

## MEETING REPORT

# Topical issues in unrelated donor haematopoietic stem cell transplants: a report from a workshop convened by the Anthony Nolan Trust in London – 2005

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**Over more than three decades, The Anthony Nolan Trust (ANT) has provided an unrelated donor (UD) for over 4000 children and adults lacking a suitable family member donor, and has remained at the forefront of developments in haematopoietic stem cell transplantation (HSCT) and bone marrow register management. These three decades have seen major changes in clinical practice of UD-HSCT, including new indications, increased use of alternative haematopoietic cell sources, significant improvement of the outcome as a result of better support care, less-toxic conditioning regimens, and better donor selection, and expansion to older patients with higher comorbidities. In order to foster our goal of improving UD-HSCT availability and outcome in a progressively more complex clinical scenario, a new initiative from ANT was launched in 2005 to convene an experts workshop to address the topical issues in this field. Four consecutive panels addressed factors influencing donor selection and transplant outcome, the use of cord blood, regulatory and accreditation issues, and future developments in this field. This report summarizes the discussions held in this workshop, which will likely develop into a periodic event where transplant clinicians, scientists and registry members will meet to share their experience and vision in the field of UD-HSCT.**

*Bone Marrow Transplantation* (2006) 37, 901–908.  
doi:10.1038/sj.bmt.1705365

**Keywords:** unrelated donor; allogeneic transplantation; workshop

### Introduction

Haematopoietic stem cell transplantation (HSCT) from unrelated donors (UDs) has seen a significant increase in

numbers and success rate in recent years. More than one-third of allogeneic transplants currently performed in Europe use haematopoietic stem cells collected from UD.<sup>1</sup> This is the result of two principal advances in the field – the improved understanding of the impact of factors on transplantation outcome, namely HLA matching and the establishment of large international volunteer registries of UD, which contain data on more than 10 million volunteer UD and stored umbilical cord blood (UCB) units (www.bmdw.org; updated 24 January 2006) in 53 UD registries in 39 countries and 37 UCB registries in 21 countries. The Anthony Nolan Trust (ANT; www.anthonynolan.org.uk), set up in London in 1974 as the first UD registry, paved the way for the development of other registries worldwide, and remains at present the largest registry in the UK and the third largest in the world. The Anthony Nolan Research Institute (ANRI), part of the ANT, has also made major contributions to our understanding of the impact of HLA immunogenetics and other factors in the outcome of transplantation.

In order to further the main goal of improving UD availability and the effectiveness of UD-HSCT, and in view of the increasing complexity introduced by new developments, a workshop addressing topical issues in the field was convened in London in June 2005. It brought together representatives from the Registry, the ANRI, and scientists and transplant clinicians from many UK transplant centres (Appendix A). Four consecutive panels addressed the following topics: factors influencing donor selection and transplant outcome, the use of UCB as a source of haematopoietic progenitors for transplantation, regulatory and accreditation issues in UD-HSCT, and a vision of future developments in this field.

### Donor selection and transplant outcome

The discussion on the impact of donor factors on transplant outcome focused primarily on the effect of HLA typing at the molecular level. Bronwen Shaw began by providing a summary of her work at the ANRI and the ANT experience in this area.<sup>2–4</sup> She presented data on 423 UD-HSCT performed between 1996 and 2003 for whom

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Received 2 March 2006; accepted 13 March 2006

four digit molecular tissue typing for 12 alleles and clinical follow-up data were available. The percentage of well-matched (10/10) donor–recipient pairs (67%) in the ANT study was greater than that in any other study (44% in the Japanese Marrow Donor Programme study<sup>5</sup> and 47% in the Fred Hutchinson Cancer Research Center study<sup>6</sup>), in part due to the time period over which the study was performed. The patients included in the ANT analysis almost all received donor cells that had been T-cell depleted with anti-CD52 (Campath) monoclonal antibody, reflecting the UK transplant practice. On the basis of this work it was possible to make a number of recommendations regarding the choice of UD, at least for the UK transplant practice:

