REPORT 7 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (A-07)
Hematopoietic Stem Cell Transplantation: Utilization of and Minority Representation on the National Bone Marrow Donor Registry
(Resolution 508, A-06)
(Reference Committee E)

EXECUTIVE SUMMARY

Objectives. To review the process of hematopoietic stem cell transplantation, the role of the National Marrow Donor Program (NMDP) in facilitating such transplants, and concerns that the National Bone Marrow Donor Registry is underutilized and underrepresentative of racial and ethnic minorities. Current projects by the NMDP to address such concerns, including the possible use of umbilical cord blood to alleviate underutilization and underrepresentation, are discussed.

Data Sources. Literature searches were conducted in the PubMed database for English-language articles published between 1997 and 2006 using the search terms "marrow donor," "National Marrow Donor Program," and "cord blood donation," in combination with the terms "minority" and "underrepresentation." The U.S. General Accounting Office's 2002 report entitled *Bone Marrow Transplants: Despite Recruitment Successes, National Program May Be Underutilized* and the NMDP Registry's 2004 Biennial Report were primary sources of information.

Results. The Registry has grown by more than 30% during the last 8 years to contain over 6 million donors, and strives to facilitate transplants for all patients who need them. Since 1998, the proportional distribution of racial and ethnic groups on the Registry has steadily approached their proportional distribution in the U.S. population. However, African-Americans and Hispanics are still somewhat underrepresented within the total number of donors, and it is estimated that the Registry is used by only approximately one-third of patients needing transplants. The NMDP has instituted programs addressing underutilization and underrepresentation, which have substantially increased the total number of donors and minority representation on the Registry. The NMDP has also increased efforts to recruit donors of umbilical cord blood.

Conclusions. NMDP-instituted programs have successfully increased the number of minorities represented in the Registry. Other programs are addressing underutilization concerns and the increase in umbilical cord blood units available on the Registry. Our American Medical Association supports these efforts and encourages the NMDP to continue its work to recruit and retain donors, and to maintain a diverse Registry.

1

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 7-A-07

Subject: Hematopoietic Stem Cell Transplantation: Utilization of and Minority Representation on the National Bone Marrow Donor Registry (Resolution 508, A-06)

Presented by: Mohamed K. Khan, MD, PhD, Chair

Referred to: Reference Committee E (Paul C. Matson, MD, Chair)

Resolution 508, introduced by the Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont Delegations at the 2006 American Medical Association (AMA) Annual Meeting and referred to the Board of Trustees, asks:

> That our American Medical Association comprehensively study the social, economic, and cultural issues surrounding bone marrow donor recruitment to make recommendations at the 2006 Interim Meeting for the purpose of:
>
> - making the donor pool larger
> - making individual potential donors more easily identifiable
> - better educating the public about the process of obtaining tissue for transplants
> - finding ways to solicit donors at the time of blood donation
> - finding ways to pay for initial typing of donors
> - increasing the availability of minority donors
> - examining the potential beneficial impact of increasing the donor pool, and
> - exploring ways the impact of cord blood banking may be used to help solve these deficiencies

Bone marrow, peripheral blood stem cell (PBSC), and umbilical cord blood (UCB) transplants can be life-saving therapies for patients diagnosed with leukemia or other blood, metabolic, or immune system disorders. However, it is often difficult for patients who need transplants to find matching donors. The National Bone Marrow Donor Registry, officially named the C.W. Bill Young Cell Transplantation Program, is operated by the National Marrow Donor Program (NMDP) and exists to help patients and physicians find an appropriate donor when no related donor is available. Concerns exist that the Registry is underutilized, in part because it fails to proportionally represent ethnic minorities in its donor population. Much of the public is uninformed about the benefits of transplantation and therefore is not aware of the need for donors. There are also misconceptions that donation is risky and painful, decreasing the pool of available donors. Our AMA has addressed this subject in several previous reports and in policy concerning transplantation of solid organs, bone marrow, and UCB (see below). This report briefly reviews the processes of bone marrow, PBSC, and UCB transplantation, and the efforts of the NMDP to recruit potential donors. It also addresses barriers to donation and strategies to increase the minority donor pool.

Methods

Literature searches were conducted in the PubMed database for English-language articles published between 1997 and 2006 using the search terms "marrow donor," "National Marrow Donor Program," and "cord blood donation," in combination with the terms "minority" and "underrepresentation." Additionally, a large amount of information was collected from 2 comprehensive reviews. The first is the 2004 Biennial Report of the National Bone Marrow Donor Registry and the second is a review of the NMDP by the U.S. General Accounting Office (GAO) that addresses concerns that the program is underutilized. Additional articles were identified by review of the literature citations in articles identified using PubMed. Web sites of the NMDP and other private donor registries were also consulted for information.

Introduction

Since the first bone marrow transplant in 1968, survival of patients who undergo hematopoietic stem cell transplantation has improved dramatically.[1] Bone marrow transplantation (BMT) and PBSC and UCB transplantation have become common therapies for patients diagnosed with leukemias or other blood, metabolic, or immune system disorders.[2] Bone marrow, peripheral blood, and UCB contain hematopoietic stem cells; ie, cells that are able to produce white blood cells, red blood cells, and platelets.[3] In patients suffering from leukemias, lymphomas, myelomas, anemias, inherited immune system disorders (such as severe combined immunodeficiency [SCID]), hemoglobinopathies, inherited metabolic disorders, myelodysplastic and myeloproliferative disorders, and hystiocytic disorders, treatment often involves aggressive chemotherapy and/or radiation, which depletes or destroys the patient's own hematopoietic stem cells.[3] Without these cells, the patient's blood no longer contains the necessary cell types to fight infection, coagulate properly, or carry oxygen. Replacement of hematopoietic stem cells with a transplant can restore the patient's immune, oxygen-carrying, and clotting functions.[1]

