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Clinical Background

Allogeneic bone marrow transplantation (BMT) offers the hope of cure to patients with otherwise fatal blood and hematological malignancies. In its simplest form the process involves replacement of a diseased bone marrow with marrow from an otherwise healthy donor. Although complex, it is now known that a balanced engraftment of both donor hematopoietic blood forming stem or progenitor cells as well as donor immune white blood cell effectors (T-lymphocytes) is required for sustained hematopoiesis and long term eradication of disease. Thus, it is not just the transplant conditioning that destroys host cancer cells but the downstream immunological consequences of a persistent attack from a donor immune system (also known as graft-versus-tumour effect).

Immune function of donor T-lymphocytes contributes to both therapeutic efficacy as well as unwanted post transplant side effects, including at times severe graft versus host disease (GVHD). Shifting the balance of therapeutic efficacy from stem cell replacement to maintenance of a transplanted immune system has led to less intense preparative regimens that focus on stable chimeric donor white blood cell immune survival. These less intense, reduced intensity conditioning (RIC) or “mini” allogeneic transplants are now routinely recommended for older patients with underlying incurable myeloid and lymphoid malignancies. BMT as an option for older patients has increased transplant activity in transplant centres across the country. In addition to RIC, other breakthroughs (i.e., use of cord blood in adult patients) in the field of stem cell transplant are transforming this procedure from a few, to many. During this growth phase we need to confirm that proper infrastructure, regulation and supports are in place to ensure success in this “high stakes” life saving procedure.

Allogeneic Transplants are Saving Lives

Once associated with a mortality of more than 60 per cent, the outcome of allogeneic BMT has dramatically improved through a blend of incremental breakthroughs. These include antimicrobials with greater specificity for bacterial and fungal infections that result from prolonged neutropenia. Preventive treatment strategies to mitigate severe systemic viral infections, rational use of growth factors and advances in general supportive care have also contributed to improved survival.

The process of safely performing allogeneic BMT is complex and requires the experience of a comprehensive multi-disciplinary team comprised of oncologists/hematologists, nurse practitioners, primary care nursing staff, pharmacy, social work, dietitians as well as consultation from a wide range of sub-specialities: gastroenterology, dermatology, infectious disease and respirology. Laboratory expertise in stem cell manipulation, enumeration and cryopreservation, utilization of blood products as well as DNA specific HLA-typing are also highly essential components of a successful transplant unit. Despite diverse backgrounds and an extensive list of steps, each specialty must properly perform and coordinate specific roles and responsibilities in an effort to ensure the optimal outcome for any individual patient. As mentioned, the hospital laboratory plays a unique and central role in the management of BMT patients which starts with ensuring that the stem cell product, either blood or marrow derived has been properly managed, modified (if requested), labelled, preserved and characterized. Given that a clinical outcome depends on the predicted performance of a specific product there is little room for error.
THE ORGANIZATION OF CANCER CARE

Stakes are High: Need for Regulation and Standardization

Bone marrow transplants are performed in 23 centres across Canada and there is a need to standardize transplant policies and procedures. Therapeutic cell products are regulated biologically and evaluation and accreditation of each transplant centre is obtained through inspections from Health Canada (mandatory) and in a growing number of centres by the Foundation of Cellular Therapy (FACT). Both organizations require a comprehensive set of validated Standard Operating Procedures (SOPs) and specific policies that ensure absolute patient/product safety. Evidence of well-developed, highly detailed and validated SOPs ensure that a program functions in an integrated manner under thorough scrutiny. Given many single points of failure, it is this absolute level of detail with a “no stone left unturned” mentality that results in consistent patient outcomes. Seeking and obtaining FACT approval remains important to Canadian transplant centres but does require appropriate support (infrastructure and staff) to establish and properly maintain. These ongoing funding requirements remain a significant current challenge in Canada; however given the direct link to patient safety there is a need to ensure that ongoing developments in transplant accreditation are maintained without compromise.

Despite important advances in the safety and outcome of allogeneic BMT patients there remains room for improvement in prevention and treatment of severe acute and chronic GVHD as well as relapse of the original disease. While research continues into the biological mechanisms of relapse, efforts to identify the best possible marrow donors in Canada also have the potential to dramatically improve transplant outcomes. In this regard increasing the collective pool of Canadian donors will also increase the likelihood of finding the “best match” thus yielding the best clinical results.

Bone Marrow Donors

Efforts to improve outcomes of patients undergoing BMT are constantly being refined and improved. Perhaps not surprisingly it is now known that the outcome of BMT largely relates to the individual that is providing the bone marrow graft. Obtaining stem cells from a donor can occur in one of three transplant situations.

Stem cells may be collected from a patient to be administered back into that patient. This is referred to as an autologous stem cell transplant and is used to treat patients up to the age of around 70 with multiple myeloma, relapsed non-Hodgkin’s lymphoma and Hodgkin’s lymphoma. Relapse of primary disease remains a predominant issue in this type of transplant.