- HLA-A, -B, -C, -DRB1, and -DQB1 (10/10) matching:
  - A mismatch for one allele appears to be tolerated. This is evident in the long-term overall survival (OS) of the group.
  - With regard to mismatches at individual loci:
    - HLA-A mismatches may be particularly well tolerated
    - HLA-B mismatches are associated with a significantly worse OS and should be avoided.
    - HLA-C mismatches may be tolerated with regard to OS, but are associated with an increase in acute and chronic forms of graft-versus-host disease (GVHD).
    - KIR ligand mismatches in the graft-versus-host (GVH) direction are associated with increased transplant-related mortality (TRM) and worse OS, and should be avoided when possible.
    - In summary, if a Class I mismatch is unavoidable, an A mismatch should be chosen first, next a C mismatch (if there is no KIR ligand incompatibility in the GVH direction), and lastly a B mismatch or a C with KIR GVH mismatch.
  - Mismatching for more than one allele resulted in significantly impaired OS.
  - Despite the smaller number of single Class II mismatches or mixed Class I and II mismatches in this study compared to others,<sup>6–8</sup> which precludes drawing any firm conclusions from the data on these subgroups, the best recommendation is to avoid them due to significant increases in severe TRM, GVHD and consequent poorer OS.
- HLA-DPB1 matching: The ANT study is the largest comprehensive analysis of the impact of DPB1 to date,<sup>3</sup> and suggests that:
  - Matching at DPB1 increases the risk of relapse, irrespective of the matching status for other HLA alleles. This is particularly relevant in diseases such as CML and ALL.
  - Therefore, all patients and donors should be DPB1 typed before transplant, and a DPB1 incompatible donor should be chosen in preference to a compatible one.
  - With regard to mismatches at individual loci:
    - HLA-DPB1 mismatches at the hypervariable region D, and at amino-acid positions 65 or 57, should be avoided due to an increase in TRM and worse OS.
    - Other ‘permissive’ DPB1 mismatches may exist.
- Donor factors other than HLA:
  - If a favourable donor is not available, the ‘unfavourable’ donor factors tend to be associated in the next best donor, for example, female donors were more likely to be CMV positive, and CMV-positive donors more likely to be older. Strikingly, HLA-mismatched donors were more likely to be female, older and CMV positive.
  - In multivariate analysis, the only significant factor was the higher risk of graft failure with female donors, which results in worse OS, in particular in diseases with high rate of graft failure (e.g. CML and non-malignant disease), where female donors should be avoided if possible.

Following Bronwen Shaw’s presentation on the ANT experience, a panel discussion on this topic was co-chaired by Charles Craddock (Birmingham) and David Marks (Bristol) with contributions from John Gribben (London), Stephen Mackinnon (London), Antonio Pagliuca (London) and Nigel Russell (Nottingham). All panellists agreed that high-resolution HLA-matching was the first factor to be considered in UD selection. John Gribben discussed results from the National Marrow Donor Program (USA),<sup>7,8</sup> and his experience with the transplant programme at the Dana-Farber Cancer Institute in Boston; he stressed the clinical importance of identifying a good (10/10) HLA-matched donor. The other panellists agreed although they added that they would consider use of donors with one or even two mismatches depending on the precise clinical situation, particularly if the transplant protocol was based on T-cell depletion with CAMPATH. The ‘permissive’ effect of CAMPATH on mismatched UD was supported across myeloablative conditioning protocols (16/27 mismatched UD from the Royal Free Hospital) and reduced-intensity conditioning protocols (24/75 mismatched UD from King’s College Hospital). Thus, according to the panel discussion, although a good (10/10) match UD is desirable, it is not essential if the transplant protocol includes CAMPATH. Furthermore, Antonio Pagliuca and Stephen Mackinnon both stated that in their transplant centres the outcome of UD-HSCT was at least comparable to that of sibling donor HSCT. In high-risk MDS/AML patients transplanted at King’s College Hospital (reduced intensity: fludarabine, CAMPATH, busulfan) a reduced risk of relapse and an improved disease-free survival (DFS) was seen in UD-HSCT compared with sibling transplants. Indeed, based on the results from King’s College Hospital, Antonio Pagliuca suggested that for older patients undergoing a reduced-intensity conditioning transplant for a high-risk MDS/AML, a younger UD may be preferable to an older sibling donor. At the Royal Free Hospital, in patients transplanted for AML (myeloablative: TBI 14.4 Gy, fludarabine, cyclophosphamide and CAMPATH *in vitro*), there was no difference in DFS between UD and sibling donor HSCT.