There are three types of transplants: in an autologous transplant, the patient receives his or her own stem cells; in a syngeneic transplant, the patient receives stem cells from his or her identical twin; in an allogeneic transplant, the patient receives stem cells from a genetically similar individual (related or non-related).[4] The type of transplant an individual receives depends on the condition for which he or she is being treated and the availability of an appropriate donor. Since most patients do not have an identical twin and since only approximately 30% of patients have a related individual who is an appropriate donor, approximately 70% of patients seeking an allogeneic transplant will need to search for an unrelated donor.[5]

The allogeneic donation/transplantation procedure varies depending on the source of the hematopoietic stem cells. Bone marrow is harvested from a matching donor using a needle to draw the marrow out of the pelvic bone or the sternum. The donor is under general or regional anesthesia, and the process takes approximately 1 hour. Small bone fragments and blood are removed from the harvested marrow, which is then transported as quickly as possible and infused intravenously into the patient.[4] A PBSC donor is usually given the drug filgrastim, a growth factor that stimulates increased production of stem cells that are then released into the blood stream. The PBSCs are collected by apheresis, a process by which the donor's blood is circulated through a cell separator that removes the PBSCs and returns the rest of the blood to the donor's body. Apheresis usually takes approximately 4 to 6 hours.[4] UCB is collected from the umbilical cord and placenta of a newborn after delivery is complete. Hematopoietic stem cells are collected from the UCB and frozen until needed.[4]

Prior to receiving donated hematopoietic stem cells, recipients undergo regimens that deplete or destroy their cancer cells or abnormal marrow. Myeloablative regimens, ie, the use of high-dose chemotherapy and/or radiation to destroy all cancer cells and abnormal marrow, are most commonly used.[6,7] However, recent advances in transplantation therapy have made non-myeloablative and reduced-intensity regimens effective as well. These regimens have increased the number of patients who can receive transplants since those who could not tolerate a myeloablative regimen may be better able to tolerate the lower toxicity associated with a non-myeloablative regimen.[6,7] Once the preparative regimen has been completed, the patient receives the stem cells through an intravenous line. The infusion usually lasts between 1 and 5 hours.[4] Depending on the source of the stem cells, engraftment, ie, the production of white and red cells and platelets by the new stem cells, occurs 2 to 4 weeks after the transplant.[4] In recipients who have undergone non-myeloablative regimens or in patients who have undergone myeloablative regimens that did not destroy all cancer cells, the transplanted stem cells often cause a graft-versus-tumor (GVT) effect, in which the new stem cells recognize the cancer cells as foreign and attack them.[4]

HLA Matching

A specific donor is chosen for each transplant recipient based on the degree of human leukocyte antigen (HLA) matching. HLA alleles are inherited; one set maternally and the other paternally. The NMDP recommends that DNA-based testing be used to type the patient at high resolution at 4 HLA sites, HLA-A, HLA-B, HLA-C, and HLA-DRB1.[8-10] There are many other HLA alleles for which it may be useful to type, but the benefit of matching at these others is not clear. Since HLA alleles are inherited, there is a possibility that the patient carries 8 different HLA alleles at the 4 sites recommended for typing (4 maternal alleles that differ from 4 paternal alleles). Once the patient is typed, his or her immediate family is also typed at high resolution using DNA-based testing.[9] This confirms the patient's HLA alleles, and identifies whether family members carry enough identical alleles to be considered appropriate donors. If an appropriate donor is not identified within the family, then an unrelated donor may be identified based on his or her HLA type, determined in the same way as that of the patient and potential related donors. The NMDP recommends that both related and unrelated donors match at no less than 5 of 6 HLA antigens at HLA-A, -B, and -DRB1 for bone marrow and PBSC transplants, and at no less than 4 of 6 HLA antigens for UCB transplants.[8-10] These NMDP minimal HLA matching criteria must be met before the NMDP will release a donor or UCB unit to a transplant center. Some transplant centers have higher HLA matching criteria. Clinical data suggest that additional matches may improve outcome.[10] If stem cells from a donor with fewer than the recommended number of matching HLA alleles are used for a transplant, the recipient is at risk of developing graft-versus-host disease (GVHD), a potentially fatal complication in which the donor's stem cells identify cells in the recipient's body as foreign and attack them.[4,8] However, even in a fully matched transplant, there is still a chance that the recipient may develop GVHD. Conversely, it is also possible that a mismatched transplant recipient will not develop GVHD.

Sources of Hematopoietic Stem Cells

Although bone marrow is a common source of hematopoietic stem cells, two other sources have been used successfully in recent years. Both peripheral blood and UCB contain hematopoietic stem cells. The selection of a stem cell source is based on both patient- and disease-specific factors.[1,11] Bone marrow is often selected because it has been the standard therapy for many years and ample data are available on transplant outcomes. Time to engraftment is somewhat slower in bone marrow transplants than in PBSC transplants, but the risk of GVHD is lower. Bone marrow is the most common stem cell source for patients under 20 years of age.[1,11] PBSC

transplants have better outcomes in adults than in children, and are now the most common stem cell choice for patients over age 20 years. Time to engraftment is often shorter than in bone marrow transplants, and the donor collection procedure is easier. However, the risk of GVHD is higher with PBSC transplants than with bone marrow.[1,11] UCB transplants are beginning to be more common in patients under age 20 years. Matching requirements are less restrictive in UCB transplants, meaning matches are found more quickly. In addition, cryopreserved UCB units are readily available in cord blood banks, meaning that UCB transplants can be performed more quickly. UCB transplants are associated with reduced GVHD risk; however, time to engraftment is slower with UCB, and the small volume of blood yields fewer cells for transplantation. Therefore, UCB transplants are most commonly used in pediatric patients and in patients who have a small body size.[1,11]