An allogeneic transplant involves the use of a stem cell graft (containing CD34+ progenitor cells) that is provided by a healthy donor to a patient. In this setting a brother or sister, or twin may be called upon to donate blood/marrow stem cells. This is known as a matched-related alloBMT. Family members will be asked to undergo typing to determine if a sibling is a match (25 per cent chance). In Canada a sibling donor may have an option of providing bone marrow (approximately 1 litre – adult) collected from the pelvis while under anesthesia or mobilized peripheral blood progenitors (collected by leukopheresis – CBMTG Canadian phase III study). If a patient does not have a suitable available sibling an unrelated donor search will be initiated.

When an HLA matched unrelated donor is sought many additional issues emerge. These otherwise healthy donors are engaging in an altruistic act with the potential to save a life. At the same time it is important to ensure that the products collected from these donors remain confidential and have the best chance of optimal clinical performance. Whereas the availability of matched related sibling donor transplants may diminish over time due to smaller families, unrelated donors are clearly a future focus for growth and development. With the importance of maintaining a strong young healthy pool of Canadian donors this article will focus on two issues that will influence the state of allogeneic BMT in Canada. One relates to science and technology and the other to public or social awareness in our younger generations.

Sources of Marrow Stem Cells

Sources of stem cells have expanded over the past decade. While stem cells were traditionally obtained from the posterior pelvis of a donor under general anesthesia, stem cells can now be obtained from peripheral blood as well as from umbilical cord blood. Each source of stem cells, blood vs. marrow vs. cord, exhibits different biological properties. If one compares a bone marrow graft (approximately 1,000ml) to mobilized blood stem cells collected by leukopheresis distinct differences can be seen in graft composition. Interestingly, a mobilized peripheral blood product usually contains a greater number of CD34+ progenitor stem cells but also a greater number of CD3+ T lymphocytes and potentially a greater risk of chronic GVHD.

The Canadian Bone Marrow Transplant Group (CBMTG) is nearing completion of a large phase III study which will address the issue of optimal graft source by comparing filgrastim-mobilized blood to filgrastim-mobilized marrow in matched related alloBMT. This Canadian-led study will indi-
categorize the optimal source of stem cells based on a composite endpoint of relapse/mortality and GVHD, and will also evaluate what is the preferred approach based on the donor’s overall experience. Understanding these properties, including the recent use of cord blood derived stem cell products for children and more recently for adults, enables the ability to tailor which graft source should perform best for a given individual clinical situation.

As previously mentioned, a donor may be asked to donate stem cells for a sibling (brother or sister) or other family member (matched related donor) or to join a large national registry (matched unrelated donor). A national marrow donor program will HLA-type potential donors and maintain information in a registry that can be searched for a range of transplant eligible patients in need of a suitable marrow donor. All donors should be in good general health and undergo rigorous donor screening. As the transplant eligible age increases so does the potential donor pool of related siblings. Co-morbidities such as COPD, diabetes, heart disease need to be taken into consideration.

Any potential donor should be in satisfactory health so as to tolerate either anaesthesia-marrow harvest or administration of filgrastim and large volume apheresis. In addition to general health bone marrow donors must be screened for active malignancies (excluding “benign” basal cell skin cancer), transmissible viral disease (HIV, hepatitis B/C, HTLV-1, West Nile virus, syphilis), haematological diseases (sickle cell) as well as bleeding disorders. A combination of comprehensive questionnaires, complete history and physical examination ensure a donor is suitable.

Once screened and considered eligible the most relevant donor factor that predicts success across several clinical endpoints is age.

Bone marrow recipients from younger donors (i.e., less than 30 years of age) demonstrate improved five-year overall and disease-free survival. A modest decrease in severe GVHD has been noted with younger donors. Other factors include CMV serological status and blood type. Finally there may be a higher rate of chronic GVHD in recipients of stem cells from a female donor with a history of multiple births.

**Finding the Best Match**

As in other transplant situations, matches are based on the human leukocyte antigen (HLA) system. HLA is comprised of a series of genes on chromosome that encode cell-surface antigen presenting proteins intrinsically linked to our immune system. The major histocompatibility complex (MHC) is made up of two basic classes involved in antigen presentation and subsequent immune activation. MHC class I is typically involved in presentation of small peptides that result from intracellular digestion. MHC class II presents those extra-cellular antigens to host T lymphocytes. MHC class I includes HLA-A, HLA-B and HLA-C, whereas MHC class II includes HLA-DR, HLA-DQ, and HLA-DP. Proteins encoded by HLA define our unique self and directly instruct the immune system to recognize self versus non-self. In any individual one set (haplotype) of HLA genes comes directly from the mother and the other set from the father, leaving only a 25 per cent chance that any given sibling will match a brother or sister.