The cumulative incidence of CMV reactivation for patients at risk reported by panellists ranged from 65 (King’s College Hospital) to 83% (Royal Free Hospital). Large NMDP studies have shown that patients at risk of CMV reactivation have a survival disadvantage.<sup>9</sup> The small

numbers and the association of CMV-positive donor serology with other donor factors such as older age, HLA mismatches or female donors, make it difficult to draw any conclusions from the data presented by the individual centres or the ANT study. Nevertheless, the recommendation of the panel was to select donors with matching CMV serology, that is, both negative or both positive. CMV matching was the second most important donor selection factor for CAMPATH users, whereas non-CAMPATH users would consider donor age, gender or parity before CMV serology. Young male donors were considered best, and parity was considered a disadvantage, although no clear order of choice for these other donor factors could be deduced from the discussion. Nigel Russell highlighted a growing trend in Nottingham and elsewhere to opt for donors who are more likely to donate peripheral blood stem cells (PBSC), and he took this factor into consideration in the donor selection process.

### Cord blood usage

Gluckman *et al.*<sup>10</sup> in Paris performed the first UCB-HSCT in 1988. Since that time many UCB banks have been established; there are over 170 000 UCB units currently available in 37 banks from 21 countries ([www.bmdw.org](http://www.bmdw.org)). Moreover, the feasibility and efficacy of the procedure has been established, with over 2500 UCB-HSCT performed to date.<sup>11–20</sup> Thus, UCB is now a realistic and attractive alternative source of progenitors for HSCT for both children and adults<sup>21</sup> for situations in which a compatible volunteer UD cannot be found in a reasonable period of time. Acceptable UCB units can be found for the majority of patients as less close compatibility with the recipient is required than with bone marrow stem cells. Another relevant advantage of cord blood is the speed with which a cord blood unit can be transplanted once it has been identified (14 days versus 60 days for a donation from a volunteer donor). The aims of this session, co-chaired by Jacqueline Cornish (Bristol) and Alejandro Madrigal (ANT), were firstly to understand the clinician's point of view on the use of UCB based on the UK experience and international published data, secondly to learn under what circumstances transplant clinicians will select UCB in preference to an adult UD and thirdly to explore the potential impact of the use of UCB in HSCT practice in the UK.

Mary Slatter discussed the experience at the Newcastle Royal Infirmary on UCB-HSCT in children with primary

immunodeficiencies (PID).<sup>22–24</sup> She presented 15 cases of unrelated UCB-HSCT in paediatric patients (median age 3.5 months, range 7 days to 3.5 years) with various forms of PID, including severe combined immunodeficiency, Wiskott–Aldrich syndrome, chronic granulomatous disease, Omen's syndrome and reticular dysgenesis. The median UCB unit TNC was  $8 \times 10^7$ /kg. Overall outcome (e.g. GVHD and OS) and immune reconstitution were as good as with other sources of progenitors, with a median time to neutrophil engraftment of 22 days, time to platelet engraftment of 51 days, and time to T-cells  $>200 \times 10^6$ /l of 61 days. Additional important advantages of UCB presented in this clinical setting were faster time to schedule the HSCT, and good tolerance to one antigen (A or C locus) HLA-mismatches in a setting where a reduced risk of GVH reactions entailed no undesirable effects on disease relapse. These characteristics may make UCB a preferable source of progenitors also for children with metabolic diseases undergoing HSCT, as reviewed by Robert Wynn (Manchester). Published results show that UCB-HSCT following conditioning without total body irradiation (TBI) can improve neurological performance and decrease somatic features of Hurler's syndrome, the most severe form of mucopolysaccharidosis, which normally leads to progressive deterioration and death in childhood.<sup>25</sup> Unfortunately, in other forms of mucopolysaccharidosis such as San Fillipo syndrome (MPS IIIA and IIIB) there is no evidence that UCB-HSCT can alter the natural history of progressive neurological deterioration. Despite this growing experience with UCB-HSCT in rare non-malignant diseases, its main indications remain haematological malignancies. Paul Veys (London) concluded the paediatric presentations by outlining the consensus summaries from a Cord Blood Transplantation Meeting held in January 2004 at the Royal Society of Medicine in London. The potential advantages and disadvantages are summarized in Table 1. Based on these, the consensus was that for HSCT in paediatric patients with haematological malignancies, the first choice of donor is a matched sibling donor or sibling cord blood unit. If neither of these were available, the second choice should be a phenotypically HLA-matched family donor, a 10/10 matched volunteer UD or a 6/6 unrelated UCB unit. The third choice may be a mismatched family donor (5/6), a volunteer UD (9/10) or an unrelated UCB ( $\geq 5/6$ ). Poorer mismatches from family donors or unrelated UCB would be considered when no other donor is available.