The National Marrow Donor Program and Registry

The NMDP, a nonprofit organization established in 1986,[12] operates the National Bone Marrow Donor Registry (Registry), the world's largest unrelated donor hematopoietic stem cell registry, under a contract with the U.S. Department of Health and Human Services (HHS) and the Health Resources and Services Administration (HRSA), with additional support from the U.S. Navy.[5,12] The operating costs of the NMDP are greater than $160 million per year. The HHS and the Navy provide approximately 22% of the NMDP budget each year, with program revenue and private sources providing the rest.[5,12] Since its establishment through 2006, the NMDP has facilitated more than 25,000 transplants.[1] The NMDP coordinates transplants by managing a network of more than 450 affiliated organizations that include donor, apheresis, collection and transplant centers, recruitment groups, cord blood banks, DNA typing and phenotyping laboratories, and sample repositories.[5,12,13] As of 2004, more than 70 of these affiliated organizations were located internationally.[12,13] The Registry currently contains more than six million potential donors; the majority of whom (ie, those who joined after 2001) are fully typed for HLA-A, -B, and -DRB1, while a small percentage (ie, those who joined in 2001 or before) are typed for HLA-A and –B.[12]

The total number of donors on the Registry has grown by more than 30% during the last eight years, and in the first five years of UCB collection, more than 40,000 units were obtained.[1] Donor recruitment is commonly achieved through local recruitment drives, with donor centers and recruitment groups often conducting a total of more than 800 drives each month in the United States.[12] Donor centers and recruitment groups work locally with civic, community, faith-based, and corporate organizations to raise awareness and recruit donors. Additionally, with the help of a donor center, families and communities can organize recruitment drives, typically intended to find a donor for a specific patient who has been unsuccessful in locating a donor. Those recruited donors, while not necessarily a match for the patient for whom the drive was organized, still become part of the Registry.[12] Volunteer donors are eligible to join the Registry at age 18 years and can remain on it until age 61 years, although they may request to be removed before that age. Donors will also be removed before age 61 years if they develop a health condition that confers an unacceptable risk to a potential recipient or to themselves (were they to donate).[5,12] The NMDP charges donors a fee of $52 to cover initial tissue typing.[14] In most cases, this fee is paid by matching funds raised by the NMDP, private sources, or the federal government. There is no charge to minority donors. If a volunteer joins the NMDP Registry through the NMDP Web site, the $52 tissue typing fee is paid by the volunteer. If the donor matches a patient in need of a transplant, there is no cost to the donor for the additional testing and donation procedures.[5] Donation of UCB is generally an option given to pregnant women over age 18 years and in good health. There is no cost to donate UCB.[15]

The donor pool is made up of volunteers from several racial and ethnic groups, including Caucasian, Hispanic, African-American, Asian/Pacific Islander, American Indian/Alaska Native, and people of mixed race.[5,12] Historically, the NMDP has focused on increasing the number of volunteer donors from the general public, with the goal of replacing donors lost through attrition and increasing the diversity of HLA types represented on the Registry.[12] Now that the Registry exceeds 6 million donors and continues to grow, it is less likely that newly recruited donors will have an HLA tissue type that differs from existing donors. For this reason, the NMDP has increased its efforts to retain existing donors and to recruit donors from minority groups that are underrepresented on the Registry.[5] Our AMA supports efforts to increase the number of donors on the Registry, and has suggested that a question inquiring about donor interest be added to the standard questionnaire that is required for blood donation (Policy H-50.980 [AMA Policy Database]; see Appendix). To date, that question has not been added. It may not be feasible for all blood centers to include such a question since there are not necessarily NMDP donor centers or recruitment groups nearby with which the blood center could partner.

Since a donor could conceivably be a part of the Registry for more than 40 years, a significant amount of time may pass before a donor is contacted about a possible match. During this period, donors may have relocated without notifying the NMDP, developed a medical condition that makes them ineligible to donate, or are no longer interested in donating. Donor retention projects aim to increase the probability of donors on the Registry remaining interested, locatable, and available for donations over the extensive period that they may be a part of the Registry.[12] Past research by the NMDP has shown that regular communication with donors increases retention, and for that reason is a key part of the retention strategy. Donors are annually mailed "The Marrow Messenger," a newsletter containing updates on the activities of the NMDP and a reminder that the donor is registered with the NMDP.[12] It contains a change-of-address card and a request in six languages for the card to be completed if the donor has relocated. It also contains a list of the donor eligibility requirements along with a request to notify the donor center if the donor believes he or she may be ineligible to donate. Issues of "The Marrow Messenger" that are returned as undeliverable are forwarded to the appropriate donor center to alert them that the particular donor is not locatable. In fiscal year 2006, more than 290,000 donor addresses were updated by this method. Regular communication is also initiated by individual donor centers, which also may mail publications to donors.[12] Other retention strategies include communication by e-mail and the mailing of greeting cards thanking donors for their commitment.[12] As a result of these varied strategies, in fiscal year 2006 the NMDP processed more than 4,000 donor updates via phone contact and more than 41,000 change of address updates via the NMDP Web site.

Donor characteristics that are related to retention were investigated in a study of approximately 750 volunteer donors.[16] A donor's volunteer history was found to significantly affect donor retention. Specifically, blood donors are less likely to drop out of the Registry, while those who have been on the Registry for more than four years were more likely to drop out.[16] Recruitment-related issues were also associated with retention. Those who delayed the decision to join the Registry, or those who were discouraged from joining by others were more likely to drop out, while those who consulted a professional or a relative were less likely.[15] Those who joined with others or joined at a community or family drive for a specific patient were more likely to drop out.[16] Concerns about the actual donation process affect retention as well. Not surprisingly, those who feared pain, needles, side-effects, and damage to their own health were more likely to drop out of the Registry.[16] Based on these findings, Switzer et al[16] suggest that to increase retention, recruitment settings should strive to reduce ambivalence about joining, shield potential donors from social pressures to join, foster intrinsic commitment to donating, and allay medical concerns.

