitative RT-PCR, and fluorescence microscopy. Additional complimentary facilities are available at the Beatson Institute, including the Beatson Advanced Imaging Resource.

Nursing and medical staff contribute regularly to undergraduate and post-graduate education. Nursing students are attached to the unit and clinical teaching of undergraduate medical students occurs weekly. All medical trainees have a full tutorial programme and the unit contributes to the West of Scotland Rolling Programme for Haematology trainees including input from the stem cell processing, molecular and tissue typing laboratories. Nursing and medical staff contribute to regional and national training programmes for undergraduate and post-graduate nursing courses and frequently contribute to sponsored symposia.

Transplant related publications

Original Publications

Alemtuzumab markedly reduces chronic GVHD without affecting overall survival in reduced-intensity conditioning sibling allo-SCT for adults with AML.

Malladi RK, Peniket AJ, Littlewood TJ, Towlson KE, Pearce R, Yin J, Cavenagh JD, Craddock C, Orchard KH, Olavarria E, McQuaker G, Collin M, Marks DI; British Society of Blood and Marrow Transplantation. *Bone Marrow Transplant*. 2009 May;43(9):709-15. Epub 2008 Nov 24.

The role of allogeneic SCT in primary myelofibrosis: a British Society for Blood and Marrow Transplantation study.

Stewart WA, Pearce R, Kirkland KE, Bloor A, Thomson K, Apperley J, McQuaker G, Marks DI, Craddock C, McCann S, Russell N, Cook G, Kottaridis PD. *Bone Marrow Transplant*. 2010 Feb 15. [Epub ahead of print]

Evidence for Direct Involvement of Epirubicin in the Formation of Chromosomal Translocations in t(15;17) Therapy-Related Acute Promyelocytic Leukemia

Ashley N Mays, Neil Osheroff, Yuanyuan Xiao, Joseph L Wiemels, Carolyn A Felix, Jo Ann W Byl, Kandeepan Saravanamuttu, Andrew Peniket, Robert Corser, Cherry Chang, Christine Hoyle, Anne N Parker, Syed K Hasan, Francesco Lo-Coco, Ellen Solomon and David Grimwade *Blood* 2010 Jan 14;115(2):326-30 epub Nov 2

The evolving management of a rare lymphoproliferative disorder-T-cell prolymphocytic leukaemia – using unrelated donor stem cell transplantation. Gallipoli P, Clark A, Leach M *Am J Hematol*. 2009 Nov;84(11):750-3.

The emergence of oseltamivir-resistant pandemic influenza A(H1N1) 2009 virus amongst hospitalised immunocompromised patients in Scotland, November-December, 2009.

Harvala H, Gunson R, Simmonds P, Hardie A, Bennett S, Scott F, Roddie H, McKnight J, Walsh T, Rowney D, Clark A, Bremner J, Aitken C, Templeton K, Euro Surveill. 2010 Apr 8;15(14). pii: 19536.

Abstracts

The impact of second generation tyrosine kinase inhibitors on the outcome of allogeneic stem cell transplantation for chronic myeloid leukaemia.

Latif A, Parker A, McQuaker G, Clark A, Copland M *British Society of Hematology 50th Annual Scientific Meeting 2010* (April). *British Journal of Haematology* 2010; 149(Supplement 1):23-4.

9.0 Financial Report - attached as Appendix 3

10.0 Service Developments and Future Plans

10.1 Accreditation

The clinical service has been established on the Gartnavel site for 2 years, the stem cell processing laboratory for 1 year. We were advised that the new lab should be in place for at least a year prior to JACIE inspection. We therefore submitted our application in April 2010 and are anticipating being inspected in July 2010. The stem cell processing laboratory was inspected by the Human Tissue Authority in June 2009 and gained accreditation. The tissue typing laboratory has gained EFI (European Federation of Immunogenetics) accreditation and is routinely performing higher resolution typing on all our potential patients and donors

10.2 Volunteer Unrelated Donors

The workload will continue to increase as new indications become established. We are currently one of the larger unrelated donor programmes in the UK – 9th out of 36 centres performing allogeneic transplants, 4th largest outwith London. As discussed in last years report, chronic lymphocytic leukaemia is becoming a significant indication for transplantation as this year there is increasing evidence to support allogeneic transplantation for Hodgkin Lymphoma. Unrelated donor transplantation is increasingly being considered in the clinical trials for acute leukaemia and is an integral part of the current UKALL 14 study which is currently awaiting R+D approval. As family size diminishes, there are fewer patients with sibling donors and we are now finding that some patients who do have identical sibling donors cannot proceed to transplant due to poor health or age of the donor. In addition, the general health of the Scottish population has improved over the past 10 years so that fewer patients are considered unfit for transplant.