While the experience in UCB-HSCT for adult patients with haematological malignancies is very limited in the UK,

**Table 1** Potential advantages and disadvantages of UCB units compared to other types of stem cell donor

Donor type	UCB	Sibling	VUD-BM	Haplo
Donor availability	$\geq 5/6 = \sim 40\%$ $\geq 4/6 = \sim 70\%$	$\sim 20\%$	$10/10 = \sim 40\%$ $\geq 9/10 = \sim 70\%$	$> 90\%$
Recall access to donor	Not available	Very probable and fast	Possible but slow	Very probable and immediate
Cost	High	Low	High	Intermediate
Risk of rejection	Low	Low	High	Low
Speed of engraftment	Slow	Fast	Moderate	Fast
Immune recovery	Moderate	Fast	Moderate	Very slow

data from three recent studies, two from registries – Eurocord/EBMT<sup>19</sup> and New York Blood Center/CIBMTR<sup>20</sup> – and one from the Medical Sciences Institute of the University of Tokyo,<sup>26</sup> confirm that UCB-HSCT can be used as an alternative to BMT from UD in adults with acute leukaemia with no available HLA-identical sibling. In particular, the Tokyo study showed that results of cord blood transplantation were superior to those obtained with bone marrow from UD in terms of acute GVHD, TRM and disease-free survival (DFS). The differences in the populations analysed in the three studies could explain some of the discordant results obtained, especially the worse results obtained with UCB-HSCT in the American series compared to the other two. The series reported by Laughlin *et al.* included transplants performed during the pioneering period of UCB-HSCT in adults, when mainly patients with no other option were transplanted and the relevance of cell dose and HLA compatibilities were not known, while in the other series the cord blood recipients were transplanted after 1998. The data from Eurocord demonstrate an improvement in the results of UCBT after this date. Additionally, the disparity of more than one HLA antigen was lower in the series of Rocha *et al.* (43%) than in the series of Laughlin *et al.* (77%) and Takahashi *et al.* (79%).

Further evidence of UCB-HSCT in adults outside the UK was provided by Rafael Duarte through updates on two previously published protocols. The standardized protocol designed by Guillermo Sanz (Valencia, Spain) (thiotepa, busulfan, cyclophosphamide and ATG, with cyclosporine and prednisone for GVHD prophylaxis) has expanded from the 22 adult patients initially reported<sup>27</sup> to include 75 patients with high-risk haematological malignancies with a median age of 30 years (16–46) and a median weight of 70 kg (41–112), who received UCBT with a median TNC dose  $2.1 (1.0-4.9) \times 10^7/\text{kg}$ . In this larger updated cohort treated with a uniform protocol, the median neutrophil engraftment remained on day +21 (11–57), and younger age (<30 vs  $\geq 30$ ) and early disease stage at transplant (vs advanced) were the main factors leading to a significantly reduced TRM at day +100 (14 and 22%, respectively) and prolonged DFS at 3 years (51% and 49%, respectively) (GF Sanz, personal communication). Rafael Duarte also reported an update on an innovative strategy developed by Manuel Fernandez (Madrid, Spain) to secure early neutrophil recovery following UCB-HSCT in adults with haematological malignancies by transplanting of a low number of highly purified CD34+ cells from an HLA haploidentical donor together with the UCB unit.<sup>28</sup> This has currently expanded from the original 15 cases to 28 patients with a median age of 30 years (16–60) and a variety of HLA matches; the median TNC of the cord blood unit was of 2.37 with CD34+ cells  $0.11 \times 10^6/\text{kg}$  (range 0.03–0.37). The haplo-identical co-transplantation had a median of  $2.31 \times 10^6/\text{kg}$  CD34+ cells (range 1.05–2.58) and a CD3+ count of  $2.5 \times 10^3/\text{kg}$  (range 0.5–9.8). This demonstrated extremely early recovery of neutrophils, at median 10 days (range 9–36). The procedure was well tolerated, with only 18.4% acute GVHD grades III–IV and 20% chronic GVHD (all limited). Morbidity was mainly due to infections unrelated

to neutropenia. Predicted 4-year overall survival was 69% for the whole group (MN Fernandez, personal communication).

The current results from both published data and the experience discussed by the assembled transplant clinicians, seemed to suggest that there is at least comparable efficacy between HLA-matched marrow and UCB for paediatric patients with acute leukaemia, and also for children with immunodeficiency or inborn errors of metabolism for whom UCB typically delivers a high TNC dose. Experience in other non-malignant disorders and for adults with haematological malignancies is currently very limited in the UK. However, the panellists agreed that there is an increased interest on UCB as an alternative source of HSC for transplant, and that an UD search strategy that explores volunteer UD panels and UCB banks simultaneously, when it is known that a donor is needed for stem cell transplant, is a reasonable way forward, in particular for ethnic minorities. This has the advantage of rapidly providing a wider choice for the physician to make a decision. In the meanwhile it is undoubtedly important to continue the drive to recruit more unrelated cord units, perhaps aiming particularly at increasing the pool of uncommon haplotypes by recruiting ethnic minority donors, who have a low representation in the current VUD panels. In the light of current data, there was enthusiasm for further exploration of the use of unrelated donor cord blood as a transplant source in the UK, and negotiations are in progress at the ANT to extend its registry activity to UCB banking.

### Regulatory and accreditation requirements

In the last decade, a complex accreditation framework for HSCT has evolved within the UK and in many other countries, and is increasingly influencing or dictating current practice on collection, processing and administration of stem cell grafts. As a consequence of this growing body of recommendations and regulations (Table 2), there was some predictable scepticism in the transplant community as to whether this increasing requirement for accreditation and regulatory compliance will be associated with improved clinical outcomes. A session of the workshop, co-chaired by Derwood Pamphilon (Bristol) and Jane Apperley (London), focused on regulatory and accreditation issues and their impact on clinical practice in UD transplants.

Derwood Pamphilon opened the session by discussing the EU Directive on Tissues and Cells, which aims to 'set standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells'. The Directive emphasizes the importance of preventing the transmission of infectious disease. It applies to stem cells from the bone marrow, peripheral and cord blood as well as foetal tissues and embryos. This is done within a regulatory framework, which is legally binding on member states of the EU. In the UK, the competent national authority is the Human Tissue Authority, created in April 2005, which will merge in 2008 with the Human Fertilization and Embryology Authority to form a new authority, the Regulatory Authority for

**Table 2** Documents addressing regulatory and accreditation aspects of HSCT in the UK

- EU Directive on Medicinal Products 2001/83/EC
- EU Directive on Clinical Trials 2001/20/EC
- A Code of Practice for Tissue Banks, DH, 2002
- Council of Europe (CoE) Guidance on the Safety and Quality of Organs, Tissue and Cells (2nd Edition, 2004)
- EU Directive on Tissues and Cells 2004/23/EC
- Joint Accreditation Committee of ISCT (Europe) and EBMT (JACIE) Standards and Accreditation Manual – 2nd Edition, 2005
- WHO: Consultation on Regulatory Requirements for Human Tissue and Cell Transplantation, 2005
- EC Proposals for a Consultation on Human Tissue Engineering and Tissue Engineered Products (TEPs), 2005. This includes somatic cell therapy products