Donor Search Process

Several steps are required when a physician and patient search the Registry for a potential donor. When a patient becomes a candidate for a hematopoietic stem cell transplant, the patient's physician submits information such as the patient's age, sex, race, disease, disease stage, and HLA type to the Registry.[5,12] Using a computer algorithm, the NMDP carries out a preliminary search of the Registry for donors and cord blood units whose HLA type matches the patient's. A list of donors and cord blood units on the Registry that are potentially matched with the patient is reported back to the physician by the next business day.[5,12] Throughout the search, all identifying information on potential donors is kept confidential from the patient and physician to prevent pressure to donate.

If the physician and patient elect to continue, a more formal search is initiated. Although any physician can initiate a preliminary search, only a physician affiliated with an NMDP transplant center may initiate a formal search. If the physician is not affiliated, the NMDP Office of Patient Advocacy handles the search request.[5,12] In the formal search, the potential donor is contacted by the NMDP and further testing is carried out. HLA types of the donor and the patient are confirmed using fresh blood samples, or if UCB is required, confirmatory typing of the unit is performed. The donor sample is also tested for possible infectious disease that could be transmitted to the patient.[5,12] If a cord blood unit is chosen, then it is shipped to the transplant center. If a donor is chosen, then the donor is further counseled and educated on the process, and a thorough physical examination is carried out to ensure that the donor is healthy enough to withstand the donation procedure.[5,12] If the donor is fit enough to donate, then he or she is asked to sign an Intent to Donate form, after which the collection of the donor's stem cells is scheduled. The donor has the option of declining to proceed at any point prior to signing the Intent to Donate form.[5,12] For a marrow or PBSC donor, the median time from initiation of the formal search to the request for a donor is 51 days. For a cord blood unit, the average time from initiation of the formal search to the request for a cord blood unit is less than two weeks (I. Terrio, personal communication). Often, the timeframe for the search process is dependent on the condition of the patient and the success of other treatments occurring at the same time the search is being conducted.[17] Time to procurement of bone marrow or PBSC is dependent on the location of patient and donor and on the urgency of the transplant. Time to procurement of UCB is usually shorter because the stem cells have already been collected and need only to be shipped (I. Terrio, personal communication).

For each formal search, the Registry bills the transplant center a one-time fee of approximately $700, plus the cost of each further test component, each of which can be more than $200 (T. Walker, personal communication). The transplant center may pay thousands of dollars for a single patient's search since multiple donors may need to be tested before an appropriate donor is chosen. The patient may ultimately pay even more once the charges from the transplant center are passed on.[5] Few insurance companies pay for a patient's search, although most pay for the collection of the stem cells and the actual transplant.[5]

Other Registries

Several registries besides the NMDP's exist, with some outside the United States approaching the number of donors on the NMDP Registry.[18-22] These registries offer alternatives to the NMDP Registry and are often utilized when a matching donor cannot be identified using the NMDP Registry.[21] Almost all registries are part of the Bone Marrow Donors Worldwide (BMDW) network.[23] As part of any search of the NMDP Registry, the NMDP will also search BMDW

registries, providing access to an additional 4 million volunteer donors. Many of the BMDW registries have cooperative relationships with the NMDP, and if a matching donor is identified in one, then the NMDP can facilitate a transplant. If the NMDP identifies a donor on a BMDW registry with whom it does not have a cooperative relationship, then the NMDP cannot facilitate the transplant and instead the patient's physician must contact the other registry to begin the procurement procedure. Frequently, physicians have more experience with one registry or another, and will choose to continue using that registry for their other patients.[5] A few of the alternative registries are focused on particular racial or ethnic groups, offering a donor pool for minorities whose ethnicity may be underrepresented on the NMDP Registry.[22] In general, search and donation procedures of alternative registries are similar to those of the NMDP Registry.[18-20]

Underutilization of the Registry and NMDP Efforts to Increase Utilization

It is not known exactly how many patients need transplants from unrelated donors each year, but it is estimated that the number of patients who utilize the Registry is about one-third of those requiring a transplant.[5] It is also estimated that only approximately one-tenth of patients requiring unrelated transplants actually obtain a transplant facilitated by the NMDP.[5] Considering that the NMDP is this country's largest facilitator of stem cell transplants and that the United States spends more than $40 million each year to partially fund it, the low number of patients utilizing it is troubling. The HHS (Office of the Inspector General) and the GAO have raised concerns about the low utilization of the NMDP, and in 2002, the GAO released a report entitled "Bone Marrow Transplants: Despite Recruitment Successes, National Program May Be Underutilized."[5] In the report, the extent to which the Registry is searched and utilized for transplants, the efforts of the NMDP to provide equal opportunity for all racial and ethnic groups to find compatible donors, and the management of donor centers were addressed.

The GAO report cited several factors contributing to the underutilization of the Registry for searches and transplants, some of which are outside of the NMDP's control. The most common reason that a preliminary search is initiated but not continued is a change in medical condition of the recipient following the preliminary search that renders him or her an inappropriate candidate for transplantation.[5] This is often due to delayed referral to a transplant physician. The NMDP and the American Society for Blood and Marrow Transplantation (ASBMT) have developed guidelines, "Recommended Timing for Transplant Consultation," to assist referring physicians in understanding when a patient is a candidate for transplantation.[24] Another factor thought to contribute to underutilization is that stem cells are obtained from a source other than the NMDP, such as a related donor or a different registry.[5] Search and collection costs may contribute to underutilization. The NMDP is one of only a few registries worldwide that charges a fee for a formal search, and the cost of stem cell procurement at NMDP tends to be higher.[5] There is also some thought among transplant center administrators that the NMDP takes longer to provide the stem cells than other programs.[5] Importantly, inability to find a matching donor was not found to significantly contribute to underutilization.[5]