10.3 Cord Blood

The Umbilical Cord Programme continues to develop. We performed our first cord transplant in 2007, performed 3 last year and 5 in 2009-10. We are now participating in a UK study of reduced intensity conditioning for cord transplantation and there is likely to be a UK study with myeloablative conditioning in the near future. Our initial cord results have been extremely encouraging, with only one transplant related death. We are still restricting the patients we consider for cord transplant to those less than 60 years with established data to support the use of cord transplantation. Participation in appropriate studies will allow the assessment of cord transplantation in less established indications and our numbers are likely to be consistently 5-10 per annum.

10.4 Staffing

The impact of 'Modernising Medical careers' on the service has had a significant effect. The loss of the 'senior' SHO grade with movement of these posts into the Specialist Training (ST) grade has impacted on service provision as many tasks eg. stem cell infusion, routine admissions etc. are not considered part of ST training. There is provision of FY2 or CMT trainees, but this is not guaranteed. In addition, there is a planned reduction in ST numbers of

close to 20% over the next 4 years, so that there will be a significant fall in ST provision. Each year will reduce the number of junior doctors available.

In order to just maintain levels of activity the gaps these changes create will need to be filled with, for example, Clinical Nurse Practitioners who can deliver many of the routine non-training tasks such as venflon insertion, bone marrow aspiration, Hickman line removal etc. It is anticipated that there will need to be a minimum of 2 Clinical Nurse Practitioners and 1 Clinical Fellow appointed in the next 1-4 years to maintain this service at its current level. In order to manage any increase in activity we will need to consider not only changes in work practice but also potentially additional ward, day care and clinic nursing support.

There is increasing pressure on BMT Consultants job plans as there is no doubt that more and more time is required for clinical transplantation in terms of organisation pre transplant, clinical care and dealing with transplant related regulatory issues in addition to the increase in patient numbers. The transplant related regulatory issues are currently included in SPA time, which is not sustainable given the increasing demands of the rising accreditation standards.

With increasing numbers of patients being transplanted and surviving there are discussions as to how to reduce the number of visits to Glasgow by patients once they have stopped immunosuppression. Outreach clinics are done on a 3 monthly basis in Ayrshire, Tayside and Dumfries & Galloway, but other health boards are keen to explore this option.

10.5 Outcome Data Benchmarking

The British Society of Blood and Marrow Transplantation are in the process of analyzing outcome data for the commissioners in England. In subsequent reports we would hope to be able to more formally benchmark our own outcomes against these data.

11.0 Summary and Conclusions

We have completed a full year with both clinical and laboratory services once again collocated on the same site. Our activity continues to increase and we performed 50 allogeneic transplants (using unrelated and sibling donors) in total last year, our busiest year to date. Increasing clinical activity is also reflected in the increasing tissue typing and stem cell laboratory support. Newer indications for transplant continue to be developed and activity is likely to continue to increase in the short-term at least. Each year the indications for transplant vary though acute leukaemias remain the commonest indication for transplantation. Given current studies encouraging this approach these numbers are likely to increase. Likewise, the number of patients undergoing cord transplantation is likely to increase as we develop more confidence in this procedure and data becomes available supporting its use for wider indications.

Staffing levels remain a concern, particularly the number of junior doctors. Clearly increasing activity will require appropriate numbers of training grades and/or staff capable of performing middle grade tasks. We are keen to look at possible alternatives to junior doctors fulfilling this role as we are not guaranteed sufficient training grade staff to maintain current levels of activity.

We have developed strong links with clinical colleagues in the West of Glasgow and for the most part have excellent clinical support. We have a clear protocol for the management of patients requiring ITU support and we meet regularly with the ITU team and this process will be audited on an on-going basis.

The median age of patients we have transplanted this year is less than last year with a median age of 45.5 versus 51.5 last year, but there is still clearly a trend to transplanting older patients and this year we have transplanted our oldest ever patient (66 years). Again we are showing that despite this, there is no increase in our transplant related mortality and published data supports the use of transplantation in carefully selected patients over the age of 60 years and potentially over 65 years. It is also clear that improvements in matching are improving outcomes and patients receiving transplants from fully matched donors do best. The outcome of mismatched transplants is disappointing and this has been confirmed by other groups and there are discussions on-going about a trial to compare cord blood transplant with mismatched marrow or peripheral blood transplants. This would hopefully determine the optimal donor source in patients without a fully matched donor and we would be keen to participate in such a trial.

The Beatson, West of Scotland Cancer Centre and new laboratories provide superb state of the art facilities to support the Glasgow Adult Alternative Donor service. The team continues to strive to provide a high quality service for the population of Scotland and to look to means to improve processes and outcomes in the next year.