Previously, HLA typing was performed using serological testing to identify HLA serotypes. This provides a low-resolution map of an individual’s HLA type. Although useful in the related setting, there have been concerns regarding its use in unrelated donors where higher resolution of HLA genetic mapping will lead to a better match. If HLA typing lacked sufficient accuracy this would undoubtedly influence the rate of GVHD. HLA laboratories now perform high resolution molecular or DNA typing to ensure a potential unrelated donor/recipient pair are as highly matched (HLA A,B,C, DR) as possible. Studies suggest that employing a molecular approach can reduce the incidence of severe GVHD and improve survival by as much as 50 per cent.

Careful donor selection and molecular typing have improved the overall quality of unrelated transplants to the point where they are considered nearly as safe as when a related donor is used. However there are downsides, the first being that employing a highly specific molecular analysis will effectively reduce the number of available donors. Moreover the process may increase the time required to identify a potential donor worldwide. On average three to six months may be required and given the nature and stability of primary diseases requiring transplant (i.e., relapsed myeloid leukemia) this may not be feasible. Various algorithms now exist that combine a serological search with latter confirmatory molecular analysis. These steps may improve the time and expense of finding a suitable marrow donor.

Issues such as the number of simultaneous potential donors to be typed by high-resolution include whether a recipient has a rare allele or haplotype as well as the clinical urgency for allogeneic BMT are important. It should also be noted that a single allele mismatch (9/10) when typing for HLA-A, -B, -C, DRB1 and DQB1 (i.e., 10/10) may be considered by some centres. In this regard a single mismatch at B or C may be less of a concern than mismatches at A or DR. Potential Canadian donors are currently represented by OneMatch Stem Cell and Marrow Network. This group is actively developing algorithms to effectively and efficiently screen for possible Canadian donors in the least time possible using the results of a blend of intermediate and high-resolution typing techniques.

Despite these challenges the OneMatch national registry has seen a marked improvement in the number of available donors and utilization of Canadian stem cell products (Figures 1 and 2) and continues to provide highly matched bone marrow donors to Canadian patients in need of a transplant.

**Donor Registry—The Challenges**

Signing up to be a marrow donor is a voluntary act. The strength of any national registry, including our own Canadian registry is the number of potential donors available as well as the time and cost to search the registry in a step-wise efficient manner. In terms of creating a robust national registry Canada faces two challenges.

First, our overall population is relatively small and spread out. Our second major challenge relates to Canada as a highly diverse ethnic population.

As can be seen in Figure 3, the ethnic composition of the current OneMatch database demonstrates a non-representa-
tive proportion of non-Caucasian donors. Thus, there is an urgent need to connect to younger demographic groups. Despite significant advances in acquisition of transplantable stem cells many potential donors have concerns about pain and suffering that may be associated with the process. On the other hand our current “young generation” appears to have a raised level of social consciousness and are becoming increasingly involved. Thus, it becomes critical to provide an accurate message about the feasibility of becoming a bone marrow registrant. Specific issues require thoughtful discussion and an understanding that a collective willingness to become involved will have a direct beneficial clinical impact.

As previously mentioned optimal clinical outcomes are seen when young and healthy donors are engaged. This requires a targeted approach and may include special events within a community or the use of social networking strategies. A complete and accurate PCR-based molecular typing approach can now be undertaken using minute amounts of DNA. This can accurately be completed by a simple swab from inside the mouth with a Q-tip. Use of these buccal swabs has been well received in local marrow donor drives and events.

**Summary**

Bone marrow transplantation is an exciting and growing field of medicine. BMT remains the only chance of cure for many adults and children with otherwise fatal blood and marrow malignancies. No one should die waiting to find a bone marrow donor.

A blend of incremental improvements has led to significant improvements in the field with more patients living disease-free. Several challenges including an effective therapy for GVHD and reduction in rates of post transplant relapse still need solutions.

The availability or potential for allogeneic BMT is now being extended to additional disease states. Moreover current strategies to reduce treatment related toxicity through reduced-intensity BMT will enable a greater number of patients to safely undergo this procedure. Given that the likelihood of finding a sibling donor will always be only 25 per cent and that family sizes will likely diminish over time, the need to turn to a national registry will increase. Finding a match will depend on how many potential donors sign up. In Canada this number is increasing but we still need to target our younger populations.

We also need to ensure that any potential donor is the best possible donor and employ

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**FIGURE 1**

**CANADIAN UNRELATED TRANSPLANTS, 2002–2010**

Data from OneMatch – Stem Cell and Marrow Network, Canadian Blood Services

Allogeneic BMT in Canada is on the rise. The use of donors from international registries remains high. Increasing the pool of Canadian donors remains a challenge.

**FIGURE 2**

**CANADIAN DONOR REGISTRATIONS, 2003–2010**

Data from OneMatch – Stem Cell and Marrow Network, Canadian Blood Services

The number of Canadian unrelated bone marrow donors is on the rise with significant improvements noted since 2007.
high resolution HLA-typing to our matching strategy. Ultimately our goal is to ensure that all transplant eligible patients find a donor (either Canadian or from another registry) in a timely manner and enable all patients the chance of being cured.

Positive clinical outcomes will continue to improve with the implementation of comprehensive accreditation organizations and suitable funding required to maintain the current excellence of BMT transplant units across our country.

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