The NMDP has attempted to increase utilization by addressing the concern of many physicians that it is slow in providing stem cells. In 2004, it instituted an urgent search pilot project to explore methods of accelerating the search process for patients in critical need of a transplant.[12] The project uses a donor selection team at the NMDP national office experienced in HLA matching that manages all aspects of the donor search. It identifies and tissue types 10 to 12 potential donors for each patient simultaneously, saving time in finding a suitable match.[12] This project has also used volunteers' frozen blood samples for confirmatory testing whenever possible instead of drawing fresh samples.[12] Using these strategies, the NMDP was able to shorten its time from formal search initiation to transplantation from 4.8 months in 1993 to 3.7

months in 2000.[5] Although the project was intended to facilitate transplants for patients needing them urgently, the NMDP has shown that it is capable of increasing its efficiency, which may increase utilization of the Registry.

Minority Representation on the Registry and Recruitment Programs

Since 1998, the proportional distribution of racial and ethnic groups on the Registry has steadily approached their proportional distribution in the U.S. population.[5,12] In fact, between 1998 and 2001, the number of minority donors increased by between 30% and 53%.[12] However, African-Americans and Hispanics are still underrepresented within the total number of donors on the Registry by 17% and 15%, respectively.[5] In 2001, Caucasians with transplantable disorders had an approximately 80% chance of finding a donor by searching the Registry, while African-American had a less than 30% chance.[25] The increase in the number of minority donors recruited to the Registry has translated into more transplants for minorities. Since 2002, there has been an average increase of 17% per year in transplants to African-American patients (T. Walker, personal communication).

A survey of nearly 600 African-Americans showed that one of the most common barriers to bone marrow donation is a lack of awareness, both of the existence of the NMDP and that transplantation can save lives.[25] Those individuals who did know that transplantation can save lives were more than twice as likely to donate.[25] Lack of opportunity to donate and the cost associated with donation were also cited as barriers.[25] Fear of pain and inconvenience were cited, although much less frequently than the previously mentioned factors.[25] Another study found a similar lack of awareness of the existence of the NMDP, but that willingness to donate was not lower among African-Americans.[26] In contrast to Laver et al,[25] Onitilo et al[26] found that for those who were not willing to donate, fear of pain was the most commonly cited reason. In general, and more so in African-Americans, many who indicated they were willing to donate were unwilling to be contacted to sign up for the Registry.[26]

Commonly cited barriers to donation in African-Americans identified by both Laver et al[25] and Onitilo et al[26] can be largely addressed by educational strategies such as group sessions conducted at churches and community centers and aimed at increasing knowledge of the existence of the NMDP, that bone marrow can save lives, and that matches are more likely within the same ethnic group. In addition to a description of the donation procedure, educational materials should include a description of the type and severity of pain that is likely to be encountered, and the risk of an adverse outcome during the donation process, since it a common misconception that donation is painful and risky.[25,26] The NMDP pays the typing costs for minority donors (see below),[12] so an effort should be made to address the misconception that donation is costly. Not surprisingly, a similar disparity in minority willingness to donate solid organs has been observed and was reviewed in Report 4 (I-02) of the Council on Scientific Affairs, entitled "Increasing Organ Donation."[27] Awareness and educational strategies similar to those aimed at increasing minority representation on the Registry were suggested for increasing the willingness of minorities to donate solid organs.[27]

The NMDP has recognized that underrepresentation of racial and ethnic groups on the Registry may lead to unequal opportunity for all patients in need of transplants to find matches and has instituted several programs, many of which address the suggestions by Laver and Onitilo, aimed at increasing minority representation on the Registry.[12] Our AMA supports efforts to increase the number of donors on the Registry, especially those in minority groups (Policy H-370.974; see Appendix).

Between 1993 and 1997, the NMDP instituted four minority recruitment initiatives aimed at African-Americans, Asian/Pacific Islanders, Hispanics, and American Indian/Alaska Natives.[12] Each initiative included public education materials such as public service announcements, recruitment brochures, and promotional materials that were distributed to donation centers either free or at reduced costs.[12] The materials were translated into five languages, and focused on educating minorities about the importance to people of their own race or ethnic background of becoming a donor.[12]

In 2003, the NMDP intensified its efforts to recruit African-American donors with a program aimed at increasing awareness of the NMDP, increasing understanding of the need for minority donors, and increasing motivation of African-Americans to join the Registry.[12] Market research was conducted to determine the most effective ways to target the African-American community, and based on the results, new print, Web, and public service announcements were developed. The NMDP also established partnerships with the African-American fraternity Phi Beta Sigma, XM Satellite Radio, and Essence Magazine.[12]

The NMDP has continued specialized efforts to recruit minorities. Currently, the NMDP pays the full costs of tissue typing for donors from minority groups with funds provided by HRSA and the Navy.[12] Also, the NMDP and each donor center negotiate minority recruitment goals based on the population demographics of the location of the donor center. Donor centers are reimbursed by the NMDP $28 for each recruited minority donor and $10 for each recruited Caucasian donor up to the number specified in its recruitment goal.[5,12] Financial penalties are levied when donor centers fail to meet their recruitment goal.[5] HRSA funds have also been made available for minority-focused recruitment of UCB donors in order to increase the ethnic diversity of cord blood in the Registry.[12]

HRSA challenges the notion that minorities continue to be underrepresented on the Registry, and reports that NMDP efforts to increase minority representation have been successful.[17] Among the group of donors who joined the Registry after 2001 and are fully typed for HLA-A, -B, and –DRB1, each racial and ethnic group with the exception of Caucasians comprises a larger proportion of the Registry than they do the general population.[17] Over 98% of donors are chosen from the fully typed group.[17]

It is important to note that it may never be possible to increase the likelihood of an African-American finding a donor to that of a Caucasian.[5,25,26] Some minority groups, including African-Americans, have more rare and varied HLA combinations than do Caucasians. Finding a match from an ethnically defined group of donors with rarer and more varied HLA types is more difficult than finding a match among Caucasian donors, even if the donor groups are the same size.[5,25,26] Although equal access to transplants for all groups is a goal of the NMDP, the recruitment of a large number of minority donors in an effort to add rare HLA types to the donor pool is expensive, and may deplete resources required to recruit donors with common HLA types that might more readily increase the number of matches.[5] The GAO report did not find that inability to find a donor contributed to underutilization.[5] Therefore, minority recruitment efforts that have increased minority representation on the Registry and have increased donor-recipient matches may not have significantly increased the Registry's utilization.