**Table 3** Transplant activities covered by JACIE and EU Tissue Directive

<i>Clinical programme</i>	<i>Collection</i>	<i>Processing</i>
Size and organization		
Facilities	Facilities	Facilities
Staffing	Staffing	Staffing
QMP	QMP	QMP
Policies and procedures	Policies and procedures	Policies and procedures
Donor evaluation and selection	Donor evaluation/care at time of collection	Processing
Administration of high dose therapy	Collection procedure (BM or PBSC)	Cryopreservation
Data management	Labels	Labels
Records	Records	Issue Transportation Storage and disposal Records

JACIE has specific requirements not covered in the Tissue Directive; everything in the Tissue Directive is covered by JACIE

Tissues and Embryos (RATE). Although the EU Tissue Directive regulates hematopoietic stem cells used for transplant, it is not explicitly stated whether or not it applies to cells for immunotherapy such as donor lymphocytes, dendritic cells or NK cells. The EU is to introduce a regulatory framework for Tissue Engineered Products which aims to distinguish between unmodified cells used in transplants and cells that have been extensively manipulated or modified to alter their functional properties, which would be covered by the Medicinal Products Directive. Derwood Pamphilon discussed the characteristics of products covered by the different directives and illustrated cellular therapies which will fall within predictable grey areas between different frameworks. In his view, the reasons for continuing to regard the cellular materials used by UD-HSCT programmes as primarily within the EU Tissue Directive were:

- They have no extensive modification. Where they are targeted to CMV or similar pathogens this is merely an augmentation of their normal function.
- They are only minimally manipulated (by EC definitions; in contrast, the JACIE rules regard some procedures, for example, CD34+ cell selection, as extensive manipulation).
- They are not subject to a manufacturing process and each donation is destined for a single recipient, that is, they are bespoke.

Diana Samson (London) reviewed the structure and operation of JACIE in Europe and discussed its importance in UD-BMT. The primary aim of JACIE, established as the Joint Accreditation Committee for ISHAGE and EBMT in

1999, is to provide a means for transplant centres, collection facilities and processing laboratories to demonstrate high-quality practice. JACIE recognizes the need to ensure harmonization where possible between its own standards and other national and international standards, in particular the EU Tissue Directive. JACIE standards cover a wide range of activities, many of which are also covered by the EU Tissue Directive (Table 3). JACIE standards also apply to donor lymphocyte infusions, and other cells for immunotherapy which are referred to as therapeutic cells, but not to genetically engineered cells. The JACIE programme does not accredit cord blood collection banking facilities; this is carried out by FACT-NETCORD. With increased complexity in UD-HSCT and more components from UD being transferred across national boundaries there is a need to ensure consistent standards internationally. The regulatory standards will impact on the operations of donor registries. In the future, European UD-registries will require that collection centres to whom they contract the process of harvesting either bone marrow or peripheral blood stem cells are fully accredited by FACT or JACIE as appropriate. Likewise, preliminary discussions have indicated support for the proposal that registries should only supply cells to BMT programmes that are FACT/JACIE accredited. In addition, all registries should be accredited by the World Marrow Donor Association (WMDA) against its own standards. WMDA global standards are probably the most effective way, in the context of multiple national regulatory bodies, to safeguard the quality of HSCT using international UD while continuing to protect international donor availability to offer some patients a life-saving procedure.<sup>29</sup>

During the first year of full implementation of the JACIE programme, 25 centres in Western Europe were inspected by JACIE, including five in the UK. All centres were found to be functioning at a high level of excellence, and deficiencies, when present, were related primarily to quality management rather than clinical practice. Four of the five UK centres have now received full accreditation, and one is fully compliant except for EFI accreditation, which is awaited.

Jacqueline Cornish discussed the specific requirements for paediatric accreditation, focusing on the need for consistently high standards for paediatric practice. This concern was fuelled by the experience gained by the Kennedy Report on children undergoing cardiothoracic surgery in adult facilities, published in 2001 in the UK,<sup>30</sup> and further supported in HSCT by data compiled by the German BFM Group from a study of matched family donor transplants in ALL. The TRM was considerably greater in paediatric programmes transplanting fewer than 10 patients than in those transplanting more than 10 patients annually ( $28 \pm 0.7$  versus  $0.7 \pm 0.3\%$ , respectively;  $P=0.014$ ) (C Peters, personal communication). Three points were discussed in this session as being of particular importance:

- Paediatric HSCT must be performed by a designated paediatric team.
- The minimum requirement for a given paediatric transplant programme must be to perform 10 procedures annually. This standard is also required in combined programmes. At this time, however, this recommendation has not been accepted by FACT-JACIE.
- The indications for paediatric transplantation must be within the EBMT Guidelines for Paediatric Practice.

### Future developments

A final panel discussion co-chaired by Ray Powles (London) and Ghulam Mufti (London) aimed to gather information and opinions from the participants regarding future trends of the use of UD-HSCT.

Anne Parker (Glasgow) and Michael Potter (London) reviewed data from registry surveys and from the experience in their own healthcare areas; they both predicted continued increases in the rates of allogeneic HSCT with higher percentage of UD-HSCT, higher use of non-myeloablative reduced-intensity conditioning regimens, and higher use of peripheral blood stem cells (PBSC) compared with bone marrow (BM). According to data presented by Anne Parker, there is an expected increase in the incidence of haematological malignancies in Scotland in the next two decades, in particular an estimated  $\sim 40\%$  increase in non-Hodgkin lymphoma (NHL). In addition, a wider analysis of the improvement on other health areas (e.g. coronary heart disease-related mortality) is likely to provide a higher number of older patients who develop NHL, have a better fitness level, and become candidates for high dose therapy and also probably for reduced intensity UD-HSCT, a trend that other panellists agreed to be universal to judge from from UK and EBMT data. Other

traditional indications for UD-HSCT, such as chronic myeloid leukaemia (CML) have substantially decreased recently as a result of new targeted therapies, as pointed out by Eduardo Olavarria (London). The overall opinion of the panel, though, was that this effect is so far limited to CML, and that despite increasing numbers of new therapies being applied to other conditions such as multiple myeloma, this was traditionally a less clear indication for UD-HSCT, and may have a small impact in wider terms. A summary of trends on UD-HSCT discussed by the panel would identify the following groups with trends towards:

- Increased activity: Adult AML and ALL, MDS, CLL, NHL and HD
- Plateau in activity: Paediatric AML and ALL, SAA
- Uncertain trend: CML, myeloma, thalassaemia, solid organ tumors

Rafael Duarte discussed data from the ANT registry on the use of PBSC or BM as a source of stem cells for UD-HSCT. The ANT currently provides  $\sim 50\%$  BM and  $\sim 50\%$  PBSC, in line with reports from EBMT (58% PBSC in UD-HSCT).<sup>1</sup> The trend for use of PBSC is clearly upwards, with 65% of allogeneic sibling donor HSCT currently being performed with PBSC. Also the opinion of the participant transplant physicians was unanimously in favour of increasing the use of PBSC for UD-HSCT. A recent analysis of volunteer UD from the ANT has shown a higher prevalence of unresolved side effects derived from donation in donors who donated BM than in PBSC donors (18.5 vs 1.3%;  $P<0.001$ ; unpublished data). These results in the ANT volunteer donors, the recent updates from the WMDA on the lack of long-term complications derived from the use of G-CSF as mobilizing agent in healthy donors and the increasing demand for PBSC were all likely to impact donor counselling and thus the preferred source of HSC provided by ANT in very near future.

### Conclusion

Over more than three decades, The Anthony Nolan Trust has provided an UD for over 4000 children and adults lacking a suitable family member donor, and has remained at the forefront of developments in haematopoietic transplantation and bone marrow register management. During these three decades, major changes have occurred in clinical practice of UD-HSCT. These include change and recognition of new indications, significant improvement of the outcome as a result of better support care and less-toxic conditioning regimens, and thus expansion of the use of UD to older patients with higher comorbidities, improvement in the assessment and selection of the most suitable donors, and the progressive increase in the use of alternative sources of hematopoietic cells such as peripheral blood or cord blood units. In order to foster our goal of improving UD-HSCT availability and outcome in a progressively more complex clinical scenario, a new initiative from The Anthony Nolan Trust was launched in 2005 to convene an experts workshop to address the topical issues in this field. This report summarizes the discussions held in this workshop, which will likely develop into a

periodic event where transplant clinicians, scientists and registry members will meet to share their experience and vision in the field of UD-HSCT.

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## Appendix A. List of participants

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