<u>UCB as an Alternative Source of Stem Cells</u>

The NMDP cord blood program was established in 1998 to increase the options for patients in need of hematopoietic stem cell transplants.[12] UCB is collected from the umbilical cord and placenta of a newborn.[28] Within 48 hours of collection, the UCB undergoes quality control

testing that includes bacterial and fungal cultures, ABO blood and Rh type, and cellular counts.[28] In addition, a sample of the mother's blood is screened for infectious diseases.[28] HLA typing is typically not done until after the cultures and maternal infectious disease markers are complete (and found to be negative). Red blood cells and plasma are often removed to reduce the volume of UCB that will be stored, and the remaining sample containing the stem cells is cryopreserved and entered into the Registry.[28] UCB transplantation, including its benefits and risks, was thoroughly reviewed in Report 2 (A-03) of the Council on Scientific Affairs, entitled "Umbilical Cord Blood Transplantation: Current Scientific Understanding."[29]

A 4-out-of-6 HLA match is required by the NMDP for a UCB transplant.[1] This contrasts to a 5-out-of-6 HLA-match requirement for bone marrow or PBSC.[1] Since the matching criteria for UCB are less restrictive, it is often easier to find a match for a patient in need of a transplant.[12] Physicians can search simultaneously for marrow donors and for cord blood units stored at NMDP-affiliated cord blood banks.[12] Since the cord blood is stored, a matched unit can take as little as 2 weeks to obtain, making cord blood a preferred source of hematopoietic stem cells for patients requiring urgent transplantations.[12] While risk of acute and chronic GVHD is reduced with UCB transplantation, time to engraftment is slower than with bone marrow or PBSC transplantation.[1]

Since HLA-matching requirements for UCB are more lenient, minorities with rarer and more varied HLA types who are in need of a transplant may have an increased chance of finding a UCB match. A minority recruitment project was initiated by the NMDP in 2001 with the goal of increasing the number of cord blood units donated by minorities.[12] The number of unique UCB HLA phenotypes on the Registry increased by approximately 7%, and substantial increases in matching rates were observed for African-Americans, Hispanics, Asian/Pacific Islanders, and Native Americans.[12] However, a 2002 study found that in general, minority donation of cord blood is less common than donation of marrow.[22] It is hypothesized that since recruitment efforts for UCB donation usually occur in doctors' offices and prenatal classes, those women who receive less prenatal care are less likely to learn about UCB donation.[22] African-American women are less likely to receive prenatal care and more likely to report barriers to prenatal care,[30] and therefore may not be aware of UCB donation opportunities. Cord blood donor centers that approach women after admission to the labor floor appear to be more successful at recruiting donors than those who focus recruitment efforts on prenatal settings.[22] General mistrust of the medical system by African-Americans is blamed in part for their lesser willingness to donate organs.[27,31,32] The same mistrust may contribute to an unwillingness to donate UCB. Ballen et al[22] suggest that recruitment strategies for minority UCB donation include hiring more minority employees for the cord blood program, recruiting donors on the labor floor, and establishing outreach programs in local churches and community organizations.

Our AMA supports efforts to inform physicians that UCB is a viable alternative to bone marrow for some patients (Policy H-370.970; see Appendix). However, ethical concerns exist about aggressively recruiting expectant mothers on the labor floor since thorough explanation of the risks and benefits of UBC donation and written consent of the parents is required (E-2.165; Appendix). Once an expectant mother is admitted to the labor floor, there may not be sufficient time for the risks and benefits to be explained, and the parents may be under such stress that they do not give full attention to the explanation before making a decision about donation.

Summary and Conclusions

Hematopoietic stem cell transplantation is a life-saving therapy for those patients who have access to a matching donor. The NMDP Registry contains more than six million donors, and

strives to facilitate transplants for all patients who need them. However, it is estimated that the program is only used by approximately one-third of patients needing transplants, and this underutilization, coupled with an apparent underrepresentation of minorities on the Registry, has caused concern. The NMDP has instituted programs addressing underutilization and underrepresentation, which have substantially increased the total number of donors and minority representation on the Registry. Our AMA supports NMDP efforts to increase the number of donors, especially from those racial and ethnic groups that are underrepresented. Our AMA also supports the use of UCB as an alternative to marrow when appropriate.

RECOMMENDATIONS

The Council on Science and Public Health recommends that the following be adopted in lieu of Resolution 508 (A-06) and that the remainder of this report be filed:

1. That our American Medical Association (AMA) monitor National Marrow Donor Program (NMDP) efforts to maintain a Registry that is large in number, representative of all racial and ethnic groups, and diverse in its human leukocyte antigen (HLA) types; these efforts include projects that aim to increase minority recruitment, retain existing donors, and recruit donors to replace those lost through attrition. (Directive to Take Action)

2. That our AMA encourage the NMDP to expand its efforts to increase utilization of the Registry through projects aimed at increasing patient and physician awareness of the NMDP, and at reducing the time and cost of stem cell procurement. (Directive to Take Action)

3. That our AMA encourage the NMDP to enhance efforts to increase the number of umbilical cord blood units donated to the Registry; particular attention should be paid to increasing donation by minorities**.** (Directive to Take Action)

4. That AMA Policy H-50.980 be amended by insertion, to read as follows:

   Our AMA supports efforts to increase blood donor awareness of bone marrow screening through the addition of a question on the questionnaire required for blood donation or through focused queries or invitations presented during the blood donation process that will assess the donor's interest in obtaining information about bone marrow donation, and that information be provided to those donors who indicate an interest. (Modify Current HOD Policy)

Fiscal Note: $1500

References

1. National Marrow Donor Program. *A Medical Professional's Guide to Unrelated Hematopoietic Cell Transplantation*; 2006. Available at: http://www.marrow.org/PHYSICIAN/Services_and_Education/Medical_Professionals_Guide/index.html. Accessed: February 1, 2007.

2. National Marrow Donor Program. *Diseases Treatable by Hematopoietic Stem Cell Transplantation*; 2006. Available at: http://www.marrow.org/PHYSICIAN/Tx_Indications_Timing_Referral/Diseases_Treatable_by_HCT/index.html. Accessed: February 12, 2007.

3. National Marrow Donor Program. *Learning More About Your Disease*; 2005. Available at: http://www.marrow.org/PATIENT/Undrstnd_Disease_Treat/Lrn_about_Disease/index.html. Accessed: December 18, 2006.

4. National Cancer Institute. *Bone Marrow Transplantation and Peripheral Blood Stem Cell Transplantation: Questions and Answers*; 2004. Available at: www.cancer.gov/PDF/FactSheet/fs7_41.pdf. Accessed: February 1, 2007.

5. U.S. General Accounting Office. *Bone Marrow Transplants: Despite Recruitment Successes, National Program May Be Underutilized*, GAO-02-994; 2002. Available at: http://www.gao.gov/new.items/d03182.pdf. Accessed: February 1, 2007.

6. National Marrow Donor Program. *Advances in Conditioning Regimens*; 2006. Available at: http://www.marrow.org/PHYSICIAN/Adv_in_Auto_Allo_Tx/Adv_in_Conditioning_Regimens/index.html. Accessed: December 18, 2006.

7. National Marrow Donor Program. *Expanded Patient Selection*; 2006. Available at: http://www.marrow.org/PHYSICIAN/Adv_in_Auto_Allo_Tx/Expanded_Patient_Selection/index.html. Accessed: December 18, 2006.

8. National Marrow Donor Program. *Advances in HLA Typing*; 2006. Available at: http://www.marrow.org/PHYSICIAN/Adv_in_Auto_Allo_Tx/Adv_in_HLA_Typing/index.html. Accessed: December 18, 2006.

9. National Marrow Donor Program. *HLA Matching for Hematopoietic Cell Transplantation*; 2006. Available at: http://www.marrow.org/PHYSICIAN/URD_Search_and_Tx/HLA_Matching_for_HTC/index.html. Accessed: February 12, 2007.

10. Hurley CK, Baxter Lowe LA, Logan B, Karanes C, Anasetti C, Weisdorf D, et al. National Marrow Donor Program HLA-matching guidelines for unrelated marrow transplants. *Biol Blood Marrow Transplant.* 2003;9(10):610-615.

11. National Marrow Donor Program. *Hematopoietic Cell Sources Tailored to the Patient*; 2006. Available at: http://www.marrow.org/PHYSICIAN/Adv_in_Auto_Allo_Tx/Hematopoietic_Cell_Sources_Tai/index.html. Accessed: December 18, 2006.

12. National Bone Marrow Donor Program. *Biennial Report of the National Bone Marrow Donor Registry*; 2004. Available at: http://www.marrow.org/ABOUT/Publications/2004_Biennial_Report/index.html. Accessed: February 1, 2007.

13. National Marrow Donor Program. *Report to the Community*; 2006. Available from the National Marrow Donor Program.

14. National Marrow Donor Program. *The Cost to Join*; 2006. Available at: http://www.marrow.org/HELP/Join_the_Registry/Cost_to_join/index.html. Accessed: February 12, 2007.

15. National Marrow Donor Program. *Donate Your Baby's Umbilical Cord Blood*; 2007. Available at: http://www.marrow.org/HELP/Donate_Babys_Umbilical_CB/index.html. Accessed: March 1, 2007.

16. Switzer GE, Dew MA, Stukas AA, Goycoolea JM, Hegland J, Simmons RG. Factors associated with attrition from a national bone marrow registry. *Bone Marrow Transplant.* 1999;24(3):313-319.

17. Health Resources and Services Administration. *HRSA Comments on the Draft GAO Report: Bone Marrow Transplantation: Despite Recruitment Successes, National Program May be Underutilized*; 2002. Available at: http://www.gao.gov/new.items/d03182.pdf. Accessed: February 1, 2007.

18. Hawkins BR, Liang R. Ten years of unrelated bone marrow transplantation in Hong Kong. *Bone Marrow Transplant.* 2002;30(8):503-507.

19. The Anthony Nolan Trust. *What We Are All About*; 2007. Available at: http://www.anthonynolan.org.uk/index.php?location=1. Accessed: March 1, 2007.

20. The Caitlin Raymond International Registry. *About Us*; 2007. Available at: http://www.crir.org/aboutus.php. Accessed: March 1, 2007.

21. Kernan NA, Bartsch G, Ash RC, Beatty PG, Champlin R, Filipovich A, et al. Analysis of 462 transplantations from unrelated donors facilitated by the National Marrow Donor Program. *N Engl J Med.* 1993;328(9):593-602.

22. Ballen KK, Hicks J, Dharan B, Ambruso D, Anderson K, Bianco C, et al. Racial and ethnic composition of volunteer cord blood donors: comparison with volunteer unrelated marrow donors. *Transfusion.* 2002;42(10):1279-1284.

23. Bone Marrow Donors Worldwide. *Annual Report of the Bone Marrow Donors Worldwide*; 2005. Available at: http://www.bmdw.org/uploads/media/BMDW2005.pdf. Accessed April 23, 2007.

24. National Marrow Donor Program. *Recommended Timing for Transplant Consultation*; 2006. Available at: http://www.marrow.org/PHYSICIAN/Tx_Indications_Timing_Referral/Recommended_Timing_for_Tx_Cons/index.html. Accessed April 20, 2007.

25. Laver JH, Hulsey TC, Jones JP, Gautreaux M, Barredo JC, Abboud MR. Assessment of barriers to bone marrow donation by unrelated African-American potential donors. *Biol Blood Marrow Transplant.* 2001;7(1):45-48.

26. Onitilo AA, Lin YH, Okonofua EC, Afrin LB, Ariail J, Tilley BC. Race, education, and knowledge of bone marrow registry: indicators of willingness to donate bone marrow among African Americans and Caucasians. *Transplant Proc.* 2004;36(10):3212-3219.

27. Council on Scientific Affairs Report 4. Increasing organ donation. American Medical Association Interim Meeting, New Orleans, LA, December 2002. Available at: http://www.ama-assn.org/ama/pub/category/13582.html. Accessed: February 11, 2007.

28. Institute of Medicine. *Cord Blood: Establishing a National Hematopoietic Stem Cell Bank Program*, 2005. Available at: http://www.iom.edu/CMS/3740/20073/26386.aspx. Accessed: December 5, 2006.

29. Council on Scientific Affairs Report 2. Umbilical cord blood transplantation: current scientific understanding. American Medical Association Annual Meeting, Chicago, IL, 2003. Available at: http://www.ama-assn.org/ama/pub/category/13542.html. Accessed February 11, 2007.

30. Tossounian SA, Schoendorf KC, Kiely JL. Racial differences in perceived barriers to prenatal care. *Matern Child Health J*. 1997;1(4):229-236.

31. Hartwig MS, Hall G, Hathaway D, Gaber AO. Effect of organ donor race on health team procurement efforts. *Arch Surg*. 1993;128(2):1331-1335.

32. Siminoff LA, Arnold R. Increasing organ donation in the African-American community: altruism in the face of an untrustworthy system. *Ann Intern Med.* 1999;130(7):607-609.

Appendix. AMA Policy

H-50.980 Increasing Bone Marrow Screening
Our AMA supports efforts to increase blood donor awareness of bone marrow screening through the addition of a question on the questionnaire required for blood donation that will assess the donor's interest in obtaining information about bone marrow donation, and that information be provided to those donors who indicate an interest. (Res. 502, I-98)

H-370.974 Working Toward an Increased Number of Minorities Registered as Potential Bone Marrow Donors
The AMA supports efforts to increase the number of all potential bone marrow donors registered in national bone marrow registries, especially minority donors, to improve the odds of successful HLA matching and bone marrow transplantation. (Res. 501, I-94; Reaffirmed: CSA Rep. 6, A-04)

H-370.970 Umbilical Cord Blood Transplantation: The Current Scientific Understanding
Our AMA: (1) urges physicians to recognize that umbilical cord blood transplantation is a viable alternative to bone marrow transplantation in appropriately selected patients; (2) encourages the development of national standardized guidance to address the ethical, economic, and social issues surrounding umbilical cord blood transplantation; and (3) will continue to study cord blood banking in this country, and work with appropriate specialty societies and organizations, such as the National Marrow Donor Program, to develop and disseminate materials to educate physicians and the public about the issues of marketing cord blood banking services directly to patients, the informed consent process, and the existence of federally mandated regulatory oversight of these processes to ensure safety and compliance with specific uniform standards. (CSA Rep. 2, A-03; Appended: Res. 503, A-06)

E-2.165 Fetal Umbilical Cord Blood
Human umbilical cord blood has been identified as a viable source of hematopoietic stem cells that can be used as an alternative to bone marrow for transplantation. It is obtained by clamping the umbilical cord immediately after delivery. The use of umbilical cord blood raises 2 main ethical problems. First, the exact timing of the clamping has a significant impact on the neonate. Studies indicate that early clamping may cause an abrupt surge in arterial pressure, resulting in intraventricular hemorrhage (particularly in premature infants). Second, there is a risk that the infant donor will develop a need for his or her own cord blood later in life. If that child was a donor and this later need arises, he or she might be without blood, when he or she could have had his or her own blood stored. To avoid health risks, normal clamping protocol should be followed and not altered in such a way that might endanger the infant. Additionally, parents of the infant must be fully informed of the risks of the donation and written consent should be obtained from them. The second concern, that the child may need the blood later in life, is more complex. The possibility that an infant donor would be in need of his or her own umbilical cord blood is highly speculative. There are a number of reasons why the infant may not need the blood later. The diseases that are treated by bone marrow transplantation are not common, and there may be other treatment alternatives available, particularly in the future when the illness would occur. Additionally, the demand for fetal umbilical cord blood will increase as it becomes medically certain that the blood may be used in persons unrelated to the donor. This situation will reduce the need to store a particular infant's blood since umbilical cord blood from other donors would be available. If the blood is sufficient for use in unrelated individuals, then the donor may obtain the cord blood from another donor later in life, making the need to store his or her own blood unnecessary. These original donors, however, should be given priority in receipt of such blood if they need a donation later in life. For all of these reasons, it would generally not be unethical to use the cord blood. However, if the child-donor is known to be at risk for an illness that is treated

by bone marrow donation, the child should not be used as a donor, and his or her blood should be stored for future use. (I, V) Issued June 1994; Updated June 